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

The results of retrospective studies indicate that venlafaxine overdosage may be associated with an increased risk of fatal outcome compared with that observed with SSRIs but lower than that associated with tricyclic antidepressants. Epidemiologic studies have shown that venlafaxine-treated patients have a higher preexisting burden of suicide risk factors than patients treated with SSRIs. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in an overdosage as opposed to other characteristics of these venlafaxine-treated patients is not clear. As with other antidepressants, FDA and the manufacturer of venlafaxine recommend that the drug be prescribed in the smallest quantity consistent with good patient management, in order to reduce the risk of overdosage.

Risk of Bipolar Disorder 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). Venlafaxine is *not* approved for use in treating bipolar depression.

Risk of Mydriasis Mydriasis has been reported in association with venlafaxine therapy. Therefore, patients with elevated intraocular pressure or those at risk of angle-closure glaucoma should be monitored during treatment with the drug.

Pediatric Precautions Safety and efficacy of venlafaxine in children younger than 18 years of age have not been established.

Although clinical studies designed to primarily assess the effect of venlafaxine on the growth, development, and maturation of children and adolescents have not been conducted to date, the results from available studies suggest that the drug may adversely affect weight, height, and appetite. Should the decision be made to prescribe venlafaxine for unlabeled (off-label) uses in pediatric patients, the manufacturer recommends regular monitoring of height and weight during therapy, particularly during long-term administration of the drug. In addition, the manufacturer states that the long-term safety of therapy with venlafaxine extended-release capsules (beyond 6 months) has not been systematically evaluated to date. Because the results of clinical studies indicate that the occurrence of blood pressure elevations considered to be clinically important in children and adolescents was similar to that observed in adults receiving venlafaxine, the manufacturer advises that the precautions for adults also should apply to pediatric patients receiving the drug. (See Risk of Sustained Hypertension under Dosage and Administration: Administration.)

In placebo-controlled clinical studies in children and adolescents† 6–17 years of age, efficacy of venlafaxine (administered as extended-release capsules) was *not* established for major depressive disorder or generalized anxiety disorder, and there were increased reports of hostility and suicide-related adverse events such as suicidal ideation and self-harm. Hostility or suicidal ideation were the most common adverse effects leading to discontinuance of the drug in clinical studies in pediatric patients with major depressive disorder, each occurring in 2% of children and adolescents receiving venlafaxine extended-release capsules compared with less than 1 or 0% of those receiving placebo, respectively. In addition, abnormal/changed behavior was the most common adverse effect leading to discontinuance of the drug in clinical studies in pediatric patients with generalized anxiety disorder, occurring in 1% of children and adolescents receiving venlafaxine extended-release capsules compared with none of those receiving placebo. There were no suicides reported in any of these clinical studies.

FDA has determined that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. However, the FDA also states that depression and certain other psychiatric disorders are themselves associated with an increased risk of suicide. (See Cautions: Pediatric Precautions, in Fluoxetine Hydrochloride 28:16.04.20.) Anyone considering the use of venlafaxine in a child or adolescent for any clinical use must therefore balance the potential risks with the clinical need. (See Risk of Suicidality and Overdosage under Dosage and Administration: Administration.)

■ **Dosage** Dosage of venlafaxine hydrochloride is expressed in terms of venlafaxine.

Although no overall differences in efficacy or safety were observed between geriatric and younger adults receiving venlafaxine, the possibility that some older patients may exhibit increased sensitivity to the drug cannot be ruled out. No age-related differences in the pharmacokinetics of venlafaxine have been identified and dosage adjustments are not necessary for geriatric patients on the basis of age alone; however, as with any drug used for the treatment of depression, generalized anxiety disorder, social phobia, or panic disorder, caution should be used when treating geriatric patients and dosage should be increased cautiously. In addition, the greater frequency of decreased hepatic and renal function observed in the elderly should be considered. (See Dosage and Administration: Dosage in Renal and Hepatic Impairment.)

