

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**21-519**

**LABELING**

**LUVOX®**  
**(Fluvoxamine Maleate) Tablets**  
**25 mg, 50 mg and 100 mg**

**R<sub>x</sub> only**

### Suicidality and Antidepressant Drugs

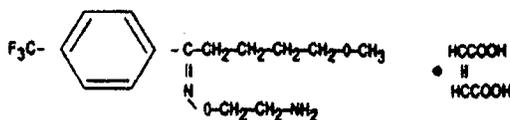
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of LUVOX® Tablets or any other antidepressant 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 Tablets are not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD). (See **WARNINGS: Clinical Worsening and Suicide Risk**, **PRECAUTIONS: Information for Patients**, and **PRECAUTIONS: Pediatric Use**.)

### DESCRIPTION

Fluvoxamine maleate is 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  $C_{15}H_{21}O_2N_2F_3 \cdot C_4H_4O_4$ . Its molecular weight is 434.41.

The structural formula is:



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

LUVOX (Fluvoxamine Maleate) Tablets are available in 25 mg, 50 mg and 100 mg strengths for oral administration. In addition to the active ingredient, fluvoxamine maleate, each tablet contains the following inactive ingredients: carnauba wax, hydroxypropyl methylcellulose, mannitol, polyethylene glycol, polysorbate 80, pregelatinized starch (potato), silicon dioxide, sodium stearyl fumarate, starch (corn), and titanium dioxide. The 50 mg and 100 mg tablets also contain synthetic iron oxides.

## 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. Receptor binding studies have demonstrated that fluvoxamine is a potent serotonin reuptake inhibitor *in vitro* as well as *in vivo*. In preclinical studies, it was found that fluvoxamine inhibited neuronal uptake of serotonin.

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:** The absolute bioavailability of fluvoxamine maleate is 53%. Oral bioavailability is not significantly affected by food.

In a dose proportionality study involving fluvoxamine maleate at 100, 200 and 300 mg/day for 10 consecutive days in 30 normal volunteers, steady state was achieved after about a week of dosing. Maximum plasma concentrations at steady state occurred within 3-8 hours of dosing and reached concentrations averaging 88, 283 and 546 ng/mL, respectively. Thus, fluvoxamine had nonlinear pharmacokinetics over this dose range, i.e., higher doses of fluvoxamine maleate produced disproportionately higher concentrations than predicted from the lower dose.

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

The mean plasma half-life of fluvoxamine at steady state after multiple oral doses of 100 mg/day in healthy, young volunteers was 15.6 hours.

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

In elderly patients, the clearance of fluvoxamine was reduced by about 50% and, therefore, LUVOX Tablets should be slowly titrated during initiation of therapy.

**Pediatric Subjects:** The multiple-dose pharmacokinetics of fluvoxamine were determined in male and female children (ages 6-11) and adolescents (ages 12-17). Steady-state plasma fluvoxamine concentrations were 2-3 fold higher in children than in adolescents. AUC and  $C_{\max}$  in children were 1.5- to 2.7-fold higher than that 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 and, therefore, lower doses of LUVOX 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.

| Pharmacokinetic Parameter<br>(body weight corrected) | Dose = 200 mg/day<br>(100 mg b.i.d.) |                        | Dose = 300 mg/day<br>(150 mg b.i.d.) |                   |
|------------------------------------------------------|--------------------------------------|------------------------|--------------------------------------|-------------------|
|                                                      | Children<br>(n = 10)                 | Adolescent<br>(n = 17) | Adolescent<br>(n = 13)               | Adult<br>(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)         |

| Pharmacokinetic Parameter<br>(body weight corrected) | Dose = 200 mg/day (100 mg b.i.d.) |                            |
|------------------------------------------------------|-----------------------------------|----------------------------|
|                                                      | Male Children<br>(n = 7)          | Female Children<br>(n = 3) |
| AUC 0-12 (ng•h/mL/kg)                                | 95.8 (83.9)                       | 293.5 (233.0)              |
| C <sub>max</sub> (ng/mL/kg)                          | 9.1 (7.6)                         | 28.1 (21.1)                |
| C <sub>min</sub> (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) 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 to 45 mL/min) after 4 and 6 weeks of treatment (50 mg b.i.d., 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

**Adult OCD Studies:** The effectiveness of LUVOX Tablets for the treatment of obsessive compulsive disorder (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, following which the dose was adjusted within a range of 100-300 mg/day (on a b.i.d. schedule), 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. Patients receiving fluvoxamine maleate experienced mean reductions of approximately 4 to 5 units on the Y-BOCS total score, compared to a 2 unit reduction for placebo patients.

