

LUVOX^{CR}

fluvoxamine maleate extended-release capsules

R_x only

100 mg and 150 mg

Brief summary. See package insert for full prescribing information.

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of LUVOX^{CR} (fluvoxamine maleate) Extended-Release Capsules or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. LUVOX^{CR} Capsules are not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS.)

INDICATIONS—LUVOX^{CR} (fluvoxamine maleate) Extended-Release Capsules are indicated for the treatment of social anxiety disorder (SAD), also known as social phobia, and for the treatment of obsessions and compulsions in patients with obsessive compulsive disorder (OCD) (both as defined in the DSM-IV).

CONTRAINDICATIONS—Co-administration of aloxetine, tizanidine, thioridazine, or pimozide; use of MAO inhibitors in combination with or within 14 days of discontinuing treatment with LUVOX^{CR}; use in patients with a history of hypersensitivity to fluvoxamine maleate or any of the excipients. (See WARNINGS and PRECAUTIONS.)

WARNINGS—**Clinical Worsening and Suicide Risk:** Adult and pediatric patients with MDD may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressants, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, 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. The pooled analyses of short-term placebo-controlled trials of antidepressants (SSRIs and others) showed that these drugs increased the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with MDD and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults ≥ 65 years. The pooled analyses of placebo-controlled trials in children and adolescents with MDD, OCD, or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressants in over 4,400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressants in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1,000 patients treated) include drug-related increases (14 additional cases in patients < 18 years old; 5 in 18- to 24-year-olds) and decreases (1 fewer case in 25- to 64-year-olds; 6 fewer cases in patients ≥ 65 years old). No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about the drug effect on suicide. It is unknown whether the suicidality risk extends to longer-term use, ie, beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression. **All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes (increases or decreases).** The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for MDD as well as for other psychiatric and nonpsychiatric indications. Although a causal link between the emergence of such symptoms 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. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION—Discontinuation of Treatment with LUVOX^{CR}). Families and caregivers of patients being treated with antidepressants for MDD or other psychiatric and nonpsychiatric indications should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Monitoring should include daily observation by families and caregivers. Prescriptions for LUVOX^{CR} should be written for the smallest quantity of capsules consistent with good patient management to reduce the risk of overdose. **Screening Patients for Bipolar Disorder:** A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. LUVOX^{CR} is not approved for use in treating bipolar depression. **Potential for Monoamine Oxidase Inhibitors (MAOIs) Interaction:** In patients receiving another serotonin reuptake inhibitor drug in combination with MAOIs, there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have discontinued that drug and have been started on an MAOI. Some cases presented with features resembling a serotonin syndrome or neuroleptic malignant syndrome. Therefore, LUVOX^{CR} should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI (see CONTRAINDICATIONS).

Potential Thioridazine Interaction: The effect of fluvoxamine (25 mg immediate-release [IR] given twice daily [bid] for 1 week) on thioridazine steady-state concentrations was evaluated in 10 male inpatients with schizophrenia. Concentrations of thioridazine and its 2 active metabolites,

mesoridazine and sulforidazine, increased 3-fold following co-administration of fluvoxamine. Thioridazine administration produces a dose-related prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsades de pointes-type arrhythmias, and sudden death. This experience likely underestimates the degree of risk that might occur with higher doses of thioridazine. Moreover, the effect of fluvoxamine may be even more pronounced at higher doses. Therefore, LUVOX^{CR} and thioridazine should not be co-administered (see CONTRAINDICATIONS and PRECAUTIONS).

Potential Tizanidine Interaction: Fluvoxamine is a potent inhibitor of CYP1A2 and tizanidine is a CYP1A2 substrate. The effect of IR fluvoxamine maleate (100 mg daily for 4 days) on the pharmacokinetics (PK) and pharmacodynamics (PD) of a single dose of tizanidine has been studied in 10 healthy male subjects. Tizanidine C_{max} was increased ~12-fold (range 5- to 32-fold), elimination half-life was increased almost 3-fold, and AUC increased 33-fold (range 14- to 103-fold). The mean maximal effect on blood pressure was a 35 mm Hg decrease in systolic blood pressure, a 20 mm Hg decrease in diastolic blood pressure, and a 4 beat/min decrease in heart rate. Drowsiness was significantly increased and performance on the psychomotor task was significantly impaired. LUVOX^{CR} and tizanidine should not be used together (see CONTRAINDICATIONS and PRECAUTIONS).

Potential Aloxetine Interaction: Fluvoxamine, an inhibitor of several CYP isozymes, has been shown to increase mean aloxetine plasma concentrations (AUC) ~6-fold and prolonged the T_{1/2} by ~3-fold. Therefore, it is recommended not to use LUVOX^{CR} in combination with aloxetine (see CONTRAINDICATIONS, PRECAUTIONS, and LotronexTM (aloxeton) package insert). Use with Ramelteon: Ramelteon should not be used in combination with LUVOX^{CR} (see PRECAUTIONS: Drug Interactions).

