LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules
100 mg and 150 mg

℞ only

Rev 0208

Suicidality and Antidepressant Drugs

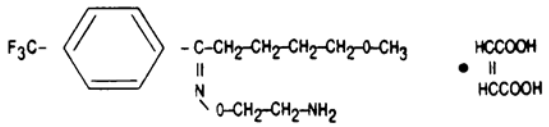
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of LUVOX® CR (fluvoxamine maleate) Extended-Release 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.)

DESCRIPTION

LUVOX® CR is an extended-release capsule for oral administration that contains fluvoxamine maleate, a selective serotonin (5-HT) reuptake inhibitor (SSRI) belonging to the distinct chemical series, the 2-aminoethyl oxime ethers of aralkylketones.

Fluvoxamine maleate is chemically unrelated to other SSRIs and clomipramine. It is chemically designated as 5-methoxy-4'-(trifluoromethyl) valerophenone-(E)-O-(2-aminoethyl)oxime maleate (1:1) and has the empirical formula $C_{15}H_{21}O_2N_2F_3 \bullet C_4H_4O_4$. Its molecular weight is 434.41.

The structural formula is:



Fluvoxamine maleate is a white to off-white, odorless, crystalline powder that is sparingly soluble in water, freely soluble in ethanol and chloroform and practically insoluble in diethyl ether.

LUVOX CR Capsules are available in 100 mg and 150 mg strengths for oral administration. In addition to the active ingredient, fluvoxamine maleate, each capsule contains the following inactive ingredients: talc, sugar spheres, ammonio methacrylate copolymer type B, dibutyl sebacate, red iron

oxide, FD&C Blue No. 2, titanium dioxide, gelatin (porcine- or bovine-derived), and Opacode Grey. LUVOX CR Capsules are gluten-free.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of fluvoxamine maleate in obsessive compulsive disorder is presumed to be linked to its specific serotonin reuptake inhibition in brain neurons. Fluvoxamine has been shown to be a potent inhibitor of the serotonin reuptake transporter in preclinical studies, both in vitro and in vivo.

In *in vitro* studies fluvoxamine maleate had no significant affinity for histaminergic, alpha or beta adrenergic, muscarinic, or dopaminergic receptors. Antagonism of some of these receptors is thought to be associated with various sedative, cardiovascular, anticholinergic, and extrapyramidal effects of some psychotropic drugs.

Pharmacokinetics

Bioavailability: A single-dose crossover study in 28 healthy subjects was conducted to compare the pharmacokinetics of fluvoxamine after administration of LUVOX CR Capsules and immediate-release fluvoxamine maleate tablets

In the single-dose crossover study, mean C_{max} was 38% lower and relative bioavailability was 84% for LUVOX CR Capsules versus immediate-release fluvoxamine maleate tablets.

In a multiple-dose proportionality study, LUVOX CR Capsules were administered over a dose range of 100 mg/day to 300 mg/day to 20 healthy volunteers. Steady-state plasma concentrations were achieved within a week of dosing. Mean maximum plasma concentrations were 47 ng/mL , 161 ng/mL, and 319 ng/mL, respectively, at the 100 mg, 200 mg, and 300 mg administered dose levels. Fluvoxamine exhibited nonlinear pharmacokinetics producing disproportionately higher concentrations over the dose range. The AUC and C_{max} values increased 5.7-fold following the 3-fold increase in dose from 100 mg to 300 mg.

Food caused the mean AUC and C_{max} of fluvoxamine to increase only slightly; therefore, administration of LUVOX CR Capsules with food does not significantly affect the absorption of fluvoxamine.

Distribution/Protein Binding: The mean apparent volume of distribution for fluvoxamine is approximately 25 L/kg, suggesting extensive tissue distribution.

Approximately 80% of fluvoxamine is bound to plasma protein, mostly albumin, over a concentration range of 20 ng/mL to 2000 ng/mL.

Metabolism: Fluvoxamine maleate is extensively metabolized by the liver; the main metabolic routes are oxidative demethylation and deamination. Nine metabolites were identified following a 5 mg radiolabelled dose of fluvoxamine maleate, constituting approximately 85% of the urinary excretion products of fluvoxamine. The main human metabolite was fluvoxamine acid which, together with its N-acetylated analog, accounted for about 60% of the urinary excretion products. A

third metabolite, fluvoxethanol, formed by oxidative deamination, accounted for about 10%. Fluvoxamine acid and fluvoxethanol were tested in an *in vitro* assay of serotonin and norepinephrine reuptake inhibition in rats; they were inactive except for a weak effect of the former metabolite on inhibition of serotonin uptake (1-2 orders of magnitude less potent than the parent compound). Approximately 2% of fluvoxamine was excreted in urine unchanged. (see **PRECAUTIONS – Drug Interactions.**)

Elimination: Following a ^{14}C-labelled oral dose of fluvoxamine maleate (5 mg), an average of 94% of drug-related products was recovered in the urine within 71 hours.

After administration of a 100 mg, single oral dose of LUVOX CR Capsules, the mean plasma half-life of fluvoxamine in healthy male and female volunteers was 16.3 hours.

Gender: In a study with 15 male and 13 female healthy volunteers who were administered LUVOX CR Capsules 100 mg, AUC and C_{max} of fluvoxamine were increased by approximately 60% in females compared to males. There were no differences in the elimination half-life between males and females.

Elderly Subjects: In a study using immediate-release fluvoxamine maleate tablets at 50 mg and 100 mg and comparing elderly (ages 66-73 years) and young subjects (ages 19-35 years), mean maximum plasma concentrations in the elderly were 40% higher. The multiple-dose elimination half-life of fluvoxamine was 17.4 hours and 25.9 hours in the elderly compared to 13.6 hours and 15.6 hours in the young subjects at steady state for 50 mg and 100 mg doses, respectively.

In elderly patients administered immediate-release fluvoxamine maleate tablets, the clearance of fluvoxamine was reduced by about 50%; therefore, LUVOX CR Capsules should be slowly titrated during initiation of therapy.

