PRODUCT MONOGRAPH

Pr LUVOX®
fluvoxamine maleate
Film-Coated, Scored Tablets (50 mg and 100 mg)

Antidepressant

Antiobsessional Agent

Abbott Laboratories, Limited
8401 Trans-Canada Highway
Saint-Laurent, Quebec
H4S 1Z1

Date of Preparation:
November 13, 1996

Date of Previous Revision:
July 30, 2012

Date of Revision:
March 6, 2013

Submission Control #: 160715

PRODUCT MONOGRAPH

^{Pr}LUVOX®
fluvoxamine maleate

ACTION

The antidepressant and antiobsessional actions of LUVOX (fluvoxamine maleate) are believed to be related to its selective inhibition of presynaptic serotonin reuptake in brain neurones.

There is minimum interference with noradrenergic processes and, in common with several other specific inhibitors of serotonin uptake, fluvoxamine maleate has very little in vitro affinity for α_1, α_2, β_1, dopamine$_2$, histamine$_1$, serotonin$_1$, serotonin$_2$ or muscarinic receptors.

Pharmacokinetics

In healthy volunteers fluvoxamine maleate is well absorbed after oral administration. Following a single 100 mg oral dose, peak plasma levels of 31 to 87 ng/mL were attained 1.5 to 8 hours post-dose. Peak plasma levels and areas under the curve (AUC's) (0 to 72 hours) are directly proportionate to dose after single oral doses of 25, 50 and 100 mg. Following single doses the mean plasma half-life is 15 hours and slightly longer (17 to 22 hours) during repeated dosing. Steady-state plasma levels are usually achieved within 10 to 14 days. The pharmacokinetic profile in the elderly is similar to that in younger patients.

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 to 8 hours of dosing and reached concentrations averaging 88, 283 and 546 ng/mL, respectively. Thus, fluvoxamine maleate had nonlinear pharmacokinetics over this dose range, i.e., higher doses of fluvoxamine maleate produced disproportionately higher concentrations than predicted from the lower dose.

Metabolism and Elimination

Fluvoxamine maleate undergoes extensive hepatic transformation, mainly via oxidative demethylation, to at least nine metabolites, which are excreted by the kidney. Ninety-four percent of an oral radioactive dose is recovered in the urine within 48 hours. The two major metabolites showed negligible pharmacological activity. Fluvoxamine is a potent inhibitor of CYP1A2 and CYP2C19. A moderate inhibition was found for CYP2C9, CYP2D6 and CYP3A4. In vitro binding of fluvoxamine maleate to human plasma proteins is about 77% at drug concentrations up to 4000 ng/mL.

INDICATIONS

Adults

Depression

LUVOX (fluvoxamine maleate) may be indicated for the symptomatic relief of depressive illness in adults.

The effectiveness of LUVOX in long-term use (i.e., for more than 5 to 6 weeks) has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use LUVOX for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Obsessive-Compulsive Disorder

LUVOX has been shown to significantly reduce the symptoms of obsessive-compulsive disorder in adults. The obsessions or compulsions must be experienced as intrusive, markedly distressing, time consuming, or interfering significantly with the person's social or occupational functioning.

The efficacy of LUVOX has been studied in double-blind, placebo-controlled clinical trials conducted in obsessive-compulsive outpatients. The usefulness of LUVOX for long-term use (i.e. for more than 10 weeks) has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use LUVOX for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Geriatrics (> 65 years of age)

Since there is limited clinical experience in the geriatric age group, caution is recommended when administering LUVOX to elderly patients.

Pediatrics (< 18 years of age)

LUVOX® is not indicated for use in patients below the age of 18 years **(see WARNINGS, POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM)**.

CONTRAINDICATIONS

LUVOX (fluvoxamine maleate) is contraindicated in patients with known hypersensitivity to fluvoxamine maleate or any of the excipients.

LUVOX should not be administered together with tizanidine or monoamine oxidase (MAO) inhibitors; including methylene blue (intravenous dye) and linezolid, an antibiotic which is a

reversible non-selective MAO inhibitor. At least two weeks should elapse after discontinuation of MAO inhibitor therapy before LUVOX treatment is initiated. MAO inhibitors should not be introduced within two weeks of cessation of therapy with LUVOX. (See **PRECAUTIONS**, **Serotonin Syndrome**)

In patients receiving selective serotonin reuptake inhibitors (SSRIs) in combination with a MAO inhibitor, 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 recently discontinued SSRI treatment and have begun treatment on a MAO inhibitor. Some cases presented with features resembling serotonin syndrome or neuroleptic malignant syndrome (See **WARNINGS** and **PRECAUTIONS, Serotonin Syndrome**).

Coadministration of thioridazine, mesoridazine, terfenadine, astemizole, pimozide, or cisapride with LUVOX is contraindicated (See **WARNINGS**, **PRECAUTIONS** and **DRUG INTERACTIONS**).

The concomitant use of LUVOX and pimozide is contraindicated as LUVOX has been shown to increase plasma pimozide levels. Elevation of pimozide blood concentration may result in QT interval prolongation and severe arrhythmias including torsade de pointes.

LUVOX should not be used in combination with ramelteon, a sleep medicine not available in Canada (See **DRUG INTERACTIONS**).

WARNINGS

POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM

Pediatrics: Placebo-Controlled Clinical Trial Data

- **Recent analyses of placebo-controlled clinical trial safety databases from SSRIs and other newer antidepressants suggest that use of these drugs in patients under the age of 18 may be associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour over that of placebo.**
- **The small denominators in the clinical trial database, as well as the variability in placebo rates, preclude reliable conclusions on the relative safety profiles among these drugs.**

Adults and Pediatrics: Additional data

- **There are clinical trial and post-marketing reports with SSRIs and other newer antidepressants, in both pediatrics and adults, of severe agitation-type adverse events coupled with self-harm or harm to others. The agitation-type events include: akathisia, agitation, disinhibition, emotional lability, hostility, aggression, depersonalization. In some cases, the events occurred within several weeks of starting treatment.**

Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages. This includes monitoring for agitation-type emotional and behavioural changes.

Young Adults (ages 18 to 24 years):

A recent FDA meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients ages 18 to 24 years with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo.

Discontinuation Symptoms

Patients currently taking LUVOX (fluvoxamine maleate) should NOT be discontinued abruptly, due to risk of discontinuation symptoms. At the time that a medical decision is made to discontinue an SSRI or other newer antidepressant drug, a gradual reduction in the dose rather an abrupt cessation is recommended (See PRECAUTIONS, Discontinuation of Treatment with LUVOX).

Bone Fracture Risk

Epidemiological studies show an increased risk of bone fractures following exposure to some antidepressants, including SSRIs and serotonin / norepinephrine reuptake inhibitors (SNRIs). The risks appear to be greater at the initial stages of treatment, but significant increased risks were also observed at later stages of treatment. The possibility of fracture should be considered in the care of patients treated with LUVOX. Elderly patients and patients with important risk factors for bone fractures should be advised of possible adverse events which increase the risk of falls, such as dizziness and orthostatic hypotension, especially at the early stages of treatment but also soon after withdrawal. Preliminary data from observational studies show association of SSRIs/SNRIs and low bone mineral density in older men and women. Until further information becomes available, a possible effect on bone mineral density with long term treatment with SSRIs/SNRIs, including LUVOX, cannot be excluded, and may be a potential concern for patients with osteoporosis or major risk factors for bone fractures.

Monoamine Oxidase Inhibitors

See **CONTRAINDICATIONS**

Potential Interaction with Thioridazine and Mesoridazine

The effect of fluvoxamine maleate (25 mg 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 threefold following coadministration of fluvoxamine maleate.

Thioridazine and mesoridazine 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 maleate may even be more pronounced when it is administered at higher doses. Therefore LUVOX and thioridazine or mesoridazine should not be co-administered (See **CONTRAINDICATIONS** and **DRUG INTERACTIONS**).

Potential Interaction with Terfenadine, Astemizole and Cisapride

Terfenadine, astemizole and cisapride are all metabolized by CYP3A4. Since fluvoxamine maleate is known to inhibit CYP3A4, theoretically, there may be a potential interaction with terfenadine, astemizole or cisapride. Consequently, it is recommended that LUVOX not be used in combination with terfenadine, astemizole or cisapride (See **CONTRAINDICATIONS** and **DRUG INTERACTIONS**).

Potential Interaction with Drugs with a Narrow Therapeutic Index

There may be a potential interaction between fluvoxamine maleate and drugs metabolized by CYP3A4 that have a narrow therapeutic index (e.g., carbamazepine, methadone and cyclosporine). Patients administered these combinations should be carefully monitored and, if necessary, dose adjustment of these drugs is recommended (See **DRUG INTERACTIONS**).

Potential Interaction with Pimozide

Elevation of pimozide blood concentration may result in QT interval prolongation and severe arrhythmias including torsade de pointes.

PRECAUTIONS

Akathisia/Psychomotor Restlessness

The use of LUVOX (fluvoxamine maleate) has been associated with the development of akathisia, characterized by a subjectively unpleasant or distressing restlessness and need to move, often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental and is not recommended.

Cognitive and Motor Disturbances

Sedation may occur in some patients. Therefore, patients should be cautioned about participating in activities requiring complete mental alertness, judgement and physical coordination - such as driving an automobile or performing hazardous tasks - until they are reasonably certain that treatment with LUVOX does not affect them adversely.

Combination with Alcohol

LUVOX may potentiate the effects of alcohol and increase the level of psychomotor impairment.

Concomitant Illness

LUVOX has 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 pre-marketing clinical studies.