Potential Pimozide Interaction: Pimozide is metabolized by the CYP3A4 isozyme. It has been demonstrated that ketoconazole, a potent inhibitor of CYP3A4, blocks the metabolism of this drug, resulting in increased plasma concentrations of parent drug. Increased plasma concentration of pimozide causes QT prolongation and has been associated with torsade de pointes-type ventricular tachycardia, sometimes fatal. A substantial PK interaction has been observed for fluvoxamine in combination with alprazolam, a drug known to be metabolized by the CYP3A4 isozyme. Although it has not been definitively demonstrated that fluvoxamine is a potent CYP3A4 inhibitor, it is likely to be, given the substantial interaction of fluvoxamine with alprazolam. Consequently, it is recommended that fluvoxamine not be used in combination with pimozide (see CONTRAINDICATIONS and PRECAUTIONS).

Other Potentially Important Drug Interactions: (Also see PRECAUTIONS—Drug Interactions).

Benzodiazepines: Benzodiazepines metabolized by hepatic oxidation (eg alprazolam, midazolam, triazolam, etc.) should be used with caution because the clearance of these drugs is likely to be reduced by fluvoxamine. The clearance of benzodiazepines metabolized by glucuronidation (eg lorazepam, oxazepam, temazepam) is unlikely to be affected by fluvoxamine. **Alprazolam:** When IR fluvoxamine maleate (100 mg once daily [qd]) and alprazolam (1 mg four times per day) were co-administered to steady state, plasma concentrations and other PK parameters (AUC, C_{max}, T_{1/2}) of alprazolam were approximately twice those observed when alprazolam was administered alone; oral clearance was reduced by about 50%. The elevated plasma alprazolam concentrations resulted in decreased psychomotor performance and memory. This interaction, which has not been investigated using higher doses of fluvoxamine, may be more pronounced if a 300 mg daily dose is co-administered, particularly since fluvoxamine exhibits non-linear PK over the dose range 100-300 mg. If alprazolam is co-administered with LUVOX^{CR}, the initial alprazolam dose should be at least halved and titration to the lowest effective dose is recommended. No dose adjustment is required for LUVOX^{CR}.

Diazepam: The co-administration of LUVOX^{CR} and diazepam is generally not advisable. Because fluvoxamine reduces the clearance of both diazepam and its active metabolite, N-desmethyldiazepam, there is a strong likelihood of substantial accumulation of both species during chronic co-administration. Evidence supporting the conclusion that it is inadvisable to co-administer fluvoxamine and diazepam derives from a study in which healthy volunteers taking 150 mg/day of IR fluvoxamine maleate were administered a single oral dose of 10 mg of diazepam. In these subjects (n=8), the clearance of diazepam was reduced by 65% and that of N-desmethyldiazepam to a level too low to measure over the course of the 2-week-long study. It is likely that this experience significantly underestimates the degree of accumulation that might occur with repeated diazepam administration. Moreover, as noted with alprazolam, the effect of fluvoxamine may even be more pronounced at higher doses. Accordingly, diazepam and fluvoxamine should not ordinarily be co-administered.

Mexiletine: The effect of steady-state IR fluvoxamine maleate (50 mg bid for 7 days) on the single-dose PK of mexiletine (200 mg) was evaluated in 6 healthy Japanese males. The clearance of mexiletine was reduced by 38% following co-administration with fluvoxamine compared to mexiletine alone. If fluvoxamine and mexiletine are co-administered, serum mexiletine levels should be monitored.

Neuroleptic Malignant Syndrome (NMS) or NMS-Like Events: Rare instances of NMS or NMS-like events have been reported in association with fluvoxamine treatment when co-administered with anti-psychotics. Additionally, a small number of such cases have been reported with fluvoxamine treatment in the absence of anti-psychotic co-administration. These serious and sometimes fatal events can include hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes. As these events may result in potentially life-threatening conditions, patients receiving this combination of therapy should be monitored for the emergence of NMS-like signs and symptoms. Treatment with fluvoxamine and any concomitant anti-psychotic agent should be discontinued immediately if such events occur and supportive symptomatic treatment should be initiated.

Theophylline: The effect of steady-state IR fluvoxamine maleate (50 mg bid) on the PK of a single dose of theophylline (375 mg as 442 mg aminophylline) was evaluated in 12 healthy, non-smoking male volunteers. The clearance of theophylline was decreased ~3-fold. Therefore, if theophylline is co-administered with fluvoxamine maleate, its dose should be reduced to 1/3 of the usual daily maintenance dose and plasma concentrations of theophylline should be monitored. No dose adjustment is required for LUVOX^{CR}.

Warfarin: When IR fluvoxamine maleate (50 mg three times per day) was administered concomitantly with warfarin for 2 weeks, warfarin plasma concentrations increased 98% and prothrombin times were prolonged. Thus patients receiving oral anticoagulants and LUVOX^{CR} should have their prothrombin time monitored and their anticoagulant dose adjusted accordingly. No dose adjustment is required for LUVOX^{CR}.

Serotonin Syndrome: The development of a potentially life-threatening serotonin syndrome may occur with LUVOX^{CR} treatment, particularly with concomitant use of serotonergic drugs (including triptans) or drugs that impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (eg agitation, hallucinations, coma), autonomic instability (eg tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (eg hyperreflexia, incoordination), and/or gastrointestinal (GI) symptoms (eg nausea, vomiting, diarrhea). The concomitant use of LUVOX^{CR} with MAOIs intended to treat depression is contraindicated (see CONTRAINDICATIONS and WARNINGS—Potential for Interactions with Monoamine Oxidase Inhibitors). If concomitant treatment of LUVOX^{CR} with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increase (see PRECAUTIONS—Drug Interactions). Concomitant use of fluvoxamine with serotonin precursors (such as tryptophan) is not recommended (see PRECAUTIONS—Drug Interactions).