Pediatric Subjects: The pharmacokinetics of LUVOX CR Capsules have not been evaluated in pediatric patients. However, the multiple-dose pharmacokinetics of immediate-release fluvoxamine maleate tablets were determined in male and female children (ages 6-11 years) (Table 2) and adolescents (ages 12-17 years) (Table 1). Steady-state plasma fluvoxamine concentrations were 2-fold to 3-fold higher in children than in adolescents. AUC and C_{max} in children were 1.5-fold to 2.7-fold higher than those in adolescents (See Table 1). As in adults, both children and adolescents exhibited nonlinear multiple-dose pharmacokinetics. Female children showed significantly higher AUC (0-12) and C_{max} compared to male children; therefore, lower doses of immediate-release fluvoxamine maleate tablets may produce therapeutic benefit (See Table 2). No gender differences were observed in adolescents. Steady-state plasma fluvoxamine concentrations were similar in adults and adolescents at a dose of 300 mg/day, indicating that fluvoxamine exposure was similar in these two populations (See Table 1). Dose adjustment in adolescents (up to the adult maximum dose of 300 mg) may be indicated to achieve therapeutic benefit.

TABLE 1

COMPARISON OF MEAN (SD) IMMEDIATE-RELEASE TABLET FLUVOXAMINE MALEATE PHARMACOKINETIC PARAMETERS BETWEEN CHILDREN, ADOLESCENTS, AND ADULTS

Pharmacokinetic Parameter (body weight corrected)	Dose = 200 mg/day (100 mg Twice Daily)		Dose = 300 mg/day (150 mg Twice Daily)	
	Children (n = 10)	Adolescent (n = 17)	Adolescent (n= 13)	Adult (n = 16)
AUC 0-12 (ng•h/mL/kg)	155.1 (160.9)	43.9 (27.9)	69.6 (46.6)	59.4 (40.9)
C_{max} (ng/mL/kg)	14.8 (14.9)	4.2 (2.6)	6.7 (4.2)	5.7 (3.9)
C_{min} (ng/mL/kg)	11.0 (11.9)	2.9 (2.0)	4.8 (3.8)	4.6 (3.2)

TABLE 2
COMPARISON OF MEAN (SD) IMMEDIATE-RELEASE TABLET FLUVOXAMINE MALEATE PHARMACOKINETIC PARAMETERS BETWEEN MALE AND FEMALE CHILDREN (6-11 YEARS)

Pharmacokinetic Parameter (body weight corrected)	Dose = 200 mg/day (100 mg Twice Daily)	
	Male Children (n = 7)	Female Children (n = 3)
AUC 0-12 (ng•h/mL/kg)	95.8 (83.9)	293.5 (233.0)
C_{max} (ng/mL/kg)	9.1 (7.6)	28.1 (21.1)
C_{min} (ng/mL/kg)	6.6 (6.1)	21.2 (17.6)

Hepatic and Renal Disease: A cross-study comparison (healthy subjects versus patients with hepatic dysfunction) using immediate-release fluvoxamine maleate tablets suggested a 30% decrease in fluvoxamine clearance in association with hepatic dysfunction. The mean minimum plasma concentrations in renally impaired patients (creatinine clearance of 5 mL/min to 45 mL/min) after 4 weeks and 6 weeks of treatment (50 mg given twice daily, N = 13) were comparable to each other, suggesting no accumulation of fluvoxamine in these patients (see **PRECAUTIONS – *Use in Patients with Concomitant Illness***).

Clinical Trials

Social Anxiety Disorder: The effectiveness of LUVOX CR Capsules in the treatment of social anxiety disorder was demonstrated in two 12-week, multicenter, placebo-controlled studies of adult outpatients with social anxiety disorder (DSM-IV). Patients in these trials were titrated in 50 mg increments over the first six weeks of the study on the basis of response and tolerance from a dose of 100 mg/day to a fluvoxamine maleate dose within a range of 100 mg to 300 mg once-a-day.

In these studies, the effectiveness of LUVOX CR Capsules compared to placebo was evaluated on the basis of change from baseline in the Liebowitz Social Anxiety Scale (LSAS). LUVOX CR Capsules demonstrated statistically significant superiority over placebo at the primary endpoint (Week 12) as assessed by the LSAS total score in both studies.

The mean daily doses of LUVOX CR Capsules administered to patients in Study 1 and Study 2 were 236 mg and 204 mg, respectively, at end of study.

Subgroup analyses generally did not indicate differences in treatment outcomes as a function of age, race, or gender.

Obsessive Compulsive Disorder (OCD): The effectiveness of LUVOX CR Capsules for the treatment of OCD was demonstrated in a 12-week, multicenter, placebo-controlled study of adult outpatients. Patients in this trial were titrated in 50 mg increments over the first six weeks of the study on the basis of response and tolerance from a dose of 100 mg/day to a fluvoxamine maleate dose within a range of 100 mg to300 mg once-a-day. Patients in this study had moderate to severe OCD (DSM-IV), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), total scores of 26.6 and 26.3 for fluvoxamine and placebo-treatment groups, respectively.

Patients receiving LUVOX CR Capsules demonstrated statistically significant improvement over placebo patients at the primary endpoint (Week 12) compared to baseline on the Y-BOCS. The mean daily dose of LUVOX CR Capsules administered to patients was 261 mg at end of study.

Exploratory analyses for age and gender effects on outcomes did not show any significant differential responsiveness on the basis of age or sex.

The effectiveness of immediate-release fluvoxamine maleate tablets for the treatment of OCD was demonstrated in two 10-week multicenter, parallel-group studies of adult outpatients. Patients in these trials were titrated to a total daily fluvoxamine maleate dose of 150 mg/day over the first two weeks of the trial, after which the dose was adjusted within a range of 100 mg/day to300 mg/day (given in two doses per day), on the basis of response and tolerance. Patients in these studies had moderate to severe OCD (DSM-III-R), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) total score of 23.

Pediatric OCD Study: LUVOX CR Capsules have not been evaluated in pediatric patients. However, the effectiveness of immediate-release fluvoxamine maleate tablets for the treatment of OCD was demonstrated in a 10-week multicenter, parallel-group study in a pediatric outpatient population (children and adolescents, ages 8-17 years). Patients in this study were titrated to a total daily fluvoxamine dose of approximately 100 mg/day over the first two weeks of the trial, following which the dose was adjusted within a range of 50 mg/day to200 mg/day (given in two doses per day) on the basis of response and tolerance. All patients had moderate-to-severe OCD (DSM-III-R) with mean baseline ratings on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) total score of 24.