Discontinuation of Treatment with LUVOX

When discontinuing treatment, patients should be monitored for symptoms which may be associated with discontinuation [e.g. dizziness, abnormal dreams, sensory disturbances (including paresthesias and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation, irritability, anxiety, fatigue, confusion, emotional instability, headache, tremor, nausea, vomiting, diarrhea, sweating, palpitations or other symptoms which may be of clinical significance] (See **ADVERSE REACTIONS**). Generally these events are mild to moderate and are self-limiting; however in some patients they may be severe and/or prolonged. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. A gradual reduction in the dosage over several weeks, rather than abrupt cessation, is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response (See **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**). If LUVOX is used until or shortly before birth, discontinuation effects in the newborn may occur (See also **PRECAUTIONS**, **Special Populations, Use in Pregnancy and Lactation**).

Disturbance of Glycemic Control

Glycemic control may be disturbed, especially in the early stages of the treatment. Reported events include hyperglycemia, hypoglycemia, diabetes mellitus and decreased glucose tolerance; these have been reported in both patients with and without pre-existing disturbance of glycemic control. Patients should therefore be monitored for signs and symptoms of glucose fluctuations. When LUVOX is given to patients with a known history of diabetes mellitus, the dosage of anti-diabetic drugs may need to be adjusted.

Electroconvulsive Therapy (ECT)

Concurrent administration of LUVOX with electroshock therapy should be avoided because of the absence of experience in this area.

Hepatic Enzymes

Treatment with LUVOX has been rarely associated with increases in hepatic enzymes, usually accompanied by symptoms. LUVOX administration should be discontinued in such cases.

Hematologic

Abnormal Bleeding

SSRIs and serotonin / norepinephrine reuptake inhibitors (SNRIs), including LUVOX, may increase the risk of bleeding events by causing abnormal platelet aggregation. Concomitant use of acetylsalicylic acid (ASA), nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin and other anticoagulants may add to the 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 or gynecological hemorrhage. 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 and NSAIDs, ASA, or other drugs that affect coagulation (See **DRUG INTERACTIONS**). Caution is advised in patients with a history of bleeding disorder or predisposing conditions (e.g. thrombocytopenia or coagulation disorders).

Hyponatremia

As with other SSRIs, hyponatremia has been rarely reported and appeared to be reversible when LUVOX was discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone secretion. The majority of reports were associated with older patients.

Mania/Hypomania

LUVOX should be used with caution in patients with a history of mania/hypomania. LUVOX should be discontinued in any patient entering a manic phase.

Ophtalmologic

Glaucoma

As with other SSRIs/SNRIs, LUVOX can cause mydriasis and should be used with caution in patients with raised intraocular pressure or those with narrow-angle glaucoma.

Seizures

Convulsions have been reported rarely during LUVOX administration. Caution is recommended when the drug is administered to patients with a history of seizures. LUVOX should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Treatment with LUVOX should be discontinued if seizures occur or if seizure frequency increases. Seizures have also been reported as a discontinuation symptom (See **PRECAUTIONS**, **Discontinuation Symptoms**; **ADVERSE REACTIONS**, **Adverse Events Leading to Discontinuation of Treatment**; **DOSAGE AND ADMINISTRATION**, **Discontinuation of LUVOX Treatment**).

Serotonin Syndrome

On rare occasions development of a serotonin syndrome or neuroleptic malignant syndrome-like events have been reported in association with treatment of LUVOX, particularly when given in combination with other serotonergic and / or neuroleptic drugs. As these syndromes may result in potentially life-threatening conditions, treatment with LUVOX should be discontinued and supportive treatment initiated if characteristic events occur, i.e., clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma (See **DRUG INTERACTIONS**, **Pharmacodynamic Interactions,** *Serotonergic Drugs*).

Sexual Function/Reproduction

Reproductive toxicity studies in rats have shown that fluvoxamine maleate impairs male and female fertility (See **TOXICOLOGY**, **Reproductive Studies**). The relevance of these findings to humans is unknown.

LUVOX should not be used in patients attempting to conceive unless the clinical condition of the patient requires treatment with LUVOX.

Suicide/Suicidal Thoughts or Clinical Worsening

The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Patients with depression may experience worsening of their depressive symptoms and / or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications. Close supervision of high-risk patients should accompany drug therapy and consideration should be given to the possible need for hospitalization. Physicians should encourage patients of all ages to report any new or worsened distressing thoughts or feelings occurring at any time. In order to minimize the opportunity for overdosage, prescriptions for LUVOX should be written for the smallest quantity of drug consistent with good patient management.

Obsessive-compulsive disorders can also be associated with an increased risk of suicide-related events.

Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at a greater risk of suicidal thoughts or suicide attempts and should receive careful monitoring during treatment. Close supervision of patients, in particular those at high risk, should accompany drug therapy, especially in early treatment and following dose changes. Patients and caregivers of patients should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Because of the well established comorbidity between depression and other psychiatric disorders, the same precautions observed when treating patients with depression should be observed when

treating patients with other psychiatric disorders, e.g. obsessive compulsive disorder (See **WARNINGS**, **POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM**).

Special Populations

Pregnant Women

Safe use of LUVOX during pregnancy has not been established. Therefore, it should not be administered to women of childbearing potential unless, in the opinion of the treating physician, the expected benefits to the patient outweigh the possible hazards to the fetus.

Complications following late third trimester exposure to SSRIs

Post-marketing reports indicate that some neonates exposed to LUVOX, SSRIs (Selective Serotonin Reuptake Inhibitors), or other newer antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support and tube feeding. 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 and other newer antidepressants or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (See **PRECAUTIONS**, **Serotonin Syndrome**). When treating a pregnant woman with LUVOX the physician should carefully consider the potential risks and benefits of treatment (See **DOSAGE AND ADMINISTRATION**).

Risk of PPHN and exposure to SSRIs:

Exposure during late pregnancy to SSRIs, including LUVOX, may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 to 2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective 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 six-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. A study of 831,324 infants born in Sweden in 1997-2005 found a PPHN risk ratio of 2.4 (95% CI 1.2-4.3) associated with patient-reported maternal use of SSRIs in “early pregnancy” and a PPHN risk ratio of 3.6 (95% CI 1.2-8.3) associated with a combination of patient-reported maternal use of SSRIs in “early pregnancy” and an antenatal SSRI prescription in “later pregnancy”.

Nursing Women

Safe use of LUVOX during lactation has not been established. Like other antidepressants, fluvoxamine maleate is excreted via human milk in small quantities. Therefore, it should not be administered to nursing mothers unless, in the opinion of the treating physician, the expected benefits to the patient outweigh the possible hazards to the child.

Pediatrics

Safety and efficacy in children under 18 years of age have not been established.

DRUG INTERACTIONS

Serious Drug Interactions

- **Monoamine Oxidase Inhibitors: See CONTRAINDICATIONS**
- **Thioridazine: See CONTRAINDICATIONS**
- **Pimozide: See CONTRAINDICATIONS**

LUVOX is contraindicated in combined use with tizanidine, thioridazine or mesoridazine. Isolated cases of cardiac toxicity have been reported when fluvoxamine maleate was combined with thioridazine (See **CONTRAINDICATIONS** and **WARNINGS**). It should also not be used in combination with MAOIs, including linezolid (an antibiotic which is a reversible non-selective MAO inhibitor) and the thiazine dye methylthioninium chloride (methylene blue), due to risk of serotonin syndrome (See **CONTRAINDICATIONS** and **WARNINGS**).

Effect of fluvoxamine on the oxidative metabolism of other drugs

Fluvoxamine maleate can inhibit the metabolism of drugs metabolized by certain cytochrome P450 isoenzymes (CYPs). A strong inhibition of CYP1A2 and CYP2C19 is demonstrated in in vitro and in vivo studies. CYP2C9, CYP2D6 and CYP3A4 are inhibited to a lesser extent. Drugs which are largely metabolised via these isoenzymes are eliminated slower and may have higher plasma concentrations when coadministered with fluvoxamine maleate. Concomitant therapy of LUVOX and these drugs should be initiated at or adjusted to the low end of their dose range. Plasma concentrations, effects or adverse effects of co-administered drugs should be monitored and their dosage should be reduced if necessary. This is particularly relevant for drugs with a narrow therapeutic index.

CYP2D6 is responsible for the metabolism of substrates such as debrisoquine, sparteine, tricyclic antidepressants (e.g., *nortriptyline, amitriptyline, imipramine* and *desipramine*), phenothiazine neuroleptics (e.g.,*perphenazine* and *thioridazine*) and Type 1C antiarrhythmics (e.g., *propafenone* and *flecainide*). In vitro data suggest that fluvoxamine maleate is a relatively weak inhibitor of CYP2D6 and hence the potential for interactions with compounds metabolized by this isoenzyme is low.

Ramelteon (a sleep medicine not available in Canada)

When fluvoxamine maleate tablets 100 mg twice daily were administered for three days prior to single-dose coadministration of ramelteon 16 mg and fluvoxamine maleate tablets, the AUC for

ramelteon increased approximately 190-fold and the C_{max} increased approximately 70-fold compared to ramelteon administered alone.

Compounds with narrow therapeutic index

Co-administration of LUVOX and drugs with a narrow therapeutic index (such as *tacrine, theophylline, methadone, mexiletine, phenytoin, carbamazepine, cyclosporine, clozapine, warfarin*) should be carefully monitored when these drugs are metabolized exclusively or by a combination of CYPs inhibited by fluvoxamine.

If necessary, dose adjustment of these drugs is recommended.

