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: Drugs Associated with Serotonin Syndrome, see Drug Interactions: Tricyclic and Other Antidepressants, and see Drug Interactions: Lithium.)

The efficacy of paroxetine for the management of major depression has been established by placebo-controlled studies of 6 weeks' duration in adult outpatients from 18–73 years of age who met DSM-III criteria for major depressive disorder. In these studies, paroxetine hydrochloride was found to be more effective than placebo in improving scores by at least 2 on the Hamilton Depression Rating Scale (HDRS) and the Clinical Global Impression and Severity of Illness Scale. Paroxetine hydrochloride also was more effective than placebo in improving HDRS subfactor scores, including the depressed mood item, sleep disturbance factor, and the anxiety factor.

The efficacy of paroxetine hydrochloride extended-release tablets for the management of depression has been established in 2 flexible-dosage, controlled studies of 12-weeks' duration in adults 18–88 years of age who met DSM-IV criteria for major depressive disorder. In these studies, paroxetine was more effective than placebo in improving scores on the HDRS, the Hamilton depressed mood item, and the Clinical Global Impression-Severity of Illness Scale.

In a study of depressed outpatients who had responded by the end of an initial 8-week open treatment phase to paroxetine (mean dosage: approximately 30 mg daily; HDRS total score of less than 8) and were randomized to continue paroxetine or receive placebo for 1 year, the relapse rate in the paroxetine-treated patients (15%) was substantially lower than that in those who received placebo (39%). An analysis of these data for possible gender-related effects on treatment outcome did not suggest any difference in efficacy based on the gender of the patient. In controlled studies of depressed patients who had responded to a 6-week course of paroxetine or imipramine and were randomized to receive either the same antidepressant or placebo for up to 1 year, both paroxetine and imipramine were more effective than placebo in maintaining euthymia; however, paroxetine was better tolerated than imipramine during long-term therapy. While the optimum duration of paroxetine 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). In placebo-controlled studies, paroxetine has been shown to be effective for the long-term (e.g., up to 1 year) management of depression. In addition, the drug has been used in some patients for longer periods (e.g., up to 4 years) without apparent loss of clinical effect or increased toxicity. However, when paroxetine is used for extended periods, the need for continued therapy should be reassessed periodically. (See Dosage and Administration: Dosage.)

The efficacy of paroxetine as an antidepressant in hospital settings has not been studied adequately to date; however, the drug has been shown to be effective in hospitalized patients with severe depression in at least one controlled study.

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

Considerations in Choosing Antidepressants A variety of antidepressant drugs are available for the treatment of major depressive disorder, including selective serotonin-reuptake inhibitor (SSRIs; e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline), tricyclic antidepressants (e.g., amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine), monoamine oxidase (MAO) inhibitors (e.g., isocarboxazid, phenelzine, tranylcypromine), and other antidepressants (e.g., bupropion, duloxetine, maprotiline, nefazodone, trazodone, venlafaxine). Most clinical studies have shown that the antidepressant effect of usual dosages of paroxetine in patients with depression is greater than that of placebo and comparable to that of usual dosages of tricyclic antidepressants (e.g., amitriptyline, imipramine, doxepin), other SSRIs (e.g., fluoxetine, fluvoxamine, sertraline), and other antidepressants (e.g., nefazodone). The onset of antidepressant action of paroxetine appears to be comparable to that of tricyclic antidepressants and other SSRIs, although there is some evidence that the onset of action may occur slightly earlier with paroxetine than with imipramine and fluoxetine.

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 Symptomology—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 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/or 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 paroxetine 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. 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 paroxetine and other drugs in this class.

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.

Data from controlled clinical studies evaluating various antidepressant agents in children and adolescents are less extensive than with adults, 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 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., paroxetine, citalopram, duloxetine, escitalopram, fluvoxamine, mirtazapine, nefazodone, sertraline, venlafaxine) was not conclusively established in clinical trials in pediatric patients with major depressive disorder. In addition, 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. (See Cautions: Pediatric Precautions.) FDA cur-

rently 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 geriatric patients 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 appear to be as effective as tricyclic antidepressants but may cause 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 paroxetine and other selective serotonin-reuptake inhibitors compared with tricyclic antidepressants 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. Some clinicians state that selective serotonin-reuptake inhibitors including paroxetine 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 selective serotonin-reuptake inhibitors, 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 selective serotonin-reuptake inhibitors 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.