PRECAUTIONS: General—Discontinuation of Treatment with LUVOX^{CR}: During marketing of IR fluvoxamine maleate and other SSRIs and SNRIs, there have been spontaneous reports of adverse events (AEs) occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (eg paresthesias, such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with LUVOX^{CR}. A gradual reduction in dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or on discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the health care provider may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION).

Abnormal Bleeding: SSRIs and SNRIs, including LUVOX^{CR}, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design)

have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of GI bleeding. Bleeding events related to use of SSRIs and SNRIs have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of LUVOX CR and NSAIDs, aspirin, or other drugs that affect coagulation. **Activation of Mania/Hypomania:** During premarketing studies of IR fluvoxamine maleate involving primarily depressed patients, hypomania or mania occurred in ~1% of patients treated with fluvoxamine. In a 10-week pediatric OCD study, 2 out of 57 patients (4%) treated with fluvoxamine experienced manic reactions, compared to none of 63 placebo patients. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other antidepressants. As with all antidepressants, LUVOX CR should be used cautiously in patients with a history of mania. **Seizures:** During premarketing studies with IR fluvoxamine maleate, seizures were reported in 0.2% of fluvoxamine-treated patients. Caution is recommended when the drug is administered to patients with a history of convulsive disorders. Fluvoxamine should be avoided in patients with unstable epilepsy, and patients with controlled epilepsy should be carefully monitored. Treatment with fluvoxamine should be discontinued if seizures occur or seizure frequency increases. **Hyponatremia:** Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including LUVOX CR. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk (see **Geriatric Use**). Discontinuation of LUVOX CR should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death. **Use in Patients with Concomitant Illness:** Closely monitored clinical experience with IR fluvoxamine maleate in patients with concomitant systemic illness is limited. Caution is advised in administering LUVOX CR to patients with diseases or conditions that could affect hemodynamic responses or metabolism. LUVOX CR or IR fluvoxamine maleate have not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from many clinical studies during premarket testing. Evaluation of the electrocardiograms (ECGs) for patients with depression or OCD who participated in premarketing studies revealed no differences between fluvoxamine and placebo in the emergence of clinically important ECG changes. In patients with liver dysfunction, following administration of IR fluvoxamine maleate, fluvoxamine clearance was decreased by ~30%. Patients with liver dysfunction should begin with a low dose of LUVOX CR and increase it slowly with careful monitoring. **Laboratory Tests:** There are no specific laboratory tests recommended. **Drug Interactions:** As with all drugs, the potential for interaction by a variety of mechanisms is a possibility. **Potential Interactions with Drugs that Inhibit or are Metabolized by Cytochrome P450 Isoenzymes:** Multiple hepatic cytochrome P450 isoenzymes are involved in the oxidative biotransformation of a large number of structurally different drugs and endogenous compounds. The available knowledge concerning the relationship of fluvoxamine and the cytochrome P450 isoenzyme system has been obtained mostly from PK interaction studies conducted in healthy volunteers, but some preliminary *in vitro* data are also available. Based on a finding of substantial interactions of fluvoxamine with certain of these drugs (see **WARNINGS**) and limited *in vitro* data for CYP3A4, it appears that fluvoxamine inhibits several cytochrome P450 isoenzymes known to be involved in the metabolism of other drugs such as CYP1A2 (eg warfarin, theophylline, propranolol, tizanidine), CYP2C9 (eg warfarin), CYP3A4 (eg alprazolam), and CYP2C19 (eg omeprazole). *In vitro* data suggest that fluvoxamine is a relatively weak inhibitor of CYP2D6. Approximately 7% of the normal population has a genetic code that leads to reduced levels of activity of CYP2D6 enzyme. Such individuals have been referred to as poor metabolizers (PMs) of drugs such as desibrasquin, dextromethorphan, and tricyclic antidepressants. While none of the drugs studied for drug interactions significantly affected the PK of fluvoxamine, an *in vivo* study of fluvoxamine single-dose PK in 13 PM subjects demonstrated altered PK properties compared to 16 extensive metabolizers (EMs): mean C_{max} , AUC, and $T_{1/2}$ were increased by 52%, 200%, and 62%, respectively, in the PM compared to the EM group. This suggests that fluvoxamine is metabolized, at least in part, by CYP2D6. Caution is indicated in patients known to have reduced levels of cytochrome P450 2D6 activity or receiving concomitant drugs known to inhibit this cytochrome P450 isoenzyme (eg quinidine). The metabolism of fluvoxamine has not been fully characterized, and the effects of potent cytochrome P450 isoenzyme inhibition, such as the ketoconazole inhibition of CYP3A4, on fluvoxamine metabolism have not been studied. A clinically significant fluvoxamine interaction is possible with drugs having a narrow therapeutic ratio such as warfarin or theophylline, certain benzodiazepines, and phenytoin. If LUVOX CR is to be administered together with a drug that is eliminated via oxidative metabolism and has a narrow therapeutic window, plasma levels and/or PD effects of the latter drug should be monitored closely, at least until steady-state conditions are reached (see **CONTRAINDICATIONS** and **WARNINGS**). **CNS Active Drugs: Antipsychotics:** See **WARNINGS—Other Potentially Important Drug Interactions, NMS or NMS-Like Events**. **MAOIs:** See **CONTRAINDICATIONS** and **WARNINGS**. **Alprazolam and Diazepam:** See **WARNINGS**. **Alcohol:** Studies involving single 40 g doses of ethanol (oral administration in 1 study and intravenous in the other) and multiple dosing with IR fluvoxamine maleate (50 mg bid) revealed no effect of either drug on the PK or PD of the other. **Carbamazepine:** Elevated carbamazepine levels and symptoms of toxicity have been reported with the co-administration of IR fluvoxamine maleate and carbamazepine. **Clozapine:** Elevated serum levels of clozapine have been reported in patients taking IR fluvoxamine maleate and clozapine. Since clozapine-related seizures and orthostatic hypotension appear to be dose related, the risk of these AEs may be higher when fluvoxamine and clozapine are co-administered. Patients should be closely monitored when LUVOX CR and clozapine are used concurrently. **Lithium:** As with other serotonergic drugs, lithium may enhance the serotonergic effects of fluvoxamine and, therefore, the combination should be used with caution. Seizures have been reported with the co-administration of IR fluvoxamine maleate and lithium. **Lorazepam:** A study of multiple doses of IR fluvoxamine maleate (50 mg bid) and a 4 mg single dose of lorazepam in healthy male volunteers (n=12) indicated no significant PK interaction. On average, both lorazepam alone and lorazepam with fluvoxamine produced substantial decrements in cognitive functioning; however, the co-administration of fluvoxamine and lorazepam did not produce larger mean decrements compared to lorazepam alone. **Methadone:** Significantly increased methadone (plasma level:dose) ratios have been reported when IR fluvoxamine maleate was administered to patients receiving maintenance methadone treatment, with symptoms of opioid intoxication in 1 patient. Opioid withdrawal symptoms were reported following fluvoxamine maleate discontinuation in another patient. **Ramelteon:** When IR fluvoxamine maleate 100 mg bid was administered for 3 days prior to single-dose co-administration of ramelteon 16 mg and IR fluvoxamine maleate, the AUC for ramelteon increased ~190-fold and the C_{max} increased ~70-fold compared to ramelteon administered alone. Ramelteon should not be used in combination with LUVOX CR (see **WARNINGS**). **Serotonergic Drugs:** Based on the mechanism of action of LUVOX CR and the potential for serotonin syndrome, caution is advised when fluvoxamine is co-administered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (see **WARNINGS—Serotonin Syndrome**). The concomitant use of LUVOX CR with other SSRIs, SNRIs, or tryptophan is not recommended. **Sumatriptan:** Rare postmarketing reports have described patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (eg fluoxetine, fluvoxamine, paroxetine, sertraline, etc.) is clinically warranted, appropriate observation of the patient is advised. **Tacrine:** In a study of 13 healthy male volunteers, a single 40 mg dose of tacrine added to IR fluvoxamine maleate 100 mg/day administered at steady state was associated with 5- and 8-fold increases in tacrine C_{max} and AUC, respectively, compared to the administration of tacrine alone. Five subjects experienced nausea, vomiting, sweating, and diarrhea following co-administration, consistent with the cholinergic effects of tacrine. **Thioridazine:** See **CONTRAINDICATIONS** and **WARNINGS**. **Triptans:** There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan.