Table 3 provides the outcome classification by treatment group on the Global Improvement item of the Clinical Global Impressions (CGI) scale for both studies combined.

| Outcome Classification | Fluvoxamine (N = 120) | Placebo (N = 134) |
|------------------------|-----------------------|-------------------|
| Very Much Improved     | 13%                   | 2%                |
| Much Improved          | 30%                   | 10%               |
| Minimally Improved     | 22%                   | 32%               |
| No Change              | 31%                   | 51%               |
| Worse                  | 4%                    | 6%                |

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

**Pediatric OCD Study:** The effectiveness of LUVOX Tablets for the treatment of OCD was also demonstrated in a 10-week multicenter, parallel group study in a pediatric outpatient population (children and adolescents, ages 8-17). 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 50-200 mg/day (on a b.i.d. schedule) 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. Patients receiving fluvoxamine maleate experienced mean reductions of approximately six units on the CY-BOCS total score, compared to a three-unit reduction for placebo patients.

Table 4 provides the outcome classification by treatment group on the Global Improvement item of the Clinical Global Impression (CGI) scale for the pediatric study.

| Outcome Classification | Fluvoxamine (N = 38) | Placebo (N = 36) |
|------------------------|----------------------|------------------|
| Very Much Improved     | 21%                  | 11%              |
| Much Improved          | 18%                  | 17%              |
| Minimally Improved     | 37%                  | 22%              |
| No Change              | 16%                  | 44%              |
| Worse                  | 8%                   | 6%               |

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 8-11 age group and essentially no effect in the 12-17 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) may be indicated to achieve therapeutic benefit.

#### **INDICATIONS AND USAGE**

LUVOX Tablets are indicated for the treatment of obsessions and compulsions in patients with obsessive compulsive disorder (OCD), as defined in the DSM-III-R. The obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of LUVOX Tablets was established in three 10-week trials with obsessive compulsive outpatients with the diagnosis of obsessive compulsive disorder as defined in DSM-III-R. (See **Clinical Trials** under **CLINICAL PHARMACOLOGY**.)

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 Tablets for long-term use, i.e., for more than 10 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use LUVOX Tablets 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 tizanidine, thioridazine, alosetron, or pimozide with LUVOX Tablets is contraindicated. (See **WARNINGS** and **PRECAUTIONS**.)

The use of MAO inhibitors within 14 days of treatment with LUVOX Tablets is contraindicated. (See **WARNINGS** and **PRECAUTIONS**.)

LUVOX Tablets are contraindicated in patients with a history of hypersensitivity to the active substance or to 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. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase 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 the 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 Table 5.

Table 5

| Age Range                            | Drug-Placebo Difference in Number of Cases of Suicidality per 1,000 Patients Treated |
|--------------------------------------|--------------------------------------------------------------------------------------|
| <b>Increases Compared to Placebo</b> |                                                                                      |
| <18                                  | 14 additional cases                                                                  |

|                  |                                      |
|------------------|--------------------------------------|
| 18-24            | 5 additional cases                   |
| <b>Age Range</b> | <b>Decreases Compared to Placebo</b> |
| 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 Tablets**, for a description of the risks of discontinuation of LUVOX Tablets).

**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 Tablets should be written for the smallest quantity of tablets 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 Tablets are 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 (MAOI), 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 a MAOI. Some cases presented with features resembling a serotonin syndrome or neuroleptic malignant syndrome. Therefore, LUVOX Tablets should not be used in combination with a MAOI, or within 14 days of discontinuing treatment with a MAOI. (See CONTRAINDICATIONS.)