When a single 40 mg dose of *tacrine* was added to fluvoxamine maleate 100 mg/day administered at steady state, an associated five and 8-fold increase in *tacrine* C_{max} and AUC, respectively, were observed.

A clinically significant interaction is possible with CYP3A4 substrates that have a narrow therapeutic index such as *carbamazepine, methadone*, *cyclosporine* and *sildenafil*. Such combinations should therefore be administered with caution, and consideration be given to lowering the dose of the concomitant agent. A significantly increased *methadone* plasma level / dose ratio was seen during concurrent administration of fluvoxamine maleate.

Tricyclic antidepressants and neuroleptics

An increase in previously stable plasma levels of those tricyclic antidepressants (e.g., *clomipramine, imipramine, amitriptyline*) and neuroleptics (e.g., *clozapine, olanzapine, quetiapine*), which are largely metabolized through CYP1A2, has been reported in patients taking fluvoxamine maleate concomitantly. Thus, the combination of these drugs with LUVOX is not recommended.

Benzodiazepines

The plasma levels of oxidatively metabolised benzodiazepines (e.g., *triazolam, midazolam, alprazolam* and *diazepam*) are likely to be increased when co-administered with fluvoxamine maleate. The dosage of these benzodiazepines should be reduced during co-administration with LUVOX.

Fluvoxamine maleate is also believed to inhibit CYP2C and thus may interact with CYP2C substrates like *diazepam*. Clearance of both *diazepam* and its active *metabolite N-desmethyldiazepam* were reduced with concurrent administration of fluvoxamine maleate.

Fluvoxamine maleate is also known to inhibit CYP3A4 and thus may interact with CYP3A4 substrates such as *alprazolam*. When fluvoxamine maleate and *alprazolam* were coadministered 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; clearance was reduced by about 50%.

Cases of increased plasma concentration

As plasma concentrations of *ropinirole* may be increased in combination with fluvoxamine maleate thus increasing the risk of overdose, surveillance and reduction in the dosage of *ropinirole* during LUVOX treatment and after its withdrawal may be required.

As plasma concentrations of *propranolol* are increased in combination with fluvoxamine maleate, the *propranolol* dose may need to be lowered; a 5-fold increase in plasma levels of *propranolol* was seen in interaction studies.

Warfarin plasma concentrations were significantly increased and prothrombin times prolonged during concurrent administration of fluvoxamine maleate; in interaction studies a 65% increase in warfarin plasma levels was seen **(See Drugs Affecting Platelet Function (e.g. NSAIDS, ASA and other anticoagulants)).**

Fluvoxamine maleate is also known to inhibit CYP3A4 and thus may interact with CYP3A4 substrates such as *diltiazem*.

Cases of increased side effects

Caffeine plasma levels are likely to be increased during coadministration with fluvoxamine maleate. Patients who consume high quantities of caffeinated beverages should lower their intake when LUVOX is administered and adverse caffeine effects (like tremor, palpitations, nausea, restlessness, insomnia) are observed.

Since *terfenadine, astemizole* and *cisapride* are metabolized by CYP3A4, theoretically there may be a potential interaction with fluvoxamine maleate that could result in an increased risk for QT prolongation / torsades de pointes. Thus, it is recommended that LUVOX not be used in combination with *terfenadine, astemizole* or *cisapride* (See **CONTRAINDICATIONS**).

Drugs Affecting Platelet Function (e.g. NSAIDS, ASA and other anticoagulants)

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies (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, have also shown that concurrent use of an NSAID, ASA or other anticoagulants may potentiate the risk of bleeding. Patients receiving LUVOX and an NSAID, ASA or other anticoagulants should therefore be closely monitored.

Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are co-administered with warfarin. Patients receiving warfarin therapy should be carefully monitored when LUVOX is initiated or discontinued. (See **WARNINGS** and **PRECAUTIONS**, HEMATOLOGIC, Abnormal Bleeding.)

Glucuronidation

Fluvoxamine maleate does not influence plasma concentrations of *digoxin*. The clearance of benzodiazepines metabolized by glucuronidation (e.g., *lorazepam, oxazepam, temazepam*) is unlikely to be affected by LUVOX.

Renal Excretion

Fluvoxamine maleate does not influence plasma concentrations of *atenolol*.

Pharmacodynamic Interactions

Serotonergic Drugs: The serotonergic effects of LUVOX may be enhanced when used in combination with other serotonergic agents (including *triptans, fentanyl* and its analogues, *dextromethorphan, tramadol, tapentadol, meperidine, methadone, pentazocine*), SSRIs and *St. John's Wort* preparations.

St. John's Wort: In common with other SSRI's, pharmacodynamic interactions between fluvoxamine maleate and the herbal remedy St. John's Wort may occur and may result in an increase in undesirable effects.

Lithium, and possibly *tryptophan*, may enhance the serotonergic effects of LUVOX; these combinations should therefore be used with caution. This may, on rare occasions, result in a serotonergic syndrome.

As with other psychotropic drugs patients should be advised to avoid alcohol use while taking LUVOX.

Metabolism of Fluvoxamine Maleate

The specific CYP isoenzymes involved in the metabolism of fluvoxamine maleate remain to be identified.

ADVERSE REACTIONS

Overview

In clinical trials the most commonly observed adverse events associated with LUVOX (fluvoxamine maleate) administration, and not seen at an equivalent incidence among placebo-treated patients, were gastrointestinal complaints including nausea (sometimes accompanied by vomiting), constipation, anorexia, diarrhea and dyspepsia; central nervous system complaints, including somnolence, dry mouth, nervousness, insomnia, dizziness, tremor and agitation; and asthenia. Abnormal (mostly delayed) ejaculation was frequently reported by patients with obsessive-compulsive disorder, primarily at doses over 150 mg/day.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse Events Leading to Discontinuation of Treatment

Approximately 14% (14.4%) of 34,587 patients who received LUVOX in clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation from depression trials included nausea and vomiting, insomnia, agitation, headache, abdominal pain, somnolence, dizziness, asthenia and anorexia. The most common events causing discontinuation in patients suffering from obsessive-compulsive disorder included insomnia, asthenia and somnolence.

Incidence of Adverse Experiences

Adverse events with an incidence of ≥ 5% reported in double-blind, placebo-controlled clinical trials in depression and in obsessive-compulsive disorder are presented in the following **Table 1** for each indication.

Table 1. Treatment-emergent adverse experience incidence (≥ 5%) in placebo-controlled clinical trials for depression and obsessive-compulsive disorder*

Percentage of Patients Reporting Event				
	Depression		OCD	
Body System / Adverse Event	Fluvoxamine (N=222)	Placebo (N=192)	Fluvoxamine (N=160)	Placebo (N=160)
Nervous System				
Somnolence	26.2	9.0	26.9	9.4
Agitation	15.7	8.9	3.8	0
Insomnia	14.4	10.4	31.3	15.0
Dizziness	14.8	13.5	9.4	4.4
Tremor	10.8	4.7	8.1	0.6
Hypokinesia	8.1	3.6	-	-
Hyperkinesia	6.7	8.9	-	-
Depression	4.0	4.2	6.3	4.4
Nervousness	2.2	1.6	15.6	5.0
Anxiety	2.3	2.1	9.4	6.9
Libido Decreased	-	-	7.5	1.9
Thinking Abnormal	-	-	6.9	3.8
Digestive System				
Nausea	36.5	10.9	28.8	6.9
Dry Mouth	25.7	23.9	11.9	3.1
Constipation	18.0	6.8	14.4	8.8
Anorexia	14.9	6.3	5.0	3.1
Diarrhea	5.9	6.3	11.9	8.8
Dyspepsia	3.2	0	13.8	9.4
Body as a Whole				
Headache	21.6	18.7	20.0	23.8
Pain	5.9	3.7	4.4	1.3
Asthenia	4.9	3.2	28.8	9.4
Infection	-	-	11.3	9.4
Abdominal Pain	3.6	3.6	5.6	8.1
Flu Syndrome	-	-	5.0	3.8
Skin				
Sweating Increased	11.2	12.5	6.9	1.9
Respiratory System				
Pharyngitis	-	-	6.3	5.0
Rhinitis	1.3	2.6	5.6	1.9
Special Senses				
Accommodation Abnormal	6.3	6.3	-	-
Taste Perversion	3.2	3.1	5.0	0
Urogenital				
Urinary Frequency	2.2	1.6	5.0	1.3
Abnormal Ejaculation	1.4	0	17.9[+]	0

* Dosage titration at study initiation varied between the depression and OCD trials. In depression, fluvoxamine maleate was administered: Day 1, 50 mg; Day 2, 100 mg; Day 3, 150 mg then titrated to response. In OCD, fluvoxamine maleate was administered: Days 1-4, 50 mg; Days 5-8, 100 mg, Days 9-14, 150 mg then titrated to response.

[+] Corrected for gender (males: n = 78)

Additional Adverse Events Reported in Clinical Trials

During pre-marketing and post-marketing studies, multiple doses of LUVOX were administered to approximately 34,587 patients. All events with an incidence of > 0.01% are listed, regardless of relation to drug, except those in terms so general as to be uninformative. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent (occurring on 1 or more occasions in at least 1/100 patients), infrequent (occurring in less than 1/100, but at least 1/1000 patients) or rare (occurring in less than 1/1000 but at least in 1/10,000 patients). Multiple events may have been reported by a single patient. It is important to emphasize that although the events reported did occur during treatment with LUVOX, they were not necessarily caused by it.

Nervous system

Frequent: Agitation, anxiety, dizziness, insomnia, nervousness, somnolence, thinking abnormal, tremor, vertigo.