If concomitant treatment of fluvoxamine with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **WARNINGS—Serotonin Syndrome**). **Tizanidine:** See **CONTRAINDICATIONS** and **WARNINGS**. **Tricyclic Antidepressants (TCAs):** Significantly increased plasma TCA levels have been reported with co-administration of IR fluvoxamine maleate and amitriptyline, clomipramine, or imipramine. Caution is indicated with the co-administration of LUVOX CR and TCAs; plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced. **Tryptophan:** Tryptophan may enhance the serotonergic effects of fluvoxamine, and the combination should, therefore, be used with caution. Severe vomiting has been reported with co-administration of IR fluvoxamine maleate and tryptophan. **Other Drugs: Theophylline and Warfarin:** See **WARNINGS**. **Allosteron:** Because allosteron is metabolized by a variety of hepatic CYP drug metabolizing enzymes, inducers or inhibitors of these enzymes may change the clearance of allosteron. Fluvoxamine is a known potent inhibitor of CYP1A2 and also inhibits CYP3A4, CYP2C9, and CYP2C19. In a PK study, 40 healthy female subjects received fluvoxamine in escalating doses from 50 mg to 200 mg a day for 16 days, with co-administration of allosteron 1 mg on the last day. Fluvoxamine increased mean allosteron plasma concentration (AUC) ~6-fold and prolonged the half-life by ~3-fold (see **CONTRAINDICATIONS**, **PRECAUTIONS**, and Lotronex[™] (alosteron) package insert). **Digoxin:** Administration of IR fluvoxamine maleate 100 mg daily for 18 days (n=8) did not significantly affect the PK of a 1.25 mg single intravenous dose of digoxin. **Diltiazem:** Bradycardia has been reported with the co-administration of IR fluvoxamine maleate and diltiazem. **Propranolol and Other Beta-Blockers:** Co-administration of IR fluvoxamine maleate 100 mg per day and propranolol 160 mg per day in normal volunteers resulted in a mean 5-fold increase (range 2- to 17-fold) in minimum propranolol plasma concentrations. In this study, there was a slight potentiation of the propranolol-induced reduction in heart rate and reduction in the exercise diastolic pressure. One case of bradycardia and hypotension and a second case of orthostatic hypotension have been reported with co-administration of IR fluvoxamine maleate and metoprolol. If propranolol or metoprolol is co-administered with LUVOX CR, a reduction in the initial beta-blocker dose and more cautious dose titration are recommended. No dose adjustment is required for LUVOX CR. Co-administration of IR fluvoxamine maleate 100 mg per day with atenolol 100 mg per day (n=6) did not affect the plasma concentrations of atenolol. Unlike propranolol and metoprolol, which undergo hepatic metabolism, atenolol is eliminated primarily by renal excretion. **Drugs that Interfere with Hemostasis (eg NSAIDs, Aspirin, and Warfarin):** Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper GI bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are co-administered with warfarin. Patients receiving warfarin therapy should be carefully monitored when LUVOX CR is initiated or discontinued. **Effects of Smoking on Fluvoxamine Metabolism:** Smokers had a 25% increase in the metabolism of fluvoxamine compared to nonsmokers. **Electroconvulsive Therapy (ECT):** No clinical studies have established the benefits or risks of combined use of ECT and fluvoxamine maleate. **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** There was no evidence of carcinogenicity in rats treated orally with fluvoxamine maleate for 30 months or hamsters treated orally with fluvoxamine maleate for 20 months (females) or 26 months (males). The daily doses in the high-dose groups in these studies were increased over the course of the study from a minimum of 160 mg/kg to a maximum of 240 mg/kg in rats, and from a minimum of 135 mg/kg to a maximum of 240 mg/kg in hamsters. The maximum dose of 240 mg/kg is ~6 times the maximum human daily dose on a mg/m² basis. **Mutagenesis:** No evidence of genotoxic potential was observed in a mouse micronucleus test, an *in vitro* chromosome aberration test, or the Ames microbial mutagen test with or without metabolic activation. **Impairment of Fertility:** In a study in which male and female rats were administered fluvoxamine (60, 120, or 240 mg/kg) orally prior to and during mating and gestation, fertility was impaired at oral doses ≥120 mg/kg, as evidenced by increased latency to mating, decreased sperm count, decreased epididymal weight, and decreased pregnancy rate. In addition, the numbers of implantations and embryos were decreased at the highest dose. The no effect dose for fertility impairment was 60 mg/kg (~2 times the maximum recommended human dose [MRHD] on a mg/m² basis). **Pregnancy—Teratogenic Effects—Pregnancy Category C:** When pregnant rats were given oral doses of fluvoxamine (60, 120, or 240 mg/kg) throughout the period of organogenesis, developmental toxicity in the form of increased embryofetal death and increased incidences of fetal eye abnormalities (folded retinas) was observed at doses ≥120 mg/kg. Decreased fetal body weight was seen at the high dose. The no effect dose for developmental toxicity in this study was 60 mg/kg (~2 times the MRHD on a mg/m² basis). In a study in which pregnant rabbits were administered oral doses of up to 40 mg/kg (~2 times the MRHD on a mg/m² basis) during organogenesis, no adverse effects on embryofetal development were observed. In other reproductive studies in which female rats were dosed orally during pregnancy and lactation (5, 20, 80, or 160 mg/kg), increased pup mortality at birth was seen at ≥80 mg/kg, and decreases in pup body weight and survival were observed at all doses (low effect dose ~0.1 times the MRHD on a mg/m² basis). **Nonteratogenic Effects:** Neonates exposed to IR fluvoxamine maleate and other SSRIs or SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. These findings are based on postmarketing reports. Complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs or SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see **WARNINGS**). Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN is associated with substantial neonatal morbidity and mortality. In a case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was ~6-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. PPHN occurs in 1-2 per 1000 live births in the general population. When treating a pregnant woman with LUVOX CR during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment (see **DOSE AND ADMINISTRATION**). Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication. **Labor and Delivery:** The effect of fluvoxamine on labor and delivery in humans is unknown. **Nursing Mothers:** Fluvoxamine is secreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** LUVOX CR has not been evaluated in pediatric patients (see **BOXED WARNING**). The efficacy of IR fluvoxamine maleate for the treatment of OCD was demonstrated in a 10-week multicenter placebo-controlled study with 120 outpatients ages 8-17. In addition, 99 of these outpatients continued open-label fluvoxamine maleate treatment for up to another 1 to 3 years, equivalent to 94 patient years. The AE profile observed in that study was generally similar to that observed in adult studies with IR fluvoxamine maleate (see **ADVERSE REACTIONS** and **DOSE AND ADMINISTRATION**). Decreased appetite and weight loss have been observed in association with the use of fluvoxamine as well as other SSRIs. Consequently, regular monitoring of weight and growth is recommended if treatment of a child with an SSRI is to be continued long term. The risks, if any, that may be associated with fluvoxamine's extended use in children and adolescents with OCD have not been systematically assessed. The prescriber should be mindful that the evidence relied upon to conclude that fluvoxamine is safe for use in children and adolescents derives from relatively short-term clinical studies and from extrapolation of experience gained with adult patients. In particular, no studies directly evaluated the effects of long-term fluvoxamine use on the growth, cognitive behavioral development, and maturation of children and adolescents. Although there is no affirmative finding to suggest that fluvoxamine possesses a capacity to adversely affect growth, development, or maturation, the absence of such findings is not compelling evidence of the absence of the potential of fluvoxamine to have