#### **Potential Thioridazine Interaction**

The effect of fluvoxamine (25 mg b.i.d. 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 threefold 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, fluvoxamine 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 fluvoxamine (100 mg daily for 4 days) on the pharmacokinetics and pharmacodynamics of a single 4 mg 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. Fluvoxamine and tizanidine should not be used together. (See CONTRAINDICATIONS and PRECAUTIONS.)

#### **Potential Pimozide Interaction**

Pimozide is metabolized by the cytochrome P4503A4 isoenzyme, 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. An increased plasma concentration of pimozide causes QT prolongation and has been associated with torsades 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 CYP3A4. 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.)

#### **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 fluvoxamine not be used in combination with alosetron (see CONTRAINDICATIONS, PRECAUTIONS, and Lotronex™ (alosectron) package insert).

#### **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 fluvoxamine maleate (100 mg q.d.) and alprazolam (1 mg q.i.d.) were co-administered to steady state, plasma concentrations and other pharmacokinetic parameters (AUC,  $C_{max}$ ,  $T_{1/2}$ ) of alprazolam were approximately twice those observed when alprazolam was administered alone; oral clearance was reduced by about 50%. The elevated plasma alprazolam concentrations resulted in decreased psychomotor performance and memory. This interaction, which has not been investigated using higher doses of fluvoxamine, may be more pronounced if a 300 mg daily dose is co-administered, particularly since fluvoxamine exhibits non-linear pharmacokinetics over the dosage range 100-300 mg. If alprazolam is co-administered with LUVOX Tablets, 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 Tablets.

**Diazepam** – The co-administration of LUVOX Tablets and diazepam is generally not advisable. Because fluvoxamine reduces the clearance of both diazepam and its active metabolite,

| BODY SYSTEM/<br>ADVERSE EVENT       | Percentage of Patients Reporting Event |                    |
|-------------------------------------|----------------------------------------|--------------------|
|                                     | FLUVOXAMINE<br>N = 892                 | PLACEBO<br>N = 778 |
| Taste Perversion                    | 3                                      | 1                  |
| Amblyopia <sup>4</sup>              | 3                                      | 2                  |
| <b>UROGENITAL</b>                   |                                        |                    |
| Abnormal Ejaculation <sup>5,6</sup> | 8                                      | 1                  |
| Urinary Frequency                   | 3                                      | 2                  |
| Impotence <sup>6</sup>              | 2                                      | 1                  |
| Anorgasmia                          | 2                                      | 0                  |
| Urinary Retention                   | 1                                      | 0                  |

- <sup>1</sup> Events for which fluvoxamine maleate incidence was equal to or less than placebo are not listed in the table above, but include the following: abdominal pain, abnormal dreams, appetite increase, back pain, chest pain, confusion, dysmenorrhea, fever, infection, leg cramps, migraine, myalgia, pain, paresthesia, pharyngitis, postural hypotension, pruritus, rash, rhinitis, thirst and tinnitus.
- <sup>2</sup> Includes "toothache," "tooth extraction and abscess," and "caries."
- <sup>3</sup> Mostly feeling warm, hot, or flushed.
- <sup>4</sup> Mostly "blurred vision."
- <sup>5</sup> Mostly "delayed ejaculation."
- <sup>6</sup> Incidence based on number of male patients.

**Adverse Events in OCD Placebo Controlled Studies Which are Markedly Different (defined as at least a two-fold difference) in Rate from the Pooled Event Rates in OCD and Depression Placebo Controlled Studies:** The events in OCD studies with a two-fold decrease in rate compared to event rates in OCD and depression studies were dysphagia and amblyopia (mostly blurred vision). Additionally, there was an approximate 25% decrease in nausea.

The events in OCD studies with a two-fold increase in rate compared to event rates in OCD and depression studies were: *asthenia, abnormal ejaculation (mostly delayed ejaculation), anxiety, infection, rhinitis, anorgasmia (in males), depression, libido decreased, pharyngitis, agitation, impotence, myoclonus/twitch, thirst, weight loss, leg cramps, myalgia and urinary retention*. These events are listed in order of decreasing rates in the OCD trials.