Infrequent: Abnormal dreams, abnormal gait, akathisia, amnesia, apathy, ataxia, confusion, depersonalization, depression, drug dependence, emotional lability, euphoria, hallucinations, hostility, hyperkinesia, hypertonia, hypoesthesia, hypokinesia, incoordination, increased salivation, libido decreased, libido increased, manic reaction, neurosis, paraesthesia, psychotic depression, stupor, twitching, vasodilatation.

Rare: Akinesia, CNS neoplasia, CNS stimulation, coma, convulsion, delirium, delusions, dysarthria, dyskinesia, dystonia, extrapyramidal syndrome, hemiplegia, hyperesthesia, hypotonia, hysteria, myoclonus, neuralgia, neuropathy, paralysis, paranoid reaction, psychosis, reflexes decreased, schizophrenic reaction, screaming syndrome, torticollis, trismus.

Digestive system

Frequent: Anorexia, constipation, diarrhea, dry mouth, dyspepsia, nausea, vomiting.

Infrequent: Colitis, dysphagia, eructation, flatulence, gastritis, gastroenteritis, increased appetite, thirst.

Rare: Biliary pain, esophagitis, fecal incontinence, gastrointestinal carcinoma, gastrointestinal haemorrhage, gingivitis, glossitis, hematemesis, hepatitis, jaundice, liver function tests abnormal, hepatic function abnormal, melena, mouth ulceration, rectal haemorrhage, stomatitis, tenesmus, tongue discoloration, tongue edema, tooth disorder.

Cardiovascular System

Frequent: Palpitation.

Infrequent: Angina pectoris, hypertension, hypotension, migraine, postural hypotension, syncope, tachycardia.

Rare: Arrhythmia, bradycardia, cerebrovascular accident, extrasystoles, haemorrhage, myocardial infarct, pallor, peripheral vascular disorder, shock.

Body as Whole

Frequent: Abdominal pain, asthenia, headache, malaise.

Infrequent: Accidental injury, allergic reaction, back pain, chest pain, chills, fever, flu syndrome, infection, neck pain, pain, suicide attempt.

Rare: Abdomen enlarged, chills and fever, face edema, halitosis, hangover effect, hernia, neck rigidity, overdose, pelvic pain.

Skin

Frequent: Sweating increased.

Infrequent: Cutaneous hypersensitivity reactions (including rash, pruritis, angioedema)

Rare: Acne, alopecia, dry skin, eczema, furunculosis, herpes simplex, herpes zoster, maculopapular rash, psoriasis, urticaria.

Respiratory System

Infrequent: Dyspnea, pharyngitis, rhinitis.

Rare: Asthma, bronchitis, cough increased, epistaxis, hiccup, hyperventilation, laryngismus, laryngitis, pneumonia, sinusitis, voice alteration, yawn.

Special Senses

Infrequent: Abnormal vision, amblyopia, hyperacusis.

Rare: Abnormality of accommodation, blepharitis, conjunctivitis, deafness, diplopia, dry eyes, ear pain, eye pain, lacrimation disorder, mydriasis, parosmia, photophobia, taste loss.

Musculoskeletal System

Infrequent: Arthralgia, arthrosis, myalgia, myasthenia, tetany.

Rare: Arthritis, bone pain, leg cramps, pathological fracture, rheumatoid arthritis.

Urogenital System

Infrequent: Abnormal ejaculation, dysuria, impotence, metrorrhagia, urinary frequency, urinary incontinence.

Rare: Amenorrhea, anorgasmia, breast pain, cystitis, dysmenorrhea, female lactation, hematuria, kidney pain, leukorrhea, menorrhagia, nocturia, polyuria, prostatic disorder, urinary retention, urinary tract infection, urinary urgency, vaginitis.

Metabolic and Nutrional System
Frequent: Weight gain.

Infrequent: Peripheral edema, weight loss.

Rare: Alcohol intolerance, dehydration, edema, obesity.

Hematic and Lymph Systems
Rare: Anemia, cyanosis, ecchymosis, lymphadenopathy, thrombocytopenia.

Hemorrhage
(See **PRECAUTIONS**, **Hematologic**, **Abnormal Bleeding**).

Adverse Reactions Following Discontinuation of Treatment (or Dose Reduction)

There have been reports of adverse reactions upon the discontinuation of LUVOX, particularly when abrupt, including but not limited to the following: dizziness, abnormal dreams, sensory disturbances (including paresthesias and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation, irritability, anxiety, fatigue, confusion, emotional instability, headache, tremor, nausea, vomiting, diarrhea, sweating, palpitations or other symptoms which may be of clinical significance (See **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). Generally these events are mild to moderate and are self-limiting; however in some patients they may be severe and/or prolonged. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose.

Patients should be monitored for these or any other symptoms. A gradual reduction in the dosage over several weeks, rather than abrupt cessation, is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response. These events are generally self-limiting. Symptoms associated with discontinuation have been reported for other selective serotonin reuptake inhibitors. Isolated cases of withdrawal symptoms in the newborn child have been described after the use of LUVOX at the end of pregnancy (See **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). Some newborns experience feeding and / or respiratory difficulties, seizures, temperature instability, hypoglycemia, tremor, abnormal muscle tone, jitteriness, cyanosis, irritability, lethargy, somnolence, vomiting, difficulty in sleeping and constant crying after third trimester exposure to SSRIs and may require prolonged hospitalization.

Post-Market Adverse Reactions

Spontaneous reports, from the marketplace, but not from clinical trials, have been collected for the following adverse experiences: galactorrhoea, photosensitivity, Stevens Johnson Syndrome, alopecia, taste perversion, tinnitus, psychomotor restlessness, hyperprolactinemia, micturition disorder (including pollakiuria and enuresis), menstrual disorders (such as amenorrhea, hypomenorrhea, metrorrhagia, menorrhagia), drug withdrawal syndrome (including drug withdrawal syndrome neonatal) and haemorrhagic manifestations e.g. eccyhmoses, purpura, gastrointestinal bleeding and gynecological hemorrhage (See **WARNINGS** and **PRECAUTIONS**).

Cases of suicidal ideation and suicidal behaviours have been reported during LUVOX therapy or early after treatment discontinuation. Rarely, serotonin syndrome, neuroleptic malignant syndrome-like events, hyponatremia and SIADH have been reported (See **PRECAUTIONS**, **Serotonin Syndrome**; and **DRUG INTERACTIONS**, **Pharmacodynamic Interactions,** *Serotonergic Drugs*).

SYMPTOMS AND TREATMENT OF OVERDOSE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms

LUVOX (fluvoxamine maleate) has a wide margin of safety in overdose. Since market introduction, reports of overdose have been rare and reports of death attributed to overdose of fluvoxamine maleate alone have been extremely rare.

The smallest estimated dose of fluvoxamine maleate alone associated with a fatal outcome is approximately 1800 mg. The highest documented dose of fluvoxamine maleate ingested by a patient is 22 000 mg. This patient recovered completely.

In the majority of reported cases the patients were taking multiple drugs in addition to fluvoxamine maleate. In such cases it is difficult to differentiate the additive drug effects or drug interactions that may have impacted patient outcome.

The most common symptoms of overdosage include gastrointestinal complaints (nausea, vomiting and diarrhea), somnolence and dizziness. Cardiac events (tachycardia, bradycardia, hypotension), liver function disturbances, convulsions and coma have also been reported.

Treatment

There is no specific antidote to fluvoxamine maleate. In situations of overdosage, the stomach should be emptied as soon as possible after tablet ingestion and symptomatic treatment initiated. The repeated use of medicinal charcoal is also recommended. Due to the large distribution volume of fluvoxamine maleate, forced diuresis or dialysis is unlikely to be of benefit.

DOSAGE AND ADMINISTRATION

LUVOX (fluvoxamine maleate) is not indicated for use in children under 18 years of age (See WARNINGS, POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM).

Depression

Adult Dosage

Treatment should be initiated at the lowest possible dose (50 mg) given once daily at bedtime and then increased to 100 mg daily at bedtime after a few days, as tolerated. The effective daily dose usually lies between 100 mg and 200 mg and should be adjusted gradually according to the individual response of the patient, up to a maximum of 300 mg. Dosage increases should be made in 50 mg increments. Doses above 150 mg should be divided so that a maximum of 150 mg is given in the bedtime dose. Tablets should be swallowed with water and without chewing.

Obsessive-Compulsive Disorder

Adult Dosage

Treatment should be initiated at the lowest possible dose (50 mg) given once daily at bedtime and then increased to 100 mg daily at bedtime after a few days, as tolerated. The effective daily dose usually lies between 100 mg and 300 mg and should be adjusted gradually according to the individual response of the patient, up to a maximum of 300 mg. If no improvement is observed within 10 weeks, treatment with LUVOX should be reconsidered. Dosage increases should be made in 50 mg increments. Doses above 150 mg should be divided so that a maximum of 150 mg is given in the bedtime dose. LUVOX should be swallowed with water and without chewing.

Discontinuation of LUVOX Treatment

Symptoms associated with the discontinuation or dosage reduction of LUVOX have been reported. Patients should be monitored for these and other symptoms when discontinuing treatment or during dosage reduction (See **PRECAUTIONS** and **ADVERSE REACTIONS**).

A gradual reduction in the dose over several weeks rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response (See **PRECAUTIONS** and **ADVERSE REACTIONS**).

Use in Hepatic or Renal Insufficiency

Patients with hepatic or renal insufficiency should begin treatment with a low dose and be carefully monitored.

Use in Children

The safety and effectiveness of LUVOX in children under 18 years of age have not been established (See **WARNINGS**, **POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM**).