Post hoc exploratory analyses for gender effects on outcomes did not suggest any differential responsiveness on the basis of gender. Further exploratory analyses revealed a prominent treatment effect in the 8 year to11 year age group and essentially no effect in the 12 year to 17 year age group. While the significance of these results is not clear, the 2-3 fold higher steady-state plasma fluvoxamine concentrations in children compared to adolescents (see **Pharmacokinetics**) is suggestive that decreased exposure in adolescents may have been a factor, and dose adjustment in adolescents (up to the adult maximum dose of 300 mg/day) may be indicated to achieve therapeutic benefit.

INDICATIONS AND USAGE

Social Anxiety Disorder: LUVOX CR Capsules are indicated for the treatment of social anxiety disorder, also known as social phobia, as defined in DSM-IV (300.23). Social anxiety disorder is characterized by a marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. Exposure to the feared situation almost invariably provokes anxiety, which may approach the intensity of a panic attack. The feared situations are avoided or endured with intense anxiety or distress. The avoidance, anxious anticipation, or distress in the feared situation(s) interferes significantly with the person's normal routine, occupational or academic functioning, or social activities or relationships, or there is marked distress about having the phobias. Lesser degrees of performance anxiety or shyness generally do not require psychopharmacological treatment.

The efficacy of LUVOX CR Capsules was demonstrated in two 12-week trials in adult patients with social anxiety disorder (DSM-IV). LUVOX CR Capsules have not been studied in children or adolescents with social anxiety disorder (see **Clinical Trials** under **CLINICAL PHARMACOLOGY**).

The effectiveness of LUVOX CR Capsules in long-term treatment of social anxiety disorder, i.e., for more than 12 weeks, has not been systematically evaluated in adequate and well-controlled trials. Therefore, the health care provider who elects to prescribe LUVOX CR Capsules for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

Obsessive Compulsive Disorder: LUVOX CR Capsules are indicated for the treatment of obsessions and compulsions in patients with obsessive compulsive disorder (OCD), as defined in the DSM-IV. The obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of LUVOX CR Capsules was demonstrated in one 12-week trial with obsessive compulsive outpatients with the diagnosis of OCD as defined in DSM-IV (see **Clinical Trials** under **CLINICAL PHARMACOLOGY**).

The efficacy of the immediate-release fluvoxamine maleate tablets in the treatment of OCD was demonstrated in two 10-week multicenter, parallel-group studies of adult outpatients.

Obsessive compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

The effectiveness of LUVOX CR Capsules for long-term use, i.e., for more than 12 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the health care provider who elects to prescribe LUVOX CR Capsules for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

Co-administration of alosetron, tizanidine, thioridazine, or pimozide with LUVOX CR Capsules is contraindicated (see **WARNINGS** and **PRECAUTIONS**).

The use of MAO inhibitors used 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 contraindicated in patients with a history of hypersensitivity to fluvoxamine maleate or any of the excipients.

WARNINGS

Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, 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 antidepressant medications, 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 antidepressant drugs (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 major depressive disorder (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 aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 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 antidepressant drugs 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 1000 patients treated) are provided in the Table 3.

TABLE 3
DRUG-PLACEBO DIFFERENCES IN NUMBER OF CASES OF SUICIDALITY PER 1000 PATIENTS TREATED

Age Range	**Drug-Related Increases**
<18	14 additional cases
18-24	5 additional cases
Age Range	**Drug-Related Decreases**

25-64	1 fewer case
≥ 65	6 fewer cases

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, i.e., 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, either 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 major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. 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 Capsules**, for a description of the risks of discontinuation of LUVOX CR Capsules).

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, 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. Such monitoring should include daily observation by families and caregivers. Prescriptions for LUVOX CR Capsules should be written for the smallest quantity of capsules consistent with good patient management, in order 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. It should be noted that LUVOX CR Capsules is not approved for use in treating bipolar depression.

Potential for Monoamine Oxidase Inhibitors Interaction

In patients receiving another serotonin reuptake inhibitor drug in combination with monoamine oxidase inhibitors (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 Capsules 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 tablets given twice daily for one week) on thioridazine steady-state concentrations was evaluated in 10 male inpatients with schizophrenia. Concentrations of thioridazine and its two 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. It is likely that this experience underestimates the degree of risk that might occur with higher doses of thioridazine. Moreover, the effect of fluvoxamine may be even more pronounced when it is administered at higher doses.

Therefore, LUVOX CR Capsules 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 immediate–release fluvoxamine maleate tablets (100 mg daily for four days) on the pharmacokinetics and pharmacodynamics of a single dose of tizanidine has been studied in 10 healthy male subjects. Tizanidine C_{max} was increased approximately 12-fold (range 5-fold to 32-fold), elimination half-life was increased by almost 3-fold, and AUC increased 33-fold (range 14-fold 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 Capsules and tizanidine should not be used together (see CONTRAINDICATIONS and PRECAUTIONS).

Potential Alosetron Interaction

Fluvoxamine, an inhibitor of several CYP isozymes, has been shown to increase mean alosetron plasma concentrations (AUC) approximately 6-fold and prolonged the half-life by approximately 3-fold. Consequently, it is recommended that LUVOX CR Capsules not be used in combination with alosetron (see CONTRAINDICATIONS, PRECAUTIONS, and Lotronex™ (alosetron) package insert).

Use with Ramelteon

Ramelteon should not be used in combination with LUVOX CR Capsules (see **PRECAUTIONS: Drug Interactions**).

Potential Pimozide Interaction

Pimozide is metabolized by the CYP3A4 isozyme, and 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. As noted below, a substantial pharmacokinetic interaction has been observed for fluvoxamine in combination with alprazolam, a drug that is 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 (e.g., 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 (e.g., lorazepam, oxazepam, temazepam) is unlikely to be affected by fluvoxamine.

Alprazolam – When immediate-release fluvoxamine maleate tablets (100 mg given once daily) and alprazolam (1 mg given 4 times per day) were co-administered to steady state, plasma concentrations and other pharmacokinetic parameters (AUC, C_{max}, T½) 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 pharmacokinetics over the dosage range 100 mg to 300 mg. If alprazolam is co-administered with LUVOX CR Capsules, the initial alprazolam dosage should be at least halved and titration to the lowest effective dose is recommended. No dosage adjustment is required for LUVOX CR Capsules.

Diazepam – The co-administration of LUVOX CR Capsules 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 is derived from a study in which healthy volunteers taking 150 mg/day of immediate-release fluvoxamine maleate tablets 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 that was too low to measure over the course of the two-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 when it is administered at higher doses.