adverse effects in chronic use (see **WARNINGS—Clinical Worsening and Suicide Risk**). Safety and effectiveness in the pediatric population other than pediatric patients with OCD have not been established (see **BOXED WARNING and WARNINGS—Clinical Worsening and Suicide Risk**). Anyone considering the use of LUVOX CR in a child or adolescent must balance the potential risks with the clinical need. **Geriatric Use:** Approximately 230 patients and 5 patients participating in controlled premarketing studies with IR fluvoxamine maleate and LUVOX CR, respectively, were 65 years of age or over. No overall differences in safety were observed between these patients and younger patients. Other reported clinical experience has not identified differences in response between the elderly and younger patients. However, SSRIs and SNRIs, including LUVOX CR, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this AE (see **PRECAUTIONS—Hyponatremia**). Furthermore, the clearance of fluvoxamine is decreased by about 50% in elderly compared to younger patients (see **Pharmacokinetics under CLINICAL PHARMACOLOGY**), and greater sensitivity of some older individuals also cannot be ruled out. Consequently, LUVOX CR should be slowly titrated during initiation of therapy. **ADVERSE REACTIONS—Associated with Discontinuation of Treatment:** Of the 279 patients with SAD and 124 patients with OCD treated with LUVOX CR in controlled clinical trials, 26% and 19% discontinued treatment due to an AE. The most common AEs ($\geq 1\%$) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate at least twice that of placebo) were as follows: *In patients with SAD—Body as a Whole:* asthenia (4%), headache (3%), abdominal pain (1%); *Digestive:* nausea (8%), diarrhea (3%), anorexia (2%); *Nervous System:* insomnia (5%), somnolence (5%), anxiety (4%), dizziness (4%), abnormal thinking (2%), nervousness (2%), depression (1%), agitation (1%), paresthesia (1%), tremor (1%); *Skin and Appendages:* sweating (1%). *In patients with OCD—Body as a Whole:* asthenia (2%), pain (2%); *Digestive:* nausea (6%), diarrhea (2%), dyspepsia (2%); *Nervous System:* insomnia (5%), somnolence (4%), anxiety (2%), dizziness (3%). **Commonly Observed AEs:** LUVOX CR has been studied in 2 controlled trials of SAD ($n=279$) and 1 trial of OCD ($n=124$). In general, AE rates were similar in the 2 data sets as well as in a study of pediatric patients with OCD treated with IR fluvoxamine maleate. The most commonly observed AEs associated with the use of LUVOX CR and likely to be drug-related (incidence $\geq 5\%$ and at least twice that for placebo) were nausea, somnolence, asthenia, diarrhea, anorexia, abnormal ejaculation, tremor, sweating, and anorgasmia. In addition, the following AEs occurred in the SAD population: insomnia, dizziness, dyspepsia, yawn. In the OCD population, the following additional events occurred: decreased libido, anxiety, pharyngitis, vomiting, myalgia, and accidental injury. **AEs Occurring at an Incidence of 2%:** The following AEs occurred in adults at a frequency of $\geq 2\%$, and were more frequent than in the placebo group, among adult patients with SAD ($n=279$) treated once-daily with 100 to 300 mg/day LUVOX CR in two 12-week controlled trials: *Body as a Whole:* headache (35%), asthenia (24%), abdominal pain (5%), chest pain (3%); *Cardiovascular:* palpitation (3%), vasodilatation (2%); *Digestive:* nausea (39%), diarrhea (14%), anorexia (14%), dyspepsia (10%), constipation (6%), liver function test abnormal (2%); *Nervous System:* insomnia (32%), somnolence (26%), dizziness (15%), dry mouth (11%), nervousness (10%), decreased libido (6%) [male (8%), female (4%)], anxiety (8%), tremor (8%), abnormal thinking (3%), abnormal dreams (3%), agitation (3%), hypotonia (2%), paresthesia (3%); *Respiratory System:* yawn (5%), bronchitis (2%); *Skin and Appendages:* sweating (6%); *Special Senses:* taste perversion (2%); *Urogenital:* abnormal ejaculation (11%), anorgasmia (5%) [male (4%), female (5%)], sexual function abnormal (3%) [male (2%), female (3%)], urinary tract infection (2%). The following AEs occurred at a frequency of $\geq 2\%$, and were more frequent than in the placebo group, among adult patients with OCD ($n=124$) treated once daily with 100 to 300 mg/day LUVOX CR in one 12-week controlled trial: *Body as a Whole:* headache (32%), asthenia (26%), pain (10%), accidental injury (5%), viral infection (2%); *Cardiovascular:* hypertension (2%); *Digestive:* nausea (34%), diarrhea (18%), anorexia (13%), dyspepsia (8%), constipation (4%), vomiting (6%), tooth disorder (2%), gingivitis (2%); *Hemic and Lymphatic:* ecchymosis (4%); *Metabolic and Nutritional Disorders:* weight loss (2%); *Musculoskeletal:* myalgia (5%); *Nervous System:* insomnia (35%), somnolence (27%), dizziness (12%), dry mouth (10%), decreased libido (6%) [male (10%), female (4%)], anxiety (6%), tremor (6%), abnormal thinking (3%), agitation (2%), apathy (3%), neurosis (2%), twitching (2%); *Respiratory System:* pharyngitis (6%), yawn (2%), laryngitis (3%), epistaxis (2%); *Skin:* sweating (7%), acne (2%); *Special Senses:* taste perversion (2%), amblyopia (2%); *Urogenital:* abnormal ejaculation (10%), anorgasmia (5%), [male (4%), female (5%)], menorrhagia (3%), sexual function abnormal (2%) [male (4%), female (0%)], polyuria (2%). These lists include the percentages of patients in each group who had at least 1 occurrence of an event during treatment. Reported AEs were classified using a COSTART-based Dictionary terminology. **Other AEs in OCD Pediatric Population:** In pediatric patients ($n=57$) treated with IR fluvoxamine maleate, the overall profile of AEs was generally similar to that seen in adult studies, as shown above. However, the following AEs, not shown above, were reported in 2 or more of the pediatric patients and were more frequent with IR fluvoxamine maleate than with placebo: cough increase, dysmenorrhea, emotional lability, fever, flatulence, flu syndrome, hyperkinesia, infection, manic reaction, rash, rhinitis, and sinusitis. **Male and Female Sexual Dysfunction with SSRIs:** Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder and with aging, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and health care providers may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. The following sexual side effects were reported by $\geq 2\%$ of patients taking LUVOX CR in placebo-controlled trials of SAD and OCD: abnormal ejaculation (11%), anorgasmia [male (4%), female (5%)], impotence (2%), decreased libido [male (8%), female (4%)], sexual function abnormal [male (3%), female (2%)]. Fluvoxamine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae and upon discontinuation of fluvoxamine. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, health care providers should routinely inquire about such possible side effects. **Changes in Weight, Vital Signs, and Laboratory Tests:** No statistically significant differences in weight gain or loss were found between patients treated with LUVOX CR or placebo. Comparisons of IR fluvoxamine maleate or LUVOX CR versus placebo groups in separate short-term trials on (1) median change from baseline and on (2) incidence of patients meeting criteria for potentially important changes from baseline showed no important differences on various vital signs variables or serum chemistry, hematology, and urinalysis variables. **ECG Changes:** Comparisons of IR fluvoxamine maleate or LUVOX CR and placebo groups in separate pools of short-term OCD and depression trials on (1) mean change from baseline on various ECG variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various ECG variables revealed no important differences. **Postmarketing Reports:** Voluntary reports of AEs in patients taking IR fluvoxamine maleate that have been received since market introduction and are of unknown causal relationship to fluvoxamine include acute renal failure, agranulocytosis, amenorrhea, anaphylactic reaction, angioedema, aplastic anemia, bullous eruption, Henoch-Schoenlein purpura, hepatitis, hyponatremia, ileus, laryngismus, neuropathy, pancreatitis, porphyria, priapism, serotonin syndrome, severe akinesia with fever when fluvoxamine was co-administered with anti-psychotic medication, Stevens-Johnson syndrome, toxic epidermal necrolysis, vasculitis, and ventricular tachycardia (including torsades de pointes). **DRUG ABUSE AND DEPENDENCE: Controlled Substance Class—LUVOX CR is not a controlled substance. Physical and Psychological Dependence:** The potential for abuse, tolerance, and physical dependence with IR fluvoxamine maleate has been studied in a nonhuman primate model. No evidence of dependency phenomena was found. The discontinuation effects of LUVOX CR were not systematically evaluated in controlled clinical trials. LUVOX CR was not systematically studied in clinical trials for potential for abuse, but there was no indication of drug-seeking behavior in clinical trials. It should be noted, however, that patients at risk for drug dependency were systematically excluded from investigational studies of IR fluvoxamine maleate. Generally, it is not possible to predict on the basis of preclinical or premarketing clinical experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, health care providers should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of LUVOX CR misuse or abuse (ie development of tolerance, incrementation of dose, drug-seeking behavior). **OVERDOSAGE: Human**