Treatment of Pregnant Women During the Third Trimester

Post-marketing reports indicate that some neonates exposed to LUVOX, SSRIs, or other newer antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (See **PRECAUTIONS**). When treating pregnant women with LUVOX the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering LUVOX in the third trimester.

Use in Geriatrics

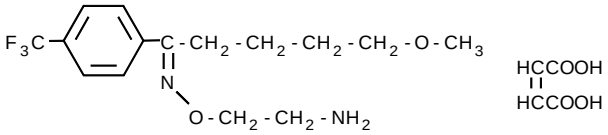
Since there is limited clinical experience in the geriatric age group, caution is recommended when administering LUVOX to elderly patients.

PHARMACEUTICAL INFORMATION

Proper Name: Fluvoxamine maleate

Chemical Name: 5-methoxy-4'-(trifluoromethyl) valerophenone(E)-0-(2-aminoethyl) oxime maleate (1:1)

Structural Formula:



Molecular Weight: 434.4

Description: White, odorless, crystalline powder, sparingly soluble in water, freely soluble in ethanol and chloroform and practically insoluble in diethyl ether.

DOSAGE FORMS, COMPOSITION AND PACKAGING

LUVOX (fluvoxamine maleate) film-coated tablets formulated for oral administration containing fluvoxamine maleate and are available in two strengths: 50 mg and 100 mg.

LUVOX 50 mg tablets are supplied as round, biconvex, scored, white to off-white, film-coated tablets, stamped "291" on either side of the score line and no embossing on the other. The tablets are available in blister packages of 30 tablets.

LUVOX 100 mg tablets are supplied as oval, biconvex, scored, white to off-white, film-coated tablets, stamped "313" on either side of the score line and no embossing on the other. The tablets are available in blister packages of 30 tablets.

Listing of Non-Medicinal Ingredients

Each LUVOX 50 mg tablet contains 50 mg fluvoxamine maleate with the following non-medicinal ingredients: colloidal anhydrous silica, maize starch, mannitol, hypromellose, polyethylene glycol 6000, pregelatinized starch, sodium stearyl fumarate, talc and titanium dioxide.

Each LUVOX 100 mg tablet contains 100 mg fluvoxamine maleate with the following non-medicinal ingredients: colloidal anhydrous silica, maize starch, mannitol, hypromellose, polyethylene glycol 6000, pregelatinized starch, sodium stearyl fumarate, talc and titanium dioxide.

STABILITY AND STORAGE RECOMMENDATIONS

Store in a dry place at temperatures between 15 to 25º C. Protect from light.

PHARMACOLOGY

In a series of in vitro and animal in vivo experiments, fluvoxamine maleate demonstrated as its primary pharmacological effect serotonin potentiating properties due to blockade of the membrane pump mechanism responsible for neuronal serotonin reuptake. Fluvoxamine was effective in inhibiting serotonin uptake by blood platelets and brain synaptosomes. The drug prevented serotonin depletion by tyramine derivatives through its membrane-pump inhibiting properties. As a result of this interference with the neuronal serotonin reuptake mechanism, fluvoxamine produced a decreased serotonin turnover in the brain. The effects of 5-hydroxytryptophan in mice and rabbits were potentiated. Fluvoxamine, in combination with MAO inhibitors (in rats together with tryptophan), induced serotonin-like behaviour in mice and rats. In receptor binding studies, fluvoxamine is practically devoid of affinity towards cholinergic, histaminergic, adrenergic, dopaminergic and serotonergic receptors.

In contrast with tricyclic antidepressants, fluvoxamine had no antihistaminic, sedative, MAO inhibiting or amphetamine-like stimulating activities in rats and cats. The drug had little effects on noradrenaline reuptake processes and reserpine effects, such as ptosis and hypothermia, were only affected at high doses. Also, no stimulating effects were found when reserpine-like compounds were given after a dose of fluvoxamine.

Further indication of the serotonin potentiating properties of fluvoxamine was evidenced by its pharmacological effects in other animal studies. Fluvoxamine decreased REM sleep in rats and cats and reduced food consumption in rats. Intraperitoneal administration of 10 mg/kg to solitary cats did not induce a lysergic acid diethylamide (LSD)-type syndrome, but increased activated behaviour.

Investigation of the parasympatholytic activity of fluvoxamine showed that the drug possesses very low affinity for muscarinic receptors in brain. The drug showed only a weak spasmolytic activity against carbachol-induced contraction of isolated guinea pig ileum, very little effect on pupil diameter and intestinal motility in mice and did not antagonize oxotremorine-induced analgesia or pilocarpine-induced behavioural effects in mice, confirming that fluvoxamine is unlikely to cause anticholinergic effects at peripheral or central sites.

The ability of fluvoxamine maleate and other antidepressants to evoke epileptogenic electrographic signs (spindles and spikes) was evaluated in recordings taken from various regions of the brain of freely moving rats. Intravenous fluvoxamine, in doses up to 60 mg/kg, showed no tendency to induce seizures. In contrast, reference compounds including amitriptyline HCl and imipramine HCl produced serious epileptogenic responses at 10 mg/kg and seizures at 50 mg/kg.

The physical dependence liability of fluvoxamine was assessed and compared with diazepam following two 28-day periods of oral administration in monkeys. The results indicated that fluvoxamine at dose levels of 90 mg/kg twice daily has no physical dependence liability whereas diazepam in doses up to 20 mg/kg produced intermediate to severe dependence liability.

No serious effects on cardiovascular (and respiratory) parameters were observed after administration of fluvoxamine.

Oral fluvoxamine (25 mg/kg) did not affect blood pressure in hypertensive rats. Following an intravenous bolus injection in cats, a dose-dependent, transient blood pressure reduction was observed; infusions of fluvoxamine over two minutes did not influence blood pressure. On isolated rabbit hearts fluvoxamine caused coronary dilatation. Fluvoxamine affected contractility of guinea pig atria in vitro markedly less than tricyclic agents.

In conscious rabbits, ECG disturbances were only observed at nearly lethal doses. In dogs, the only ECG abnormality that was seen after intravenous fluvoxamine was a slight prolongation of the QT interval due to a reduction in heart rate at doses of 10 mg/kg or higher.

Combined administration of fluvoxamine with an MAO inhibitor (tranylcypromine sulphate) exacerbated serotonergic symptoms and a potentiation of the depressant activity of benzodiazepines and butabarbital was found when these drugs were given in combination with fluvoxamine. With amphetamine the interactions of fluvoxamine were variable depending upon test conditions. However, the drug did not have any effect upon the sympathetic blocking properties of guanethidine and did not potentiate the hypotensive activity of α-methyldopa.

Pharmacokinetics

Fluvoxamine is rapidly absorbed following oral administration. In dogs, peak plasma levels were reached in 2-4 hours; in rats and hamsters in one hour. The drug is completely absorbed but, the bioavailability of orally administered fluvoxamine in dogs was restricted to 60% at 1 mg/kg by first-pass metabolism.

The elimination rate varied from species to species. In the dog, the half-life was estimated at three hours after 1 mg/kg and appeared to increase with increasing dose. In rats the half-life was shorter than in dogs, and in hamsters it was shorter than in rats.

The excretion rates were in accordance with the plasma half-lives. In dogs, about 70% of the urinary excretion occurred within 24 hours after 1 mg/kg, but only 50% after 25 mg/kg. In mice and hamsters, excretion was rapid; 90% took place within 24 hours. The main metabolic pathway was similar in the rat, dog, hamster, rabbit and man and consisted of elimination of the methoxyl group leading to the corresponding carboxylic acid as the main metabolite. However, in the mouse, the intermediate alcohol in conjugated form is a major metabolite.

The two main metabolites of fluvoxamine maleate in man were tested for antidepressant activity in four relevant test models. The results indicate that these metabolites are not pharmacologically active in serotonergic or noradrenergic processes.

TOXICOLOGY

Acute Toxicity

The following table presents the results of the acute toxicity studies in mice, rats and dogs:

SPECIES	SEX	ROUTE	LD_{50} mg/kg (95% confidence limits)
Mouse	M	Oral	1100 (550-2200)
	F	Oral	1330 (737-2410)
	M & F	I.V.	61 (46-80)
Rat	M	Oral	2000 (1370-2910)
	F	Oral	1470 (862-2500)
	M	I.V.	43.0 (29.5-62.6)
	F	I.V.	68.1 (46.4-100.0)
Dog	M & F	Oral	> 464

The main acute toxic symptoms noted in mice and rats following oral administration of fluvoxamine occurred at lethal or near lethal dose levels and included convulsions, bradypnea, mydriasis and ataxia with increased muscle tone. In dogs, ataxia was associated with rhythmic side-to-side head movements and mydriasis. Fluvoxamine also induced emesis in the dog at dose levels of 25 mg/kg and higher. Autopsy of rats, which succumbed to the treatment, revealed marked erosion and hemorrhage of the intestinal mucosa. All symptoms were completely reversible in surviving animals.

The signs observed in rats given the drug intravenously were indicative of an effect on the central and autonomic nervous systems, muscle tone and awareness. Haemoglobinuria at concentrations of ≥ 10 mg/mL was indicative of a haemolytic effect. Mice given the drug intravenously showed signs of dyspnea.

Subacute Toxicity

Tolerance was evaluated in hamsters and mice with particular attention to lipid parameters.

