and clinical response of the patient, dosage may be increased by increments of 50 mg daily at intervals of 4–7 days up to a maximum of 300 mg daily. Because fluvoxamine clearance may be reduced in geriatric patients and/or such patients may have increased sensitivity to the adverse effects of CNS-active drugs, fluvoxamine maleate therapy may be initiated with a lower dosage (i.e., 25 mg daily) and subsequent dosage adjustments made. While a relationship between dosage and therapeutic effect in obsessive-compulsive disorder has not been established, efficacy of fluvoxamine maleate was demonstrated in clinical trials employing 100–300 mg daily. Although the optimum duration of fluvoxamine therapy has not been established, obsessive-compulsive disorder may require several months of sustained drug therapy. If therapy with the drug is prolonged, the lowest possible dosage should be employed and the need for continued therapy reassessed periodically.

Pediatric Dosage. For the management of obsessive-compulsive disorder in pediatric patients 8–17 years of age, the recommended initial dosage of fluvoxamine maleate is 25 mg at bedtime. This dosage may be increased in increments of 25 mg every 4–7 days, as tolerated, until maximum therapeutic benefit is achieved. In one clinical study, dosages for pediatric patients 8–17 years of age were titrated within a range of 50–200 mg daily. However, in a multiple-dose, pharmacokinetic study, steady-state plasma fluvoxamine concentrations were found to be twofold to threefold higher in children 6–11 years of age than in adolescents 12–17 years of age, and the area under the plasma concentration-time curve (AUC) and peak plasma concentrations were 1.5-2.7 times higher in children than in adolescents. Both children and adolescents exhibited nonlinear pharmacokinetics, and female children exhibited higher AUC values and peak plasma concentrations compared with male children. Steady-state plasma concentrations were similar in adults and adolescents receiving 300 mg of fluvoxamine daily, suggesting that fluvoxamine exposure was similar in these two groups. Clinicians should consider both age and gender differences when selecting a fluvoxamine dosage in pediatric patients. The maximum dosage of fluvoxamine in children up to 11 years of age should not exceed 200 mg daily, and therapeutic effects of the drug in female children may be achieved with a lower dosage than in male children. In adolescents, fluvoxamine dosage adjustment up to the maximum daily dosage of 300 mg daily used in adults may be necessary to achieve optimal therapeutic benefit.

The optimum duration of fluvoxamine therapy in pediatric patients has not been established. If therapy with the drug is prolonged (i.e., longer than 10 weeks), the lowest possible dosage should be employed and the need for continued therapy reassessed periodically. (See Pediatric Precautions under Dosage and Administration: Dosage.)

Suicidality Precautions. 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 Pediatric Precautions under Dosage and Administration: Dosage) 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 longstanding 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 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 with placebo in adults older than 24 years of age, and a reduced risk was observed in adults 65 years of age or older.

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 duringinitiation 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, fluvoxamine dosage should be tapered as rapidly as is feasible but with recognition of the risks of abrupt discontinuance. 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.

Bipolar Disorder Precautions. 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). Fluvoxamine is *not* approved for use in treating bipolar depression.

Pediatric Precautions. Safety and efficacy of fluvoxamine for the treatment of obsessive-compulsive disorder in children younger than 8 years of age have not been established. In addition, the safety and efficacy of fluvoxamine in the management of pediatric patients with conditions other than obsessive-compulsive disorder have not been established.

The safety and efficacy of fluvoxamine in pediatric patients with obsessive-compulsive disorder were established in a 10-week, placebo-controlled trial in children and adolescents 8–17 years of age. The majority of these patients continued receiving fluvoxamine therapy for up to 1–3 years longer in an open-label extension of the initial study. Adverse effects generally were similar to those reported in adults. Agitation, depression, dysmenorrhea, flatulence, hyperkinesia, and rash were reported in at least 5% of the pediatric patients and with an incidence at least twice that reported with placebo. In addition, abnormal thinking, increased cough, ecchymosis, emotional lability, epistaxis, hyperkinesia, infection, manic reaction, rash, sinusitis, and weight loss were reported in 2 or more of the 57 pediatric patients receiving fluvoxamine and more frequently than among the patients receiving placebo.

The risks, if any, that may be associated with extended use of fluvoxamine in children and adolescents with obsessive-compulsive disorder have not been systematically evaluated. The evidence relied upon to conclude that fluvoxamine is safe for use in children and adolescents was derived from relatively short-term clinical studies and from extrapolation of experience gained with adult patients. In addition, the effects of long-term fluvoxamine use on the growth, development, and maturation of children and adolescents have not been established. Regular monitoring of weight and growth is recommended if treatment of a child with an SSRI is to be continued long term.

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, 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 fluvoxamine in a child or adolescent for any clinical use must therefore balance the potential risks with the clinical need. (See Suicidality Precautions under Dosage and Administration: Dosage.)

For further information on use of SSRIs in the treatment of major depressive disorder and considerations in choosing the most appropriate antidepressant agent for a particular patient, see Uses: Major Depressive Disorder, in Fluoxetine Hydrochloride 28:16.04.20.

Other Considerations Concomitant use of fluvoxamine is contraindicated in patients receiving astemizole (no longer commercially available in the US), cisapride, pimozide, or terfenadine (no longer commercially available in the US), since fluvoxamine may inhibit metabolism of these drugs and increase the potential for serious adverse cardiac effects.

Since mean AUCs of alosetron were increased approximately sixfold and the elimination half-life was increased approximately threefold during concurrent fluvoxamine administration in one pharmacokinetic study, concurrent use of these drugs is contraindicated.

In a limited number of male patients with schizophrenia, concomitant use of thioridazine and low-dosage fluvoxamine (25 mg twice daily for 1 week) resulted in a threefold increase in plasma concentrations of thioridazine and its two active metabolites (mesoridazine and sulforidazine). Thioridazine produces a dose-related prolongation of the QT_c interval, which is associated with serious ventricular arrhythmias (e.g., torsades de pointes) and sudden death. The possible effects of combining higher dosages of thioridazine and/or fluvoxamine are not yet known, but may be even more pronounced. Therefore, concurrent administration of fluvoxamine and thioridazine is contraindicated.

In a limited number of healthy individuals, concurrent administration of fluvoxamine (100 mg daily for 4 days) and tizanidine (single 4-mg dose) resulted in a 12-fold increase in peak plasma tizanidine concentrations, a threefold increase in elimination half-life of tizanidine, and a 33-fold increase in the AUC of tizanidine. The mean cardiovascular effects observed in this study were a decrease in systolic blood pressure of 35 mm Hg, a decrease in diastolic blood pressure of 20 mm Hg, and a decrease in heart rate of 4 beats/minute. In addition, drowsiness was substantially increased and psychomotor performance was substantially impaired during concurrent therapy. Since fluvoxamine has been shown to markedly affect the pharmacokinetics of tizanidine and to increase the risk of adverse cardiovascular (including substantial hypotension) and CNS (e.g., drowsiness, psychomotor impairment) effects associated with tizanidine use, concomitant use of tizanidine and fluvoxamine is contraindicated.

Caution should be exercised if fluvoxamine is used concomitantly with benzodiazepines that are metabolized by hepatic oxidation (e.g., alprazolam, midazolam, triazolam). Concomitant use of diazepam and fluvoxamine generally should be avoided. The clearance of diazepam was reduced by 65% and that of its active metabolite *N*-desmethyldiazepam could not be determined during concomitant administration with fluvoxamine in one study. Concomitant use of fluvoxamine (100 mg daily) and alprazolam (1 mg 4 times daily) resulted