Accordingly, diazepam and fluvoxamine should not ordinarily be co-administered.

Mexiletine - The effect of steady-state immediate-release fluvoxamine maleate tablets (50 mg given twice daily for 7 days) on the single-dose pharmacokinetics 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 neuroleptic malignant syndrome (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 immediate-release fluvoxamine maletate tablets (50 mg tablets given twice daily) on the pharmacokinetics 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 approximately 3-fold. Therefore, if theophylline is co-administered with fluvoxamine maleate, its dose should be reduced to one third of the usual daily maintenance dose and plasma concentrations of theophylline should be monitored. No dosage adjustment is required for LUVOX CR Capsules.

Warfarin: When immediate-release fluvoxamine maleate tablets (50 mg given three times per day) were administered concomitantly with warfarin for two weeks, warfarin plasma concentrations

increased by 98% and prothrombin times were prolonged. Thus patients receiving oral anticoagulants and LUVOX CR Capsules should have their prothrombin time monitored and their anticoagulant dose adjusted accordingly. No dosage adjustment is required for LUVOX CR Capsules.

Serotonin Syndrome: The development of a potentially life-threatening serotonin syndrome may occur with LUVOX CR Capsules treatment, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs that impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms 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 gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of LUVOX CR Capsules 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 Capsules with a 5-hydroxtryptamine receptor agonist (triptan) is clinically warranted careful observation of the patient is advised, particularly during treatment initiation and dose increase (see **PRECAUTIONS – Drug Interactions**).

The 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 Capsules: During marketing of immediate-release fluvoxamine maleate tablets and other SSRIs and SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., 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 Capsules. A gradual reduction in 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 (see **DOSAGE AND ADMINISTRATION**).

Abnormal Bleeding: SSRIs and SNRIs, including LUVOX CR Capsules, may increase the risk of bleeding events.Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, 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 gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use 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 Capsules and NSAIDs, aspirin, or other drugs that affect coagulation.
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Activation of Mania/Hypomania: During premarketing studies of immediate-release fluvoxamine maleate tablets involving primarily depressed patients, hypomania or mania occurred in approximately 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 marketed antidepressants. As with all antidepressants, LUVOX CR Capsules should be used cautiously in patients with a history of mania.

Seizures: During premarketing studies with immediate-release fluvoxamine maleate tablets, 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 if seizure frequency increases.

Hyponatremia: Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including LUVOX CR Capsules. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than110 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 Capsules 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 immediate-release fluvoxamine maleate tablets in patients with concomitant systemic illness is limited. Caution is advised in administering LUVOX CR Capsules to patients with diseases or conditions that could affect hemodynamic responses or metabolism.

LUVOX CR Capsules or immediate-release fluvoxamine maleate tablets 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 the product's premarketing testing. Evaluation of the electrocardiograms 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 immediate-release fluvoxamine maleate tablets, fluvoxamine clearance was decreased by approximately 30%. Patients with liver dysfunction should begin with a low dose of LUVOX CR Capsules and increase it slowly with careful monitoring.

Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with LUVOX CR Capsules and should counsel them in the appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions" is available for LUVOX CR Capsules. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking LUVOX CR Capsules.

Abnormal Bleeding: Patients should be cautioned about the concomitant use of fluvoxamine and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding.

Clinical Worsening and Suicide Risk: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate the need for very close monitoring and possibly changes in the medication.

Interference with Cognitive or Motor Performance: Since any psychoactive drug may impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are certain that LUVOX CR Capsules therapy does not adversely affect their ability to engage in such activities.

Pregnancy: Patients should be advised to notify their health care providers if they become pregnant or intend to become pregnant during therapy with LUVOX CR Capsules.

Nursing: Patients receiving LUVOX CR Capsules should be advised to notify their health care providers if they are breast feeding an infant (see **PRECAUTIONS – Nursing Mothers**).

Concomitant Medication: Patients should be advised to notify their health care providers if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for clinically important interactions with LUVOX CR Capsules. Patients should be cautioned about the concomitant use of LUVOX CR Capsules and NSAIDs, aspirin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding.

Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of LUVOX CR Capsules and triptans, tramadol or other serotonergic agents.

Because of the potential for the increased risk of serious adverse reactions, including severe lowering of blood pressure and sedation, when LUVOX CR Capsules and tizanidine are used together, fluvoxamine should not be used with tizanidine.

Because of the potential for the increased risk of serious adverse reactions when LUVOX CR Capsules and alosetron are used together, fluvoxamine should not be used with Lotronex™ (alosetron).

Alcohol: Patients should be advised to avoid alcohol while taking LUVOX CR Capsules.

Allergic Reactions: Patients should be advised to notify their health care providers if they develop a rash, hives, or a related allergic phenomenon during therapy with LUVOX CR Capsules.

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 pharmacokinetic 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 later parts of this section and also **WARNINGS** for details) and limited *in vitro* data for CYP3A4, it appears that fluvoxamine inhibits several cytochrome P450 isoenzymes that are known to be involved in the metabolism of other drugs such as: CYP1A2 (e.g. warfarin, theophylline, propranolol, tizanidine), CYP2C9 (e.g. warfarin), CYP3A4 (e.g. alprazolam), and CYP2C19 (e.g. 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" (PM) of drugs such as debrisoquin, dextromethorphan, and tricyclic antidepressants. While none of the drugs studied for drug interactions significantly affected the pharmacokinetics of fluvoxamine, an *in vivo* study of fluvoxamine single-dose pharmacokinetics in 13 PM subjects demonstrated altered pharmacokinetic properties compared to 16 "extensive metabolizers" (EM): mean C_{max}, AUC, and half-life 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 and those receiving concomitant drugs known to inhibit this cytochrome P450 isoenzyme (e.g., 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 Capsules are to be administered together with a drug that is eliminated via oxidative metabolism and has a narrow therapeutic window, plasma levels and/or pharmacodynamic effects of the latter drug should be monitored closely, at least until steady-state conditions are reached (see **CONTRAINDICATIONS** and **WARNINGS**).

CNS Active Drugs:

Anti-psychotics: See **WARNINGS – Other Potentially Important Drug Interactions – *Neuroleptic Malignant Syndrome (NMS) or NMS-Like Events***.