#### **Other Adverse Events in OCD Pediatric Population**

In pediatric patients (N = 57) treated with LUVOX Tablets, the overall profile of adverse events was generally similar to that seen in adult studies, as shown in Table 7. However, the following adverse events, not appearing in Table 7, were reported in two or more of the pediatric patients and were more frequent with LUVOX Tablets than with placebo: abnormal thinking, cough increase, dysmenorrhea, ecchymosis, emotional lability, epistaxis, hyperkinesia, infection, manic reaction, rash, sinusitis, and weight decrease.

#### **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 physicians 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 8 displays the incidence of sexual side effects reported by at least 2% of patients taking LUVOX Tablets in placebo-controlled trials in depression and OCD.

**TABLE 8**  
**PERCENTAGE OF PATIENTS REPORTING SEXUAL ADVERSE EVENTS IN**  
**ADULT PLACEBO-CONTROLLED TRIALS IN OCD AND DEPRESSION**

|                       | <b>LUVOX Tablets</b><br><b>N = 892</b> | <b>Placebo</b><br><b>N = 778</b> |
|-----------------------|----------------------------------------|----------------------------------|
| Abnormal Ejaculation* | 8%                                     | 1%                               |
| Impotence*            | 2%                                     | 1%                               |
| Decreased Libido      | 2%                                     | 1%                               |
| Anorgasmia            | 2%                                     | 0%                               |

\* Based on the number of male patients.

There are no adequate and well-controlled studies examining sexual dysfunction with fluvoxamine treatment.

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, physicians should routinely inquire about such possible side effects.

### **Vital Sign Changes**

Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression 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 vital signs variables revealed no important differences between fluvoxamine maleate and placebo.

### **Laboratory Changes**

Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression 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 fluvoxamine maleate 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 LUVOX Tablets**

During premarketing clinical trials conducted in North America and Europe, multiple doses of fluvoxamine maleate 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 standard 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 7, 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:** accidental injury, 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, tachycardia; **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, gingivitis, 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, ecchymosis, leukocytosis, lymphadenopathy, thrombocytopenia; **Rare:** leukopenia, purpura.

**Metabolic and Nutritional Systems:** **Frequent:** edema, weight gain, weight loss; **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, epistaxis, hoarseness, hyperventilation; **Rare:** apnea, congestion of upper airway, hemoptysis, hiccups, laryngismus, obstructive pulmonary disease, pneumonia.

**Skin:** **Infrequent:** acne, 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<sup>1</sup>, dysuria, female lactation<sup>1</sup>, hematuria, menopause<sup>1</sup>, menorrhagia<sup>1</sup>, metrorrhagia<sup>1</sup>, nocturia, polyuria, premenstrual syndrome<sup>1</sup>, urinary incontinence, urinary tract infection, urinary urgency, urination impaired, vaginal hemorrhage<sup>1</sup>, vaginitis<sup>1</sup>; **Rare:** kidney calculus, hematospermia<sup>2</sup>, oliguria.

- <sup>1</sup> Based on the number of females.
- <sup>2</sup> Based on the number of males.

### **Postmarketing Reports**

Voluntary reports of adverse events in patients taking LUVOX Tablets that have been received since market introduction and are of unknown causal relationship to LUVOX Tablets 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 Tablets are not controlled substances.

### **Physical and Psychological Dependence**

The potential for abuse, tolerance and physical dependence with fluvoxamine maleate has been studied in a nonhuman primate model. No evidence of dependency phenomena was found. The discontinuation effects of LUVOX Tablets were not systematically evaluated in controlled clinical trials. LUVOX Tablets 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 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, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of fluvoxamine maleate misuse or abuse (i.e., development of tolerance, incrementation of dose, drug-seeking behavior).