Experience: Exposure to IR fluvoxamine maleate includes over 45,000 patients treated in clinical trials and an estimated exposure of 50,000,000 patients treated during worldwide marketing experience (end of 2005). Of the 539 cases of deliberate or accidental overdose involving fluvoxamine reported from this population, there were 55 deaths. Of these, 9 were in patients thought to be taking IR fluvoxamine alone, and the remaining 46 were in patients taking fluvoxamine along with other drugs. Among nonfatal overdose cases, 404 patients recovered completely. Five patients experienced adverse sequelae of overdose, to include persistent mydriasis, unsteady gait, hypoxic encephalopathy, kidney complications (from trauma associated with overdose), bowel infarction requiring a hemicolectomy, and vegetative state. In 13 patients, the outcome was provided as abating at the time of reporting. In the remaining 62 patients, the outcome was unknown. The largest known ingestion of fluvoxamine IR involved 12,000 mg (equivalent to 2 to 3 months' dosage). The patient fully recovered. However, ingestions as low as 1,400 mg have been associated with lethal outcome, indicating considerable prognostic variability. In the controlled clinical trials with 403 patients treated with LUVOX CR, there was 1 nonfatal intentional overdose. Commonly ($\geq 5\%$) observed AEs associated with fluvoxamine maleate overdose include GI complaints (nausea, vomiting, and diarrhea), coma, hypokalemia, hypotension, respiratory difficulties, somnolence, and tachycardia. Other notable signs and symptoms seen with IR fluvoxamine maleate overdose (single or multiple drugs) include bradycardia, ECG abnormalities, (such as heart arrest, QT interval prolongation, first degree atrioventricular block, bundle branch block, and junctional rhythm), convulsions, dizziness, liver function disturbances, tremor, and increased reflexes. **Management of Overdose:** Treatment should consist of those general measures employed in the management of overdose with any antidepressant. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients. Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for fluvoxamine are known. A specific caution involves patients taking, or recently having taken, fluvoxamine maleate who might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (see **Tricyclic Antidepressants (TCAs) under PRECAUTIONS**). In managing overdose, consider the possibility of multiple drug involvement. The health care provider should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference*. **DOSEAGE AND ADMINISTRATION: SAD and OCD—**The recommended starting dose for LUVOX CR in adults is 100 mg qd. LUVOX CR should be administered, with or without food, as a single daily dose at bedtime. The dose should be increased in 50 mg increments every week, as tolerated, until maximum therapeutic benefit is achieved, not to exceed 300 mg per day. Capsules should not be crushed or chewed. **Special Populations—Dosage for Elderly or Hepatically Impaired Patients:** Elderly patients and those with hepatic impairment have been observed to have a decreased clearance of fluvoxamine maleate. Consequently, it may be appropriate to titrate slowly following the initial dose of 100 mg in these patient groups. **Treatment of Pregnant Women During the Third Trimester:** No neonates have been exposed to LUVOX CR. Neonates exposed to IR fluvoxamine maleate and other SSRIs or SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see **PRECAUTIONS**). When treating pregnant women with LUVOX CR during the third trimester, the health care provider should carefully consider the potential risks and benefits of treatment. The health care provider may consider tapering LUVOX CR in the third trimester. **Maintenance/Continuation of Extended Treatment:** Although the efficacy of LUVOX CR beyond 12 weeks of dosing for SAD and OCD has not been documented in controlled trials, SAD and OCD are chronic conditions, and it is reasonable to consider continuation for a responding patient. Dose adjustments should be made to maintain the patient on the lowest effective dose, and patients should be periodically reassessed to determine the need for continued treatment. **Switching Patients To or From a Monoamine Oxidase Inhibitor:** At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with LUVOX CR. Similarly, at least 14 days should be allowed after stopping LUVOX CR before starting an MAOI. **Discontinuation of Treatment with LUVOX CR:** Symptoms associated with discontinuation of other SSRIs or SNRIs have been reported (see **PRECAUTIONS**). Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the health care provider may continue decreasing the dose but at a more gradual rate.