Monoamine Oxidase Inhibitors: See **CONTRAINDICATIONS** and **WARNINGS.**

Alprazolam: See **WARNINGS.**

Diazepam: See **WARNINGS.**

Alcohol: Studies involving single 40 g doses of ethanol (oral administration in one study and intravenous in the other) and multiple dosing with immediate-release fluvoxamine maleate tablets (50 mg given twice daily) revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of the other.

Carbamazepine: Elevated carbamazepine levels and symptoms of toxicity have been reported with the co-administration of immediate-release fluvoxamine maleate tablets and carbamazepine.

Clozapine: Elevated serum levels of clozapine have been reported in patients taking immediate-release fluvoxamine maleate tablets and clozapine. Since clozapine related seizures and orthostatic hypotension appear to be dose related, the risk of these adverse events may be higher when

fluvoxamine and clozapine are co-administered. Patients should be closely monitored when LUVOX CR Capsules 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 immediate-release fluvoxamine maleate tablets and lithium.

Lorazepam: A study of multiple doses of immediate-release fluvoxamine maleate tablets (50 mg given twice daily) in healthy male volunteers (N = 12) and a single dose of lorazepam (4 mg single dose) indicated no significant pharmacokinetic 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 immediate-release fluvoxamine maleate tablets were administered to patients receiving maintenance methadone treatment, with symptoms of opioid intoxication in one patient. Opioid withdrawal symptoms were reported following fluvoxamine maleate discontinuation in another patient.

Ramelteon: When immediate-release fluvoxamine maleate tablets 100 mg twice daily was administered for 3 days prior to single-dose co-administration of ramelteon 16 mg and immediate-release fluvoxamine maleate tablets, the AUC for ramelteon increased approximately 190-fold and the C_{max} increased approximately 70-fold compared to ramelteon administered alone. Ramelteon should not be used in combination with LUVOX CR Capsules (see **WARNINGS**).

Serotonergic Drugs: Based on the mechanism of action of LUVOX CR Capsules 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 Capsules with other SSRIs, SNRIs, or tryptophan is not recommended (see **PRECAUTIONS – Drug Interactions**).

Sumatriptan: There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., 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 immediate-release fluvoxamine maleate tablets 100 mg/day administered at steady state was associated with 5-fold 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 the co-administration of immediate-release fluvoxamine maleate tablets and amitriptyline, clomipramine, or imipramine. Caution is indicated with the co-administration of LUVOX CR Capsules 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 the co-administration of immediate-release fluvoxamine maleate tablets and tryptophan.

Other Drugs:

Theophylline: See **WARNINGS.**

Warfarin: See **WARNINGS.**

Alosetron: Because alosetron is metabolized by a variety of hepatic CYP drug metabolizing enzymes, inducers or inhibitors of these enzymes may change the clearance of alosetron. Fluvoxamine is a known potent inhibitor of CYP1A2 and also inhibits CYP3A4, CYP2C9, and CYP2C19. In a pharmacokinetic 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 alosetron 1 mg on the last day. Fluvoxamine increased mean alosetron plasma concentration (AUC) approximately 6-fold and prolonged the half-life by approximately 3-fold. (see **CONTRAINDICATIONS, PRECAUTIONS**, and Lotronex™ (alosetron) package insert).

Digoxin: Administration of immediate-release fluvoxamine maleate tablets 100 mg daily for 18 days (N = 8) did not significantly affect the pharmacokinetics of a 1.25 mg single intravenous dose of digoxin.

Diltiazem: Bradycardia has been reported with the co-administration of immediate-release fluvoxamine maleate tablets and diltiazem.

Propranolol and Other Beta-Blockers: Co-administration of immediate-release fluvoxamine maleate tablets 100 mg per day and propranolol 160 mg per day in normal volunteers resulted in a mean 5-fold increase (range 2-fold 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 the co-administration of immediate-release fluvoxamine maleate tablets and metoprolol.

If propranolol or metoprolol is co-administered with LUVOX CR Capsules, a reduction in the initial beta-blocker dose and more cautious dose titration are recommended. No dosage adjustment is required for LUVOX CR Capsules.

Co-administration of immediate-release fluvoxamine maleate tablets 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 (e.g., NSAIDs, Aspirin, and Warfarin) – Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal 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 coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when LUVOX CR Capsules 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): There are no clinical studies establishing 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 approximately 6 times the maximum human daily dose on a mg/m^2 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 mg/kg, 120 mg/kg, or 240 mg/kg) orally prior to and during mating and gestation, fertility was impaired at doses of 120 mg/kg or greater, 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 (approximately 2 times the maximum recommended human dose [MRHD] on a mg/m^2 basis).

Pregnancy

Teratogenic Effects – Pregnancy Category C: When pregnant rats were given fluvoxamine (60 mg/kg, 120 mg/kg, or 240 mg/kg) orally 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 of 120 mg/kg or greater. Decreased fetal body weight was seen at the high dose. The no effect dose for developmental toxicity in this study was 60 mg/kg (approximately 2 times the maximum recommended human dose [MRHD] on a mg/m^2 basis).

In a study in which pregnant rabbits were administered doses of up to 40 mg/kg (approximately 2 times the MRHD on a mg/m^2 basis) orally 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 mg/kg, 20 mg/kg , 80 mg/kg , or 160 mg/kg), increased pup mortality at birth was seen at doses of 80 mg/kg or greater and decreases in pup body weight and survival were observed at all doses (low effect dose approximately 0.1 times the MRHD on a mg/m^2 basis).

Nonteratogenic Effects: Neonates exposed to immediate-release fluvoxamine maleate tablets and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs) late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. These findings are based on Postmarketing reports. Such 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 approximately 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 Capsules during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment (see **DOSAGE 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 from LUVOX CR Capsules, 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 Capsules have not been evaluated in pediatric patients (see **BOXED WARNING**). The efficacy of fluvoxamine maleate administered as immediate-release tablets 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 one to three years, equivalent to 94 patient years. The adverse event profile observed in that study was generally similar to that observed in adult studies with immediate-release fluvoxamine maleate tablets (see **ADVERSE REACTIONS** and **DOSAGE 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, there are no studies that directly evaluate 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 Capsules 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 immediate-release fluvoxamine maleate tablets and LUVOX CR Capsules, 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, fluvoxamine has been associated with several cases of clinically significant hyponatremia in elderly patients (see **PRECAUTIONS – General**). 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 Capsules should be slowly titrated during initiation of therapy. SSRIs and SNRIs, including LUVOX CR Capsules, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event (see PRECAUTIONS, Hyponatremia).