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 and 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. Although patients may present with depressed mood alone, the possibility of more extensive depressive symptomatology should be considered. Therefore, patients should be monitored carefully for indices of major depression, suicidal ideation, and neurovegetative signs since safety measures (e.g., hospitalization for suicidal ideation) and more vigorous and aggressive therapy (e.g., relatively high dosages, multiple drug trials) may be needed in some patients.

If pharmacotherapy is initiated for depressive symptoms in Alzheimer's patients, most experts recommend selective serotonin-reuptake inhibitors such as paroxetine, citalopram, escitalopram, fluoxetine, or sertraline as first-line therapy because of their favorable adverse effect profile in this population compared with other currently available antidepressants (e.g., tricyclic antidepressants, MAO inhibitors). Although evidence of efficacy from controlled studies currently is limited, 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 depressive 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. In a controlled study comparing paroxetine and imipramine in patients with coexisting depression and dementia, both drugs were found to be effective; however, paroxetine was better tolerated (fewer anticholinergic and serious adverse effects).

Cardiovascular Considerations. The relatively low incidence of adverse cardiovascular effects, including orthostatic hypotension and conduction disturbances, associated with paroxetine and other SSRIs may be advantageous in patients in whom the cardiovascular effects associated with tricyclic antidepressants may be hazardous. In a controlled trial comparing paroxetine and nortriptyline in patients with stable ischemic disease, both antidepressants were found to be effective in treating depression and neither drug substantially affected blood pressure or conduction intervals; however, paroxetine did not produce sustained effects on heart rate or rhythm or heart rate variability whereas nortriptyline increased heart rate and reduced heart rate variability. Most clinical studies of paroxetine for the management of depression did not include individuals with cardiovascular disease (e.g., those with a recent history of myocardial infarction or unstable cardiovascular disease), and further experience in such patients is necessary to confirm the relative lack of cardiotoxicity reported with the drug to date. (See Cautions: Cardiovascular Effects and see Cautions: Precautions and Contraindications.)

Sedative Considerations. Because paroxetine and other selective serotonin-reuptake inhibitors generally are 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 or in patients who are prone to accidents; however, an antidepressant with more prominent sedative effects 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 is currently 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 patients of all ages who are receiving antidepressant therapy are recommended. (See Suicidality under Cautions: Nervous System Effects, and see Cautions: Precautions and Contraindications.)

Other Considerations. Paroxetine has been effective in patients with moderate to severe depression, endogenous depression, reactive depression (including traumatic grief), depression associated with human immunodeficiency virus (HIV) infection, and depression associated with anxiety and/or agitation.

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

The efficacy of paroxetine hydrochloride for the management of obsessive-compulsive disorder in adults has been established by 2 multicenter, placebo-controlled studies of 12 weeks' duration. In these clinical studies, paroxetine was more effective than placebo in reducing the severity of obsessive-compulsive manifestations in adult outpatients with moderate to severe obsessive-compulsive disorder (Yale-Brown Obsessive-Compulsive Scale [YBOCS] baseline values of 23–26). In a fixed-dose study of 12 weeks' duration involving paroxetine dosages of 20, 40, or 60 mg daily, patients receiving 40 or 60 mg of the drug daily experienced substantially greater reductions in the YBOCS total score (approximately 6 and 7 points, respectively) than those receiving paroxetine 20 mg daily (approximately 4 points) or placebo (approximately 3 points). The effective dosage of paroxetine was 40 or 60 mg daily. In a 12-week study with flexible dosing of paroxetine (20–60 mg daily) or clomipramine (25–250 mg daily) compared with placebo, paroxetine-treated patients exhibited a mean reduction of approximately 7 points on the YBOCS total score, which was substantially greater than the mean reduction of approximately 4 points in patients receiving placebo. No age- or gender-related differences in outcome were noted in either of these studies.

The efficacy of paroxetine for long-term use (i.e., longer than 12 weeks) has been demonstrated in a 6-month relapse prevention trial, which was an extension of the fixed-dose study of 12 weeks' duration in patients who had responded to paroxetine. Patients who received paroxetine relapsed substantially less frequently than those receiving placebo in a double-blind placebo-controlled study. The manufacturers and many experts state that obsessive-compulsive disorder is chronic and requires several months or longer of sustained therapy. Therefore, it is reasonable to continue therapy in responding patients. If paroxetine is used for extended periods, dosage should be adjusted so that patients are maintained on the lowest effective dosage, and the need for continued therapy with the drug should be reassessed periodically.