Venlafaxine also should be used with caution in patients whose underlying medical condition might be compromised by increases in heart rate (e.g., patients with hyperthyroidism, heart failure, or recent myocardial infarction), particularly when the venlafaxine dosage exceeds 200 mg daily.

Patients should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Risk of Suicidality and Overdosage under Dosage and Administration: Administration.)

Major Depressive Disorder For the treatment of major depressive disorder in adults, the recommended initial dosage of venlafaxine is 75 mg daily administered in 2 or 3 divided doses as conventional tablets or as a single daily dose when using the extended-release capsules. According to the manufacturer, an initial dosage of 37.5 mg daily (as extended-release capsules) for the first 4–7 days (followed by an increase to 75 mg daily) may be considered for some patients. If no clinical improvement is apparent, the dosage may be increased by increments of up to 75 mg daily at intervals of not less than 4 days. If clinically necessary, dosage can be increased up to 225 mg daily in divided doses as conventional tablets or in a single daily dose when using the extended-release capsules. Although studies with venlafaxine conventional tablets in outpatient settings did not demonstrate additional benefit from dosages exceeding 225 mg daily in moderately depressed patients, patients with more severe depression responded to a mean dosage of 350 mg daily. Whether higher dosages of venlafaxine extended-release capsules are needed for more severely depressed patients is unknown; however, the manufacturer states that experience with dosages of venlafaxine extended-release capsules exceeding 225 mg daily is very limited. The manufacturer states that venlafaxine dosage should not exceed 375 mg daily (usually administered in 3 divided doses) as conventional tablets or 225 mg daily as extended-release capsules.

If desired, patients with depression who are undergoing treatment with a therapeutic dose of conventional tablets may be switched to the extended-release capsules at the nearest equivalent daily venlafaxine dose (e.g., change 37.5 mg twice daily administered as conventional tablets to a 75-mg extended-release capsule administered once daily).

Although the optimum duration of venlafaxine therapy has not been established, the manufacturer states that acute depressive episodes require several months or longer of sustained antidepressant therapy. Results of 2 relapse prevention trials indicate that the antidepressant efficacy of venlafaxine is maintained for up to 6 months in patients receiving 75–225 mg once daily as extended-release capsules and for up to 12 months in those receiving 100–200 mg daily in 2 divided doses as conventional tablets. In these studies, the same dosage of venlafaxine was used for both acute-phase and maintenance treatment. Based on these limited data, it is not known whether the dosage required to induce remission of depression would be comparable to that required to maintain euthymia. The usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically.

Generalized Anxiety Disorder For the management of generalized anxiety disorder in adults, the initial dosage of venlafaxine as extended-release capsules recommended for most patients is 75 mg once daily. In some patients, it may be desirable to initiate therapy with a dosage of 37.5 mg daily given for the first 4–7 days, followed by an increase to 75 mg daily. Although a dose-response relationship for effectiveness in generalized anxiety disorder was not clearly established in clinical studies, certain patients not responding to a venlafaxine dosage of 75 mg daily may benefit from higher dosage. Dosage in these patients may be increased in increments of up to 75 mg daily at intervals of not less than 4 days up to a maximum dosage of 225 mg daily.

The optimum duration of venlafaxine therapy for the management of generalized anxiety disorder has not been established. Although the drug has been used for up to 6 months in controlled clinical studies, the usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically.

Social Phobia For the management of social phobia in adults, the recommended initial dosage of venlafaxine for most patients is 75 mg once daily as extended-release capsules. In some patients, it may be desirable to initiate therapy with a dosage of 37.5 mg daily given for the first 4–7 days, followed by an increase to 75 mg daily. Although a dose-response relationship for effectiveness in social phobia was not clearly established in clinical studies, certain patients not responding to a venlafaxine dosage of 75 mg daily may benefit from a higher dosage. Dosage in these patients may be increased in increments