HOW SUPPLIED: Storage: LUVOX CR Capsules should be protected from high humidity and stored at 25°C (77°F); excursions permitted to 15°–30°C (59°–86°F) [see USP Controlled Room Temperature]. Avoid exposure to temperatures above 30°C (86°F). Dispense in light containers. **Keep out of reach of children.**

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LUVOX CR
fluvoxamine maleate extended-release capsules

**For social anxiety disorder (SAD) and
obsessive compulsive disorder (OCD)**

Introducing New Once-A-Day

LUVOX[®] CR
fluvoxamine maleate extended-release capsules

Available in 100 mg and 150 mg capsules

Important Safety Information

CONTRAINDICATIONS

The use of alosetron, tizanidine, thioridazine, or pimozide with Luvox CR Capsules is contraindicated. The use of MAO inhibitors in combination with Luvox CR Capsules, or within 14 days of discontinuing treatment with Luvox CR Capsules, is contraindicated (see **WARNINGS** and **PRECAUTIONS**). Luvox CR Capsules are also contraindicated in patients with a history of hypersensitivity to fluvoxamine maleate or any of its excipients.

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of LUVOX[®] CR (fluvoxamine maleate) Extended-Release Capsules or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. LUVOX CR Capsules are not approved for use in pediatric patients. (See **WARNINGS: Clinical Worsening and Suicide Risk**, **PRECAUTIONS: Information for Patients**, and **PRECAUTIONS: Pediatric Use**.)



www.LuvoxCR.com

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Please see brief summary for Luvox CR.

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CASE REPORT

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1 2 3 4 5

Trends in Psychopharmacology

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The Well-Rounded Brain

1 2 3 4 5

Clinical Updates in Neuropsychiatry

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