Results from comparative studies to date suggest that paroxetine and other SSRIs (e.g., fluoxetine, fluvoxamine, sertraline) are as effective as or somewhat less effective than clomipramine 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., paroxetine, fluoxetine, fluvoxamine, sertraline) 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,

months) and during periods of dosage adjustments. Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, also should be advised to monitor patients on a daily basis for the emergence of agitation, irritability, or unusual changes in behavior, as well as the emergence of suicidality, and to report such symptoms immediately to a health-care provider.

Although a causal relationship between the emergence of symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and/or mania and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consequently, consideration should be given to changing the therapeutic regimen or discontinuing therapy in patients whose depression is persistently worse or in patients experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, particularly if such manifestations are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If a decision is made to discontinue therapy, paroxetine 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).

Because clinical experience with paroxetine in patients with concurrent systemic disease, including cardiovascular disease, hepatic impairment, or renal impairment, is limited, caution should be exercised when paroxetine 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.)

Because paroxetine may cause mydriasis, the drug should be used with caution in patients with angle-closure glaucoma.

Paroxetine should be used with caution in patients with severe renal or hepatic impairment, since increased plasma concentrations of the drug may occur in such patients. (See Pharmacokinetics: Elimination and see Dosage and Administration: Dosage in Renal and Hepatic Impairment.)

Although current evidence suggests that paroxetine is less cardiotoxic than most older antidepressant agents (see Cautions: Cardiovascular Effects), the safety of paroxetine in patients with a recent history of myocardial infarction or unstable cardiovascular disease has not been adequately evaluated to date.

Because of the potential for adverse drug interactions, the manufacturers recommend that patients receiving paroxetine 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 paroxetine 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.

Paroxetine generally is less sedating than most other currently available antidepressants and does not appear to produce substantial impairment of cognitive or psychomotor function nor to potentiate psychomotor impairment induced by other CNS depressants. However, patients should be cautioned that paroxetine may impair their ability to perform activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle), particularly at dosages of 40 mg or more daily, and to avoid such activities until they experience how the drug affects them. In addition, the possibility that paroxetine may potentiate other (i.e., nonpsychomotor) adverse nervous system effects of CNS depressants should be considered.

The manufacturers recommend that patients receiving paroxetine be advised that while they may notice improvement within 1–4 weeks after starting therapy, they should continue therapy with the drug as directed by their physician.

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

Activation of mania and hypomania has occurred in patients receiving therapeutic dosages of paroxetine. The drug should be used with caution in patients with a history of mania. (See Cautions: Nervous System Effects.)

Paroxetine and other selective serotonin-reuptake inhibitors have been associated with the development of akathisia, which is characterized by an inner sense of restlessness and psychomotor agitation such as an inability to sit or stand still usually associated with subjective distress. Akathisia is most likely to occur within the first few weeks of therapy with these drugs.

Hyponatremia has been reported in patients receiving selective serotonin-reuptake inhibitors (SSRIs), including paroxetine, and selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs). Hyponatremia appears to be more likely to occur in geriatric patients and/or in those concurrently receiving diuretics or who are otherwise volume depleted. Hyponatremia also has been reported following paroxetine overdosage in a geriatric patient. Discontinuance of paroxetine therapy should be considered in patients with symptomatic hyponatremia and appropriate medical intervention (e.g., fluid restriction) should be instituted. (See Cautions: Geriatric Precautions.)

The manufacturers state that there have been several cases of abnormal bleeding (mostly ecchymosis and purpura) and a case of impaired platelet aggregation in patients receiving paroxetine. (See Cautions: Hematologic Effects.)

Because paroxetine is the active moiety in both paroxetine mesylate conventional tablets (Pexeva®) and commercially available paroxetine hydrochloride preparations (e.g., Paxil®, nonproprietary [generic] preparations), concurrent administration of paroxetine hydrochloride and paroxetine mesylate should be avoided.

Potentially life-threatening serotonin syndrome may occur with selective serotonin-reuptake inhibitors (SSRIs), including paroxetine, or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs), particularly with concurrent administration of other serotonergic drugs (e.g., serotonin [5-hydroxytryptamine; 5-HT] type 1 receptor agonists ["triptans"]) or drugs that impair the serotonin metabolism (e.g., monoamine oxidase [MAO] inhibitors). Symptoms of serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or GI symptoms (e.g., nausea, vomiting, diarrhea). Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of paroxetine and 5-HT_1 receptor agonists (triptans), tramadol, or other serotonergic agents. Because of the risk of serotonin syndrome, caution also is advised when paroxetine is concurrently administered with other drugs affecting serotonergic neurotransmission, including linezolid, lithium, tramadol, and St. John's Wort. (See Drug Interactions: Drugs Associated with Serotonin Syndrome.)