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Of the 279 patients with social anxiety disorder and 124 patients with OCD treated with LUVOX CR Capsules in controlled clinical trials, 26% and 19% discontinued treatment due to an adverse event. The most common events (≥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) are provided in Table 4.

TABLE 4
ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATION OF TREATMENT IN SOCIAL ANXIETY DISORDER AND OCD POPULATIONS

	PERCENTAGE OF PATIENTS			
	SOCIAL ANXIETY DISORDER		OBSESSIVE COMPULSIVE DISORDER	
BODY SYSTEM/ ADVERSE EVENT	**LUVOX CR**	**PLACEBO**	**LUVOX CR**	**PLACEBO**
BODY AS A WHOLE				
Asthenia	4	<1	2	0
Headache	3	<1	–	–
Abdominal Pain	1	0	–	–
Pain	–	–	2	0
DIGESTIVE				
Nausea	8	<1	6	0
Diarrhea	3	0	2	0
Anorexia[1]	2	0	–	–
Dyspepsia	–	–	2	0
NERVOUS SYSTEM				
Insomnia	5	<1	5	2
Somnolence	5	<1	4	0
Anxiety	4	<1	2	<1
Dizziness	4	0	3	0
Abnormal Thinking	2	<1	–	–
Nervousness	2	<1	–	–
Depression	1	0	–	–

	PERCENTAGE OF PATIENTS			
	SOCIAL ANXIETY DISORDER		OBSESSIVE COMPULSIVE DISORDER	
BODY SYSTEM/ ADVERSE EVENT	**LUVOX CR**	**PLACEBO**	**LUVOX CR**	**PLACEBO**
Agitation	1	0	–	–
Paresthesia	1	0	–	–
Tremor	1	0	–	–
SKIN AND APPENDAGES				
Sweating	1	0	–	–

[1] Includes, but is not limited to, loss of appetite and decreased appetite.

Incidence in Controlled Trials

Commonly Observed Adverse Events: LUVOX CR Capsules have been studied in two controlled trials of social anxiety disorder (N = 279) and one trial of OCD (N = 124). In general, adverse event rates were similar in the two data sets as well as in a study of pediatric patients with OCD treated with immediate-release fluvoxamine maleate tablets. The most commonly observed adverse events associated with the use of LUVOX CR Capsules and likely to be drug-related (incidence of 5% or greater and at least twice that for placebo) for patients in social anxiety disorder and in OCD derived from Table 5 were: *abnormal ejaculation, anorexia, anorgasmia asthenia, diarrhea, nausea, somnolence, sweating and tremor*. In addition, the following events occurred in the social anxiety disorder population: *dyspepsia, dizziness, insomnia, and yawning*. In the OCD population, the following additional events occurred: *accidental injury, anxiety, decreased libido, myalgia, pharyngitis, and vomiting* . In a study evaluating immediate-release fluvoxamine maleate tablets in pediatric patients with OCD, the following additional events were identified using the above rule: *agitation, depression, dysmenorrhea, flatulence, hyperkinesia, and rash.*

Adverse Events Occurring at an Incidence of 2%: Table 5 enumerates adverse events that occurred in adults at a frequency of 2% or more, and were more frequent than in the placebo group, among patients treated with LUVOX CR Capsules in two short-term, placebo-controlled social anxiety disorder trials (12 week) and one short-term placebo-controlled OCD trial (12 week) and in which patients were dosed once-a-day in a range of 100 to 300 mg/day. This table shows the percentage of patients in each group who had at least one occurrence of an event at some time during their treatment. Reported adverse events were classified using a COSTART-based Dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors may differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing health care provider with some basis for estimating the relative contribution of drug and non-drug factors to the side-effect incidence rate in the population studied.

TABLE 5

976 **TREATMENT-EMERGENT ADVERSE EVENT INCIDENCE RATES**
977 **BY BODY SYSTEM IN ADULT**
978 **SOCIAL ANXIETY DISORDER AND OCD POPULATIONS[1]**

	PERCENTAGE OF PATIENTS REPORTING EVENT			
	SOCIAL ANXIETY DISORDER		OBSESSIVE COMPULSIVE DISORDER	
BODY SYSTEM/ ADVERSE EVENT	**LUVOX CR N = 279**	**PLACEBO N = 276**	**LUVOX CR N = 124**	**PLACEBO N = 124**
BODY AS A WHOLE				
Headache	35	30	32	31
Asthenia	24	10	26	8
Pain[2]	–	–	10	8
Abdominal Pain	5	4	–	–
Accidental Injury	–	–	5	3
Chest Pain	3	1	–	–
Viral Infection	–	–	2	<1
CARDIOVASCULAR				
Palpitation	3	1	–	–
Vasodilatation	2	<1	–	–
Hypertension	–	–	2	<1
DIGESTIVE SYSTEM				
Nausea	39	11	34	13
Diarrhea	14	5	18	8
Anorexia[3]	14	1	13	5
Dyspepsia	10	4	8	5
Constipation	6	5	4	<1
Vomiting	–	–	6	2
Tooth Disorder	–	–	2	<1
Liver Function Test Abnormal	2	<1	–	–
Gingivitis	–	–	2	0
HEMIC AND LYMPHATIC				
Ecchymosis	–	–	4	2
METABOLIC AND NUTRITIONAL DISORDERS				
Weight Loss	–	–	2	<1
MUSCULOSKELETAL				
Myalgia	–	–	5	2
NERVOUS SYSTEM				
Insomnia	32	13	35	20
Somnolence	26	9	27	11
Dizziness	15	7	12	10
Dry Mouth	11	8	10	9
Nervousness	10	9	–	–
Libido Decreased	6	4	6	2
Male	8	6	10	5
Female	4	3	4	1
Anxiety	8	5	6	2
Tremor	8	<1	6	0
Abnormal Thinking	3	2	3	<1
Abnormal Dreams	3	2	–	–
Agitation	3	<1	2	<1