In one of two studies involving hamsters, the effects of fluvoxamine, imipramine and amitriptyline on serum and liver lipids were compared. Drug was administered daily for two weeks at dose levels of 100 and 200 mg/kg for fluvoxamine, and 25, 50 and 100 mg/kg for imipramine and amitriptyline. Fluvoxamine caused a slight decrease in serum lipids and an increase in liver lipids at 200 mg/kg whereas amitriptyline 100 mg/kg caused a rise in serum cholesterol and a decrease in the relative weights of the spleen. Other effects seen with all three compounds included a decrease in body weight gain and food consumption and minor histological changes (cloudy swelling) in the liver. With fluvoxamine, these occurred at the 200 mg/kg dose level.

The second study, in which hamsters were administered oral doses of 0, 9, 36, 142 and 432 mg/kg/day fluvoxamine, was of 30 days duration. Body weight gain and food consumption were significantly lower in the high-dose group and in male hamsters receiving 142 mg/kg/day. There was a significant treatment-related decrease in serum lipid levels in all treatment groups. However,

after the 30-day recovery period, no treatment-related differences were evident except for a lower phospholipid level in the males of the high-dose group.

Analysis of liver lipids revealed a significant decrease in cholesterol levels in all treatment groups except the high-dose group and a significant increase in phospholipids and total lipids in the high-dose group. Histopathological examination of the kidneys revealed a significant increase in the incidence of renal tubular changes in the treated groups. In the liver, traces of fat droplets were observed in a proportion of both treated and control groups.

The effects of fluvoxamine (100, 200 mg/kg), imipramine and amitriptyline (25, 50, 100 mg/kg) on serum lipids were also compared in groups of mice given daily oral doses of each drug for two weeks. All three drugs exerted similar effects, with amitriptyline showing the strongest and fluvoxamine the mildest. In mice treated with 200 mg/kg fluvoxamine, there was a dose-related decrease in body weight gain and food consumption and an increase in the weights of the liver and spleen. Slight histological changes were observed in the liver, lung, spleen and mesenteric lymph nodes. In addition, a dose-related hypolipidemia and, in the high-dose group, a significant increase in liver lipids was found. However, there was no evidence of phospholipidosis.

Fluvoxamine was administered to mice in two separate studies at dose levels of 0, 75, 150, 300 and 600 mg/kg/day for four weeks.

In the first study, there was a significant increase in body weight gain in females in the 150 mg/kg group and males in the 300 mg/kg group. In addition, there was a reduction in water intake at 300 mg/kg in female mice and at 600 mg/kg in both sexes. Packed cell volume and hemoglobin content were significantly reduced in females at all dose levels and liver weight was also significantly increased in both sexes in the 150, 300 and 600 mg/kg groups. Histopathological examination of the liver indicated hypertrophy of the centrilobular hepatocytes in males in the 300 mg/kg group and in mice of both sexes receiving 600 mg/kg. There was fine vacuolation of the cytoplasm in one male mouse at the 300 and 600 mg/kg dose levels, and vacuolation and distension of the hepatocytes at 600 mg/kg.

Similar changes were observed in the second mouse study involving another mouse strain. There was a significant increase in body weight gain in males in the 75, 150 and 300 mg/kg groups and a reduction in water consumption in males in the 300 and 600 mg/kg groups. Packed cell volume was significantly reduced in males in the 300 and 600 mg/kg groups and liver weight was significantly increased in males in the 300 mg/kg group and in mice of both sexes in the 600 mg/kg group. Histopathological examination of the liver revealed hypertrophy of the centrilobular hepatocytes and vacuolation and/or distension of hepatocytes in the 300 and 600 mg/kg groups.

The toxic effects of orally administered fluvoxamine were further evaluated in mice in two additional 4-week studies involving doses ranging from 200 to 1600 mg/kg/day.

In one study, mice received 0, 200, 300 or 400 mg/kg/day. Changes observed were a decrease in the body weight gain in male mice of the high-dose group and a dose-related accentuation of hepatic lobular pattern.

Daily doses of 0, 400, 600, 800 or 1600 mg/kg were administered to mice in the other study of 4-weeks duration. Poor general body condition, piloerection, lethargy and body tremors were observed at the highest dose level and one male mouse died during week four. Examination at necropsy revealed only autolytic changes. There was an increase in body weight gain in the 800 and 1600 mg/kg groups and a decrease in food consumption in the 1600 mg/kg group.

At necropsy, there were generalized discolouration of the liver and an increase in the absolute and relative weights of the liver in all treatment groups except for the absolute weight of the liver in the 1600 mg/kg group. Also, all increases were dose related except for animals receiving the highest dosage. In addition, there was a decrease in the absolute and relative weights of the thymus in the highest dose group and treatment-related lesions were found in hepatic sections of all drug groups, possibly reflective of intracellular lipid accumulation.

Long-Term Toxicity

The long-term toxicological effects of orally administered fluvoxamine maleate were investigated in seven studies involving hamsters, rats and dogs for treatment periods ranging from 13 weeks to two years.

During the 13-week evaluation in hamsters, fluvoxamine was administered in the diet in doses of 0 or 233 mg/kg/day. Fluvoxamine treatment significantly reduced body weight gain and increased water consumption. Also, there was a reduction in plasma lipid concentration in male hamsters only and an increase in liver lipid concentration with a corresponding increase in fat droplets in the hepatocytes in both sexes.

Organ weight data revealed a significant decrease in the weights of the kidney (both sexes) and liver (males only) and a significant decrease in brain weight in female hamsters.

When fluvoxamine was administered in the diet of mice at dose levels of 0, 10, 80 or 640 mg/kg/day, an increase in body weight gain was noted in the mid-dose group in male mice during the first 12 of the 21 weeks of treatment and in female mice during weeks 8-16. Lower body weight gain was recorded throughout the treatment period in the high-dose group.

Blood chemistry results revealed a significant increase in alanine amino-transferase and aspartate amino-transferase activities in the high-dose group and in male mice in the mid-dose group. Serum lipid levels were significantly lower in the high-dose group and cholesterol levels were marginally lower in the mid-dose group. Also, serum lipoprotein electrophoresis revealed an apparent lowering of the pre-ß fraction in mice of all treatment groups. In addition, there was an increase in the absolute and relative weights of the liver in mice of both sexes within the high-dose group and in male mice within the mid-dose group, and an increase in the absolute weights of the liver in female mice in the mid-dose group.

Autopsy of mice sacrificed after 10 or 21 weeks of treatment revealed an increased incidence of hepatic macropathological changes including accentuation of lobular pattern and a generalized pallor sometimes associated with yellow-green colouration. Dose-related changes in the liver of animals within the mid- and high-dose groups included fine fatty vacuolation of periacinal

hepatocytes, large fatty vacuolation of centroacinar hepatocytes and pleomorphic cell inflammation.

Histopathological examination of the liver of mice allowed to recover after treatment revealed an almost total loss of the fine fatty vacuolation and loss of centroacinar hepatocytic large fatty vacuolation. However, a dose-related incidence of panacinar hepatocytic large fatty vacuolation had surfaced in the mid- and high-dose groups.

Two hours following autoradiography, radioactivity was detected within the hepatocellular cytoplasm, vascular endothelium, around and within fat vacuoles, cell borders and connective tissue around blood vessels and bile canaliculi in the mid- and high-dose groups. Twelve hours post dosing, a less distinct pattern was apparent. Significant hepatocytic enlargement was present in male mice from all treatment groups, but was virtually absent in female mice.

Analysis of liver specimens showed a significant increase in liver lipids in male animals within the mid- and high-dose groups and an increase in phospholipid levels at 10 mg/kg/day. In female mice there were significantly higher levels of total lipids, triglycerides and cholesterol in the mid- and high-dose groups and an increase in phospholipids at 80 mg/kg/day.

Daily oral doses of 0, 5, 20 and 80 mg/kg/day fluvoxamine were administered to rats for six months with the 80 mg/kg dose increased to 100 mg/kg after nine weeks then further increased to 150 mg/kg after 20 weeks. Increased food consumption and body weight gain occurred in female animals at 20 and 80 mg/kg and water consumption was higher in male rats in the 80 mg/kg group. There was an increase in the absolute weights of the liver in females and in the relative weights of the liver in males at the 80/mg/kg dose level. In addition, the relative weights of the spleen and thymus were reduced in the 80 mg/kg group. The higher liver weights in females and lower spleen weights in males in the 80 mg/kg group appeared to be drug related. However, no histopathological changes were observed in these organs.

Dogs were treated with fluvoxamine 0, 5, 15 or 45 mg/kg/day (capsules) for seven months, with the high dose increased to 60 mg/kg/day after seven weeks then maintained throughout the study at this level except during weeks 14 and 15 when the dose was raised to 80 mg/kg/day. Two dogs died while receiving 60 mg/kg or 80 mg/kg. At 45 mg/kg animals displayed frowning, bouts of "coughing" and rhythmic side-to-side head movements. At 80 mg/kg, ataxia, anorexia and weight loss occurred and one dog had convulsions. Mydriasis was noted at all dose levels, persisting for up to 24 hours after dosing and regressing over a period of six days after treatment was stopped.

Histopathological examination revealed the presence of foamy macrophages in the spleen, mesenteric, cervical and intestinal lymph nodes. These macrophages were observed only in animals from the high-dose group (45, 60 or 80 mg/kg). The lesions gave the appearance of lipid granulomata in which phagocytosis of lipid material had occurred and were more evident in the Peyer's patches in comparison to the other lymph organs, indicating an effect on fat metabolism.