If concurrent therapy with paroxetine and a 5-HT_1 receptor agonist (triptan) is clinically warranted, the patient should be observed carefully, particularly during initiation of therapy, when the dosage is increased, or when another serotonergic agent is initiated.

Concomitant use of paroxetine and serotonin precursors (e.g., tryptophan) is not recommended.

Paroxetine is contraindicated in patients currently receiving, or having recently received (i.e., within 2 weeks), monoamine oxidase (MAO) inhibitor therapy. Serious, sometimes fatal reactions, including features resembling serotonin syndrome (e.g., hyperthermia, myoclonus, autonomic instability), have occurred with other serotonin-reuptake inhibitors in such patients, and the possibility exists that similar reactions could occur with paroxetine. For additional information on potentially serious drug interactions that may occur between paroxetine and MAO inhibitors or other serotonergic agents, see Drug Interactions: Drugs Associated with Serotonin Syndrome. At least 2 weeks also should elapse after discontinuing paroxetine before initiating MAO inhibitor therapy.

Paroxetine is contraindicated in patients currently receiving pimozide. (See Drug Interactions: Pimozide.)

Paroxetine is contraindicated in patients hypersensitive to the drug or any ingredient in the formulation.

■ **Pediatric Precautions** The manufacturers state that safety and efficacy of paroxetine in children younger than 18 years of age have not been established.

Paroxetine has not demonstrated efficacy in several placebo-controlled trials in 752 children and adolescents with major depressive disorder. Adverse effects reported in at least 2% of the paroxetine-treated pediatric patients in these trials and that occurred at least twice as frequently as in pediatric patients receiving placebo included emotional lability (including self-harm, suicidal thoughts, attempted suicide, crying, and mood fluctuations), hostility, decreased appetite, tremor, sweating, hyperkinesias, and agitation. Upon discontinuance of paroxetine in these pediatric trials following a taper phase regimen, adverse events that occurred in at least 2% of the paroxetine-treated pediatric patients and occurred at least twice as frequently as in pediatric patients receiving placebo included emotional lability (including suicidal ideation, suicide attempt, mood changes, and tearfulness), nervousness, dizziness, nausea, and abdominal pain.

In June 2003, the United Kingdom (UK) regulatory agency warned clinicians to avoid the off-label use of paroxetine for the treatment of depression in children younger than 18 years of age. This action was taken in response to concern about a possible association between selective serotonin reuptake inhibitors and suicidal behavior, which includes a broad range of symptoms ranging from episodes of self-harm to attempted suicide. Proprietary data examined by the UK regulatory agency showed a slight increase in suicidal behavior among patients who were randomly assigned to selective serotonin reuptake inhibitor treatment, as compared with subjects who received placebo.

The US Food and Drug Administration (FDA) determined that the available data at that time were not sufficient either to establish or to rule out an association between the use of these drugs and increased suicidal thoughts or actions by pediatric patients. However, following the results of independent classification and analysis of the suicidal events and behaviors observed in controlled studies, 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. 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., paroxetine, bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, sertra-

line, venlafaxine) in over 4400 children and adolescents with major depressive disorder, obsessive-compulsive disorder (OCD), or other psychiatric disorders. The analysis revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in pediatric patients receiving antidepressants than in those receiving placebo. The average risk of such events was 4% among children and adolescents receiving these drugs, twice the risk (2%) that was observed among those receiving placebo. However, a more recent meta-analysis of 27 placebo-controlled trials of 9 antidepressants (SSRIs and others) in patients younger than 19 years of age with major depressive disorder, OCD, or non-OCD anxiety disorders suggests that the benefits of antidepressant therapy in treating these conditions may outweigh the risks of suicidal behavior or suicidal ideation. No suicides occurred in these pediatric trials.