	PERCENTAGE OF PATIENTS REPORTING EVENT			
	SOCIAL ANXIETY DISORDER		OBSESSIVE COMPULSIVE DISORDER	
BODY SYSTEM/ ADVERSE EVENT	**LUVOX CR N = 279**	**PLACEBO N = 276**	**LUVOX CR N = 124**	**PLACEBO N = 124**
Hypertonia	2	1	–	–
Apathy	–	–	3	0
Paresthesia	3	2	–	–
Neurosis	–	–	2	<1
Twitching	–	–	2	0
RESPIRATORY SYSTEM				
Pharyngitis	–	–	6	<1
Yawn	5	<1	2	0
Laryngitis	–	–	3	0
Bronchitis	2	1	–	–
Epistaxis	–	–	2	0
SKIN				
Sweating	6	2	7	<1
Acne	–	–	2	0
SPECIAL SENSES				
Taste Perversion	2	<1	2	<1
Amblyopia	–	–	2	<1
UROGENITAL				
Abnormal Ejaculation	11	2	10	0
Anorgasmia	5	1	5	0
Male	4	2	4	0
Female	5	0	5	0
Menorrhagia	–	–	3	0
Sexual Function Abnormal	3	<1	2	<1
Male	2	1	4	3
Female	3	0	0	0
Urinary Tract Infection	2	<1	–	–
Polyuria	–	–	2	<1

[1] Events for which fluvoxamine maleate incidence was equal to or less than placebo include the following for social anxiety disorder patients: abdominal pain, accidental injury, back pain, flu syndrome, infection, pain, flatulence, pharyngitis, rhinitis, rash, and dysmenorrhea. In OCD patients the following events were seen: abdominal pain, flu syndrome, infection, palpitation, flatulence, increased appetite, weight gain, abnormal dreams, amnesia, hypertonia, nervousness, paresthesia, increased cough, dyspnea, rhinitis, and ear pain.

[2] Term includes body aches/pains, dental pain, pain from surgery, unspecified pain, and general pain secondary to injuries (sprains, fractures).

[3] Includes, but is not limited to, loss of appetite and decreased appetite.

Other Adverse Events in OCD Pediatric Population

In pediatric patients (N = 57) treated with immediate-release fluvoxamine maleate tablets, the overall profile of adverse events was generally similar to that seen in adult studies, as shown in Table 5. However, the following adverse events, not appearing in Table 5, were reported in two or more of the pediatric patients and were more frequent with immediate-release fluvoxamine

maleate tablets 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 selective serotonin reuptake inhibitors (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.

Table 6 displays the incidence of sexual side effects reported by at least 2% of patients taking LUVOX CR capsules in placebo-controlled trials of social anxiety disorder and OCD.

TABLE 6
PERCENTAGE OF PATIENTS REPORTING SEXUAL ADVERSE EVENTS IN PLACEBO-CONTROLLED TRIALS

	LUVOX CR N=403	**Placebo N=400**
Abnormal Ejaculation	11	2
Anorgasmia		
Male	4	1
Female	5	0
Impotence	2	3
Libido Decreased		
Male	8	5
Female	4	2
Sexual Function Abnormal		
Male	3	5
Female	2	0

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.

Weight and Vital Sign Changes

No statistically significant differences in weight gain or loss were found between patients treated with LUVOX CR Capsules or placebo. Comparisons of immediate-release fluvoxamine maleate tablets or LUVOX CR Capsules versus placebo groups in separate short-term trials on (1) median change from baseline on various vital signs variables and on (2) incidence of patients meeting

criteria for potentially important changes from baseline on various measures of vital signs variables revealed no important differences between fluvoxamine maleate and placebo.

Laboratory Changes

Comparisons of immediate-release fluvoxamine maleate tablets or LUVOX CR Capsules versus placebo groups in separate short-term trials on (1) median change from baseline on various serum chemistry, hematology, and urinalysis variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various serum chemistry, hematology, and urinalysis variables revealed no important differences between fluvoxamine maleate and placebo.

ECG Changes

Comparisons of immediate-release fluvoxamine maleate tablets or LUVOX CR Capsules 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 between fluvoxamine maleate and placebo.

Other Events Observed During the Premarketing Evaluation of Fluvoxamine

During premarketing clinical trials conducted in North America and Europe, multiple doses of immediate-release fluvoxamine maleate tablets were administered for a combined total of 2737 patient exposures in patients suffering OCD or Major Depressive Disorder. Untoward events associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a limited (i.e., reduced) number of standard event categories.

In the tabulations which follow, a COSTART-based Dictionary terminology has been used to classify reported adverse events. If the COSTART term for an event was so general as to be uninformative, it was replaced with a more informative term. The frequencies presented, therefore, represent the proportion of the 2737 patient exposures to multiple doses of fluvoxamine maleate who experienced an event of the type cited on at least one occasion while receiving fluvoxamine maleate. All reported events are included in the list below, with the following exceptions: 1) those events already listed in Table 2, which tabulates incidence rates of common adverse experiences in placebo-controlled OCD and depression clinical trials, are excluded; 2) those events for which a drug cause was considered remote (i.e., neoplasia, gastrointestinal carcinoma, herpes simplex, herpes zoster, application site reaction, and unintended pregnancy) are omitted; and 3) events which were reported in only one patient and judged to not be potentially serious are not included. It is important to emphasize that, although the events reported did occur during treatment with fluvoxamine maleate, a causal relationship to fluvoxamine maleate has not been established.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring between 1/100 and 1/1000 patients; and rare adverse events are those occurring in less than 1/1000 patients.

Body as a Whole: **Frequent:** malaise; **Infrequent:** allergic reaction, neck pain, neck rigidity, overdose, photosensitivity reaction, suicide attempt; **Rare:** cyst, pelvic pain, sudden death.

Cardiovascular System: **Frequent:** hypertension, hypotension, syncope; **Infrequent:** angina pectoris, bradycardia, cardiomyopathy, cardiovascular disease, cold extremities, conduction delay, heart failure, myocardial infarction, pallor, pulse irregular, ST segment changes; **Rare:** AV block, cerebrovascular accident, coronary artery disease, embolus, pericarditis, phlebitis, pulmonary infarction, supraventricular extrasystoles.

Digestive System: **Frequent:** elevated liver transaminases; **Infrequent:** colitis, eructation, esophagitis, gastritis, gastroenteritis, gastrointestinal hemorrhage, gastrointestinal ulcer, glossitis, hemorrhoids, melena, rectal hemorrhage, stomatitis; **Rare:** biliary pain, cholecystitis, cholelithiasis, fecal incontinence, hematemesis, intestinal obstruction, jaundice.