In a second study involving beagle dogs, fluvoxamine was administered orally via capsules for 53 weeks at dose levels of 0, 10, 25 or 62.5 mg/kg/day for 53 weeks. Clinical signs following drug treatment included moderate mydriasis at all dose levels, reduced weight gain and anorexia in the

high-dose group, periodic reduction in water and food consumption and slight increase in the incidence of diarrhea in males in the mid- and high-dose groups. In addition, there was an increase in the levels of plasma alkaline phosphatase, an increase in the incidence of glomerular atrophy (also present in the control group) and occasional increases in plasma urea, creatinine and urine volume in the high-dose animals. Kidney weight was increased in male dogs in the mid- and high-dose groups. A foam-cell reaction in the reticuloendothelial system was observed in the mid- and high-dose groups and the lipid content of these cells was predominantly phospholipid.

Histopathological signs of adverse effects on the kidney were confined to the high-dose group and included distension of Bowman's capsule, shrinkage of the glomerular tuft and interstitial fibrosis. The relative weights of the liver, spleen (males) and lungs (females) were increased in animals within the high-dose group sacrificed after 53 weeks of treatment. However, these changes were not associated with any unusual histopathological changes and the weight increases were not present in animals sacrificed following withdrawal of treatment.

In a special study to investigate lipid distribution in the tissues of rats, fluvoxamine was administered for 52 weeks at dose levels of 0, 10, 40 and 160 mg/kg/day with the high dose increased to 200 mg/kg/day during weeks 40 to 52. There was a dose-related decrease in food and water consumption and a decrease in body weight in animals in the high-dose group. Histopathological changes included a slight increase in the incidence of lipid-containing vacuoles in hepatocytes and a larger number of lamellar cytoplasmic inclusions in the lymphocytes of treated male rats. Further examination of the mesenteric lymph nodes by electron microscopy showed a 6-fold increase in the total number of cytoplasmic lamellar inclusions. The inclusions were of the same type as observed for phospholipidosis-inducing drugs suggesting that fluvoxamine induces a mild form of phospholipidosis.

Fluvoxamine was administered to the diet of rats at dose levels of 0, 10, 40, 160 mg/kg/day for 81 weeks with the high-dose level increased to 200 mg/kg at week 40, then further increased to 240 mg/kg at week 47. Drug-related changes were primarily confined to the high-dose group and included decreases in body weight gain (males only), food and water consumption, the absolute weights of the brain and increases in urine concentration, the relative weights of the lung and liver (males only), the relative and absolute weights of the ovaries, lymphocytic infiltrations in the kidneys, the incidence of vacuolation of hepatocytes and the incidence of macrophage aggregations in the lungs. In the mid-dose group there was a decrease in body weight gain (females only) and an increase in the incidence of vacuolation of hepatocytes (males only). No drug-related changes were observed in the low-dose group. However, there was a significant decrease in the absolute and relative weights of the thyroid in females in this group. The biological significance of this finding is unclear.

Carcinogenicity

Rats were given fluvoxamine as a day/diet mixture at dosage levels of 0, 10, 40 and 160 to 240 mg/kg/day for 2-1/2 years. Initially, the high-dose level was 160 mg/kg/day, but this was increased to 200 mg/kg/day after 40 weeks and to 240 mg/kg/day after 53 weeks. At 160-240 mg/kg/day there was a decrease in weight gain and a dose-related increase in centrilobular hepatocyte degeneration. However, fluvoxamine did not contribute to mortality or tumour incidence.

Fluvoxamine was also given to hamsters in a lifetime study (about two years) at dosages of 0, 9, 36, 144/180/240 mg/kg/day (the high dose was raised from 144-180 mg/kg/day at week 14, then to 240 mg/kg/day at week 19 of treatment). No drug or dose-related effects on mortality rates or incidence of tumours were found.

Mutagenicity

Fluvoxamine did not have mutagenic activity in the Ames test with five bacterial test strains, the micronucleus test and a cytogenetic test using lymphocytes cultured in vitro.

Teratology

The teratologic effects of fluvoxamine were studied in both rats and rabbits. When fluvoxamine was administered to rats from day 6-15 of gestation in single daily doses of 0, 5, 20 and 80 mg/kg/day, the drug did not affect the general health, pre- and post-implantation loss and fetal morphology of the animals.

In the two rabbit studies, oral doses of 0, 5, 10, and 20 mg/kg day (first study) and 0, 5, 10 and 40 mg/kg day (second study) were given during days 6-18 of gestation. In the first rabbit study, the incidence of minor visceral and skeletal anomalies was higher among the treatment groups than in the control group. A statistically significant incidence of skeletal variants was observed in the low-dose group, but the incidence in the mid- and high-dose groups was comparable to the controls. The rabbit teratology study was repeated and the results of the second study indicated that incidences of malformations, anomalies and skeletal variants appeared essentially unaffected by treatment with fluvoxamine for doses up to 40 mg/kg/day.

Reproductive Studies

Reproductive studies in rats revealed impaired fertility and developmental toxicity.

In a study in which male and female rats were administered fluvoxamine (60, 120, or 240 mg/kg) prior to and during mating and gestation, fertility was impaired at oral 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).

When pregnant rats were given oral doses of fluvoxamine (60, 120, or 240 mg/kg) throughout the period of organogenesis, increased embryofetal death, decreased fetal body weight and increased incidences of fetal eye abnormalities (folded retina) were observed in fluvoxamine exposures exceeding by about 4 times human exposures at maximum recommended human doses. The no-effect dose for developmental toxicity in this study was 60 mg/kg (approximately 2 times the maximum recommended human dose on a mg/m^2 basis). The potential risk for humans is unknown.

The effects of fluvoxamine on peri- and postnatal development of the rat were assessed in two studies. In one study, the drug was given in single daily doses of 0, 5, 20 and 80 mg/kg from day 15 of pregnancy, through lactation to 21 days postpartum. There was an increase in pup mortality at all dosages leading to a reduction in litter size.

In the second rat study daily dosages of 0 and 160 mg/kg were administered and a proportion of litters from the test group were cross-fostered with control litters on day one postpartum to distinguish between direct and indirect (maternally mediated) effects on postnatal development of offspring. Fluvoxamine was found to exert a primary toxic effect on the parent animal, rather than an effect on late fetal development and the immediate perinatal period. However, weight gain was slightly lower in fostered and non-fostered offspring from test dams during days 8-21 of lactation.

REFERENCES

1. Anon. Fluvoxamine (Faverin): Another Antidepressive Drug. Drug Ther Bull 1988; 26(3):11-2.
2. Baldessarini RJ. Current Status of Antidepressants: Clinical Pharmacology and Therapy. J Clin Psychiatry 1989; 50(4):117-126.
3. Becquemont L., Ragueneau I., Le Bot M., Riche C., Funck-Brentano C., Jaillon P. Pharmacokinetics and Drug Disposition. Influence of the CYP1A2 Inhibitor Fluvoxamine on Tacrine Pharmacokinetics in Humans. Clinical Pharmacology and Therapeutics 1997; 61 (6): 619-627.
4. Benfield P, Ward A. Fluvoxamine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depressed illness. Drugs 1986; 32:313-34.
5. Bertschy G., Baumann P., Eap C. B., Baettig D. Probable metabolic interaction between methadone and fluvoxamine in addict patients. Therapeutic Drug Monitoring 1994; 16: 42-45.
6. Berwish, NJ, Amsterdam JD. An Overview of Investigational Antidepressants. Psychosomatics 1989; 30(1):1-18.
7. Blumhardt C. Advances in the Diagnosis and Management of Depression. Am Pharm, Part II 1988; NS28(2):33-7.
8. Brosen K., Skjelbo E., Rasmussen B.B., Poulsen H.E., Loft S. Fluvoxamine is a potent inhibitor of cytochrome P4501A2. Biochemical Pharmacology 1993; 45 (6): 1211-1214.
9. Burrows GD, McIntyre IM, Judd FK, Norman TR. Clinical Effects of Serotonin Reuptake Inhibitors in the Treatment of Depressive Illness. J Clin Psychiatry 1988; 49(8):18-22.
10. Carillo JA, et al. Pharmacokinetic Interaction of Fluvoxamine and Thioridazine in Schizophrenic Patients. J Clin Psychopharmacol 1999; 19:494-499.
11. Claassen V. Review of the animal pharmacology and pharmacokinetics of fluvoxamine. Br J Clin Pharmacol 1983; 15:349S-55S.
12. Crewe H.K., Lennard M.S., Tucker G.T., Woods F.R., Haddock R.E. The effect of selective serotonin re-uptake inhibitors on cytochrome P4502D6 (CYP2D6) activity in human liver microsomes. British Journal of Clinical Pharmacology 1992; 34: 262-265.
13. Dallaire S. Thioridazine (Mellaril) and mesoridazine (Serentil): prolongation of the QTc interval. Canadian ADR Newsletter, Jan 2001; Vol. 11, No. 1.
14. Daniel D.G. et al. Coadministration of fluvoxamine increases serum concentrations of haloperidol. Journal of Clinical Psychopharmacology 1994; 14(5): 340-343.
15. Daniel W.A., Syrek M., Haduch A., Wojcikowski J. The influence of selective serotonin reuptake inhibitors (SSRIs) on the pharmacokinetics of thioridazine and its metabolites: in vivo and in vitro studies. Exp. Toxic Pathol. 1999; 51: 309-314.
16. De Bree H, Van Der Schoot JB, Post LC. Fluvoxamine maleate; Disposition in man. Eur J Drug Metab Pharmacokinet 1983; 8(2):175-9.

17. Dick P, Ferrero E. A double-blind comparative study of the clinical efficacy of fluvoxamine and chlorimipramine. Br J Clin Pharmacol 1983; 15:419S-25S.

18. Dillenkoffer RL, et al. Electrocardiographic Evaluation of Mesoridazine (Serentil). Current Therapeutic Research 1972; 14(2):71-72.