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

As a result of this analysis and public discussion of the issue, FDA has directed manufacturers of all antidepressants to add a boxed warning to the labeling of their products to alert clinicians of this suicidality risk in children and adolescents and to recommend appropriate monitoring and close observation of patients receiving these agents. (See Cautions: Precautions and Contraindications.) The drugs that are the focus of the revised labeling are all drugs included in the general class of antidepressants, including those that have not been studied in controlled clinical trials in pediatric patients, since the available data are not adequate to exclude any single antidepressant from an increased risk. In addition to the boxed warning and other information in professional labeling on antidepressants, FDA currently recommends that a patient medication guide explaining the risks associated with the drugs be provided to the patient each time the drugs are dispensed. 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 paroxetine discontinued). *Patients should not discontinue use of paroxetine without first consulting their clinician; it is very important that paroxetine not be abruptly discontinued (see Dosage and Administration: Dosage), as withdrawal effects may occur.*

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

■ **Geriatric Precautions** While safety and efficacy of paroxetine in geriatric patients have not been established specifically, 17% of patients (approximately 700) receiving the drug for depression in clinical trials were 65 years of age or older. Although no overall differences in efficacy or the adverse effect profile of paroxetine were observed between geriatric and younger patients and other clinical experience revealed no evidence of age-related differences, pharmacokinetic studies have revealed a decreased clearance of paroxetine in geriatric patients. (See Pharmacokinetics: Elimination.) For this reason, the manufacturers and some clinicians recommend initiating paroxetine therapy in patients 65 years of age or older at a lower dosage than in younger patients. (See Dosage and Administration: Dosage in Geriatric or Debilitated Patients.)

Geriatric patients appear to be more likely than younger patients to develop paroxetine-induced hyponatremia and transient syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Therefore, clinicians prescribing paroxetine 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.

In studies comparing paroxetine and various tricyclic antidepressants, including amitriptyline, clomipramine, and doxepin, in geriatric patients, paroxetine was at least as effective and as well tolerated as or better tolerated than tricyclic antidepressants. In addition, serum anticholinergicity of paroxetine was found to be substantially lower than that of nortriptyline in geriatric depressed patients; complaints of dry mouth and tachycardia also occurred more frequently in nortriptyline-treated patients than in those receiving paroxetine. These findings indicate that, at therapeutic plasma concentrations, paroxetine has approximately 20% the anticholinergic potential of nortriptyline in older patients. Overall, paroxetine was less frequently associated with dry mouth, somnolence, constipation, tachycardia, or confusion than tricyclic antidepressants, although certain adverse effects (e.g., nausea, diarrhea, headache) were more common with paroxetine. In geriatric patients with depression, paroxetine appears to be at least as effective as fluoxetine.

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.)

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, 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 selective serotonin-reuptake inhibitors 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.

■ **Mutagenicity and Carcinogenicity** Paroxetine was not mutagenic in several in vitro tests including the bacterial mutation assay, mouse lymphoma mutation assay, and unscheduled DNA synthesis assay. The drug also was not mutagenic in tests for cytogenetic aberrations in vivo in mouse bone marrow, in vitro in human lymphocytes, and in a dominant lethal test in rats.

Studies to determine the carcinogenic potential of paroxetine were performed in mice receiving oral dosages of 1, 5, and 25 mg/kg daily and in rats receiving dosages of 1, 5, and 20 mg/kg daily for 2 years. In mice, the maximum dosage was up to approximately 2.4 times the maximum human dose for depression, social anxiety disorder, generalized anxiety disorder, and PTSD on a mg/m^2 basis. In rats, the maximum dosage was up to approximately 3.9 times the maximum human dose for depression on a mg/m^2 basis. Because the maximum recommended human dosage for depression, social anxiety disorder, generalized anxiety disorder, and PTSD is slightly lower than that for obsessive-compulsive disorder (50 versus 60 mg daily, respectively), the dosages used in these carcinogenicity studies were only about 2 and 3.2 times the maximum recommended human dosage for obsessive-compulsive disorder in mice and rats, respectively. A substantially greater number of male rats in the high-dose group had reticulum cell sarcomas (1/100, 0/50, 0/50, and 4/50 for control, low-, middle-, and high-dose groups, respectively), and a substantially increased linear trend across dose groups was evident for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The relationship of these findings to human exposure to paroxetine is not known.

■ **Pregnancy, Fertility, and Lactation** Some neonates exposed to paroxetine and other selective serotonin-reuptake inhibitors (SSRIs) or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) late in the third trimester of pregnancy have developed complications that occasionally have 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 for 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, 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: Drugs Associated with Serotonin Syndrome). When treating a pregnant woman with paroxetine 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 paroxetine therapy in the third trimester prior to delivery if the drug is administered during pregnancy. (See Dosage: Treatment of Pregnant Women during the Third Trimester in Dosage and Administration.)

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, compared 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. Persistent pulmonary hypertension of the newborn 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 persistent pulmonary hypertension of the newborn 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 persistent pulmonary hypertension of the newborn associated with individual SSRIs, and the findings have not been confirmed. Although the risk of persistent pulmonary hypertension of the newborn 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 serotonergic effects.