## **OVERDOSAGE**

### **Human Experience**

Worldwide exposure to fluvoxamine 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 fluvoxamine 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 overdose, to include persistent mydriasis, unsteady gait, hypoxic encephalopathy, kidney complications (from trauma associated with overdose), bowel infarction requiring a hemicolectomy, and vegetative state. In 13 patients, the outcome was provided as abating at the time of reporting. In the remaining 62 patients, the outcome was unknown. The largest known ingestion of fluvoxamine 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.

Commonly ( $\geq 5\%$ ) 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 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 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 physician 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**

### **Dosage for Adults**

The recommended starting dose for LUVOX Tablets in adult patients is 50 mg, administered as a single daily dose at bedtime. In the controlled clinical trials establishing the effectiveness of LUVOX Tablets in OCD, patients were titrated within a dose range of 100 to 300 mg/day. Consequently, the dose should be increased in 50 mg increments every 4 to 7 days, as tolerated, until maximum therapeutic benefit is achieved, not to exceed 300 mg per day. It is advisable that a total daily dose of more than 100 mg should be given in two divided doses. If the doses are not equal, the larger dose should be given at bedtime.

### **Dosage for Pediatric Population (children and adolescents)**

The recommended starting dose for LUVOX Tablets in pediatric populations (ages 8-17 years) is 25 mg, administered as a single daily dose at bedtime. In a controlled clinical trial establishing the effectiveness of LUVOX Tablets in OCD, pediatric patients (ages 8-17) were titrated within a dose range of 50 to 200 mg/day. Physicians should consider age and gender differences when dosing pediatric patients. The maximum dose in children up to age 11 should not exceed 200 mg/day. Therapeutic effect in female children may be achieved with lower doses. Dose adjustment in adolescents (up to the adult maximum dose of 300 mg) may be indicated to achieve therapeutic benefit. The dose should be increased in 25 mg increments every 4 to 7 days, as tolerated, until maximum therapeutic benefit is achieved. It is advisable that a total daily dose of more than 50 mg should be given in two divided doses. If the two divided doses are not equal, the larger dose should be given at bedtime.

### **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 modify the initial dose and the subsequent dose titration for these patient groups.

#### ***Treatment of Pregnant Women During the Third Trimester***

Neonates exposed to LUVOX 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 Tablets during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering LUVOX Tablets in the third trimester.

### **Maintenance/Continuation Extended Treatment**

Although the efficacy of LUVOX Tablets beyond 10 weeks of dosing for OCD has not been documented in controlled trials, OCD is a chronic condition, 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.

### **Discontinuation of Treatment with LUVOX Tablets**

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 physician may continue decreasing the dose but at a more gradual rate.

### **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. Similarly, at least 14 days should be allowed after stopping LUVOX before starting an MAOI.

### **HOW SUPPLIED**

**Tablets 25 mg:** unscored, white, elliptical, film-coated (debossed "LT25" on one side)  
 Bottles of 100.....NDC 68727-500-01

**Tablets 50 mg:** scored, yellow, elliptical, film-coated (debossed "LT50" on one side and scored on the other)  
 Bottles of 100.....NDC 68727-501-01

**Tablets 100 mg:** scored, beige, elliptical, film-coated (debossed "LT100" on one side and scored on the other)  
 Bottles of 100.....NDC 68727-502-01

### **Storage**

LUVOX Tablets should be protected from high humidity and stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Dispense in tight containers.

**Keep out of reach of children.**

Lotronex<sup>™</sup> is a trademark of GlaxoSmithKline  
 LUVOX® is a registered trade of Solvay Pharmaceuticals, Inc.

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

**LUVOX® (LUUV-ox) (fluvoxamine maleate) Tablets**

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 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   | • new or worse irritability                           |
| • attempts to commit suicide        | • acting aggressive, being angry, or violent          |
| • new or worse depression           | • acting on dangerous impulses                        |
| • new or worse anxiety              | • an extreme increase in activity and talking (mania) |
| • feeling very agitated or restless |                                                       |
| • panic attacks                     |                                                       |
| • trouble sleeping (insomnia)       |                                                       |

- 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.

**Jazz Pharmaceuticals, Inc.**  
Palo Alto, CA 94304

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