Endocrine System: **Infrequent:** hypothyroidism; **Rare:** goiter.

Hemic and Lymphatic Systems: **Infrequent:** anemia, leukocytosis, lymphadenopathy, thrombocytopenia; **Rare:** leukopenia, purpura.

Metabolic and Nutritional Systems: **Frequent:** edema, weight gain; **Infrequent:** dehydration, hypercholesterolemia; **Rare:** diabetes mellitus, hyperglycemia, hyperlipidemia, hypoglycemia, hypokalemia, lactate dehydrogenase increased.

Musculoskeletal System: **Infrequent:** arthralgia, arthritis, bursitis, generalized muscle spasm, myasthenia, tendinous contracture, tenosynovitis; **Rare:** arthrosis, myopathy, pathological fracture.

Nervous System: **Frequent:** amnesia, apathy, hyperkinesia, hypokinesia, manic reaction, myoclonus, psychotic reaction; **Infrequent:** agoraphobia, akathisia, ataxia, CNS depression, convulsion, delirium, delusion, depersonalization, drug dependence, dyskinesia, dystonia, emotional lability, euphoria, extrapyramidal syndrome, gait unsteady, hallucinations, hemiplegia, hostility, hypersomnia, hypochondriasis, hypotonia, hysteria, incoordination, increased salivation, increased libido, neuralgia, paralysis, paranoid reaction, phobia, psychosis, sleep disorder, stupor, twitching, vertigo; **Rare:** akinesia, coma, fibrillations, mutism, obsessions, reflexes decreased, slurred speech, tardive dyskinesia, torticollis, trismus, withdrawal syndrome.

Respiratory System: **Frequent:** cough increased, sinusitis; **Infrequent:** asthma, bronchitis, hoarseness, hyperventilation; **Rare:** apnea, congestion of upper airway, hemoptysis, hiccups, laryngismus, obstructive pulmonary disease, pneumonia.

Skin: **Infrequent:** alopecia, dry skin, eczema, exfoliative dermatitis, furunculosis, seborrhea, skin discoloration, urticaria.

Special Senses: **Infrequent:** accommodation abnormal, conjunctivitis, deafness, diplopia, dry eyes, ear pain, eye pain, mydriasis, otitis media, parosmia, photophobia, taste loss, visual field defect; **Rare:** corneal ulcer, retinal detachment.

***Urogenital System*: Infrequent:** anuria, breast pain, cystitis, delayed menstruation[1], dysuria, female lactation[1], hematuria, menopause[1], metrorrhagia[1], nocturia, premenstrual syndrome[1], urinary incontinence, urinary urgency, urination impaired, vaginal hemorrhage[1], vaginitis[1]; **Rare:** kidney calculus, hematospermia[2], oliguria.

[1] Based on the number of females.
[2] Based on the number of males.

Postmarketing Reports

Voluntary reports of adverse events in patients taking fluvoxamine maleate immediate-release tablets that have been received since market introduction and are of unknown causal relationship to fluvoxamine use 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 antipsychotic 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 immediate release fluvoxamine maleate has been studied in a nonhuman primate model. No evidence of dependency phenomena was found. The discontinuation effects of LUVOX CR Capsules were not systematically evaluated in controlled clinical trials. LUVOX CR Capsules were 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 immediate-release 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 (i.e., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

Exposure to immediate-release fluvoxamine maleate tablets 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 immediate-release fluvoxamine tablets alone and the remaining 46 were in patients taking fluvoxamine along with other drugs. Among non-fatal overdose cases, 404 patients recovered completely. Five patients experienced adverse sequelae of overdosage, 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 immediate-release tablets 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 Capsules, there was one nonfatal intentional overdose.

Commonly (≥5%) observed adverse events associated with fluvoxamine maleate overdose include gastrointestinal complaints (nausea, vomiting, and diarrhea), coma, hypokalemia, hypotension, respiratory difficulties, somnolence, and tachycardia. Other notable signs and symptoms seen with immediate-release 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 overdosage 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 overdosage, 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* (PDR).

DOSAGE AND ADMINISTRATION

Social anxiety disorder and OCD

The recommended starting dose for LUVOX CR Capsules in adult patients is 100 mg once per day. LUVOX CR Capsules should be administered, with or without food, as a single daily dose at

bedtime. In the controlled clinical trials establishing the effectiveness of LUVOX CR Capsules in social anxiety disorder and OCD, patients were titrated in 50 mg increments within a dose range of 100 mg/day to 300 mg/day. Consequently, 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 Capsules. Neonates exposed to immediate-release fluvoxamine maleate tablets 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 Capsules 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 Capsules in the third trimester.

Maintenance/Continuation of Extended Treatment

Although the efficacy of LUVOX CR Capsules beyond 12 weeks of dosing for social anxiety disorder and OCD has not been documented in controlled trials, social anxiety disorder and OCD are chronic conditions, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, 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 Capsules. Similarly, at least 14 days should be allowed after stopping LUVOX CR Capsules before starting an MAOI.

Discontinuation of Treatment with LUVOX CR Capsules

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

100 mg Extended-Release Capsules: Available in a two-piece gelatin capsule (dark blue opaque cap/white opaque body) imprinted with ℗ on one side of the cap and LCR 100 on the other side of the cap.
Bottles of 30..... NDC 68727-600-01

150 mg Extended-Release Capsules: Available in a two-piece gelatin capsule (dark blue opaque cap/powder blue opaque body) imprinted with ℗ on one side of the cap and LCR 150 on the other side of the cap.
Bottles of 30..... NDC 68727-601-01

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 30^0C (86^0F).

Dispense in tight containers.

Keep out of reach of children.
Lotronex™ is a trademark of GlaxoSmithKline
LUVOX® is a registered trademark of Solvay Pharmaceuticals, Inc.

Distributed by:

Jazz Pharmaceuticals, Inc.
Palo Alto, CA 94304

LCR-PI-01 Rev 0607

Medication Guide
Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with your or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thought or actions?

1. **Antidepressant medicines may increase suicidal thoughts and actions in some children, teenagers, and young adults within in the first few months of treatment.**
2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts and actions.
3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or family member?**
   - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
   - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
   - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show

the healthcare provider. Do not start new medicines without first checking with your healthcare provider.

- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

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