19. Dominguez RA, Goldstein BJ, Jacobson AF, Steinbook RM. A double-blind placebo-controlled study of fluvoxamine and imipramine in depression. J Clin Psychiatry 1985; 46:84-7.

20. Ereshefsky L, Riesenman C., Lam Y.W.F. Antidepressant drug interactions and the cytochrome P450 system. The role of cytochrome P450 2D6. Clinical Pharmacokinetics 1995; 29, supp.1: 10-19.

21. Fleishaker J.C., Hulst L.K. A pharmacokinetic and pharmacodynamic evaluation of the combined administration of alprazolam and fluvoxamine. European Journal of Clinical Pharmacology 1994; 46: 35-39.

22. Fritze J., Unsorg B., Lanczik M. Interaction between carbamazepine and fluvoxamine. Acta Psychiatr. Scand. 1991; 84 (6): 583-584.

23. Guelfi JD, Dreyfus JF, Pichot P. Fluvoxamine and imipramine: Results of a long-term controlled trial. Int Clin Psychopharmacol 1987; 2:103-9.

24. Guy W, Wilson WH, Ban TA, King DL, Manov G, Fjetland OK. A double-blind clinical trial of fluvoxamine and imipramine in patients with primary depression. Drug Dev Res 1984; 4:143-53.

25. Hartigan-Go K, et al. Concentration-related pharmacodynamic effects of thioridazine and its metabolites in humans. Clin Pharmacol Ther 1996; 60:543-553.

26. Hiemke C. et al. Elevated Levels of Clozapine in Serum After Addition of Fluvoxamine. J Clin Pyschopharmacol 1994; 14 (4): 279-281.

27. Lapierre YD, Browne M, Horn E, Oyewumi LK, Sarantidis D, Roberts N, Badoe K, Tessier P. Treatment of major affective disorder with fluvoxamine. J Clin Psychiatry 1987; 48(2):65-8.

28. Lapierre YD, Oyewumi LK, Coleman B. The efficacy of fluvoxamine as an antidepressant. Clin Trials J 1981; 18(5):313-20.

29. Lydiard RB, Laird LK, Morton WA, Steele TE, Kellner C, Laraia MT, Ballenger JC. Fluvoxamine, Imipramine, and Placebo in the Treatment of Depressed Outpatients: Effects on Depression. Psychopharmacol Bull 1989; 25(1):68-70.

30. Mallya, G, White, K, Gunderson, C. Is There a Serotonergic Withdrawal Syndrome? Biol Psychiatry 1996; 33:851-852.

31. Marrs-Simon PA, et al. Cardiotoxic manifestations of mesoridazine overdose. Ann Emerg Med 1988;17(10):1984-90.

32. Martin AJ, Tebbs VM, Ashford JJ. Affective disorders in general practice. Treatment of 6000 patients with fluvoxamine. Pharmatherapeutica 1987; 5(1):40-9.

33. Martin AJ, Wakelin J. Fluvoxamine - a baseline study of clinical response, long term tolerance and safety in a general practice population. Br J Clin Pract 1986; 40:95-9.

34. McHardy, KC. Syndrome of inappropriate antidiuretic hormone secretion due to fluvoxamine therapy. Br J Clin Pract 1993; 47(2):62-63.

35. Mithani, H, Hurwitz, TA. Paroxetine-Induced Angioedema and Tongue Swelling. J Clin Psychiatry 1996; 57(10):486.

36. Niemann JT, et al. Cardiac conduction and rhythm disturbances following suicidal ingestion of mesoridazine. Ann Emerg Med 1981; 10(11):585-8.

37. Nolen WA, van de Putte JJ, Dijken WA, Kamp JS, Blansjaar BA, Kramer HJ, Haffmans J. Treatment strategy in depression. Acta Psychiatr Scand 1988; 78:668-75.

38. Norton KRW, Sireling LI, Bhat AV, Rao B, Paykel ES. A double-blind comparison of fluvoxamine, imipramine and placebo in depressed patients. J Affective Disord 1984; 7:297-308.

39. Ochs HR, Greenblatt DJ, Verburg-Ochs B, Labedski L. Chronic Treatment with Fluvoxamine, Clovoxamine, and Placebo: Interaction with Digoxin and Effects on Sleep and Alertness. J Clin Pharmacol 1989; 29:91-5.

40. Ottevanger EA. Controlled study with Fluvoxamine in outdoor psychiatric patients diagnosed of depressive syndrome with somatization. Psiquis Rev Psiquiatr Psicol Psicosom 1988; 9(3):34-40.

41. Overmars H, Scherpenisse PM, Post LC. Fluvoxamine maleate: metabolism in man. Eur J Drug Metab Pharmacokinet 1983; 8(3):269-80.

42. Perucca E., Gatti G., Cipolla G., Spina E., Barel S., Soback S., Gips M., Bialer M. Inhibition of diazepam metabolism by fluvoxamine: A pharmacokinetic study in normal volunteers. Clinical Pharmacology and Therapuetics 1994; 56 (5): 471-476.

43. Rasmussen B.B., Maenpaa J., Pelkonen O., Loft S., Poulsen H., Lykkesfeldt J., Brosen K. Selective serotonin reuptake inhibitors and theophylline metabolism in human liver microsomes: potent inhibition by fluvoxamine. British Journal of Pharmacology 1995; 39: 151-159.

44. Sperber A.D. Toxic interaction between fluvoxamine and sustained release theophylline in an 11-year-old boy. Drug Safety 1991; 6 (6): 460-462.

45. Stevens, I, Gaertner, HJ. Plasma Level Measurement in a Patient With Clozapine Intoxication. J. Clin. Pharmacology 1996; 16(1):86-87.

46. van Harten J. Overview of the pharmacokinetics of fluvoxamine. Clinical Pharmacokinetics 1995; 29, suppl. 1: 1-9.

47. Vella J.P., Mohamed H.S. Interactions between cyclosporine and newer antidepressant medications. American Journal of Kidney Diseases 1998; 31(2): 320-323.

48. Vertees JE and Siebel G. Rapid death resulting from mesoridazine overdose. Vet Hum Toxicol 1987:29(1):65-7.

49. von Bahr C, et al. Plasma levels of thioridazine and metabolites are influenced by the debrisoquin hydroxylation phenotype. Clin Pharmacol Ther 1991; 49(3):234-240.

50. von Moltke L.L., Greenblatt D.J., Court M.H., Duan S.X., Harmatz J.S., Shader R.I. Inhibition of alprazolam and desipramine hydroxylation in vitro by paroxetine and

fluvoxamine. Comparison with other selective serotonin reuptake inhibitor antidepressants. Journal of Clinical Psychopharmacology 1995; 15 (2): 125-131.

51. Wagner, W, Zaborny, BA, Grat, TE. Fluvoxamine. A review of its safety profile in world-wide studies. International Clinical Psychopharmacology 1994; 9:223-227.
52. Wakelin JS. Fluvoxamine in the treatment of the older depressed patient; double-blind, placebo-controlled data 1986. Int Clin Psychopharmacol 1986; 1:221-30.
53. Wakelin JS. A review of the properties of a new specific 5-HT reuptake inhibitor - fluvoxamine maleate. Front Neuropsychiatric Res 1983; 159-73.
54. Weiss E.L., Potenza M.N., McDougle C.J., Epperson C.N. Olanzapine addition in obsessive-compulsive disorder refractory to selective serotonin reuptake inhibitors: an open-label case series. J Clin Psychiatry 1999; 60 (8): 524-527.
55. Wright, S, Dawling, S, Ashford, JJ. Excretion of fluvoxamine in breast milk. Br. J. Clin. Pharmacology 1994; 31:209.
56. Yun C., Okerholm R.A., Guengerich F. P. Oxidation of the Antihistaminic Drug Terfenadine in Human Liver Microsomes. Role of Cytochrome P-450 3A(4) in N-Dealkylation and C-Hydroxylation. Drug Metabolism and Disposition 1993; 21 (3): 403-409.

PART III: CONSUMER INFORMATION

[Pr]LUVOX®
fluvoxamine maleate

This leaflet is part III of a three-part "Product Monograph" and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about LUVOX®. Contact your doctor or pharmacist if you have any questions about the drug.

Please read this information before you start to take your medicine, even if you have taken this drug before. Keep this information with your medicine in case you need to read it again.

ABOUT THIS MEDICATION

What the medication is used for:
LUVOX has been prescribed by your doctor to relieve your symptoms of:
- depression (feeling sad, a change in appetite or weight, difficulty concentrating or sleeping, feeling tired, headaches, unexplained aches and pain), or
- obsessive-compulsive disorder (recurrent and intrusive thought, feeling, idea or sensation; recurrent pattern of behaviour, or unwanted thoughts or actions)

What it does:
LUVOX belongs to a group of medicines called selective serotonin reuptake inhibitors (SSRIs). LUVOX is thought to work by increasing the levels of a chemical in the brain called serotonin.

When it should not be used:
Do not use LUVOX if you are:
- allergic to it or any of the components of its formulation (See **What the nonmedicinal ingredients are**).
- currently taking or have recently taken monoamine oxidase (MAO) inhibitor antidepressants (e.g. phenelzine sulphate, moclobemide) or a MAO inhibitor antibiotic (e.g. linezolid).
- currently taking or have recently taken thioridazine or pimozide.
- currently taking or have recently taken tizanidine, mesoridazine, terfenadine, astemizole and cisapride.
- taking ramelteon, a medicine not available in Canada.

What the medicinal ingredient is:
Fluvoxamine maleate.

What the nonmedicinal ingredients are:
Colloidal anhydrous silica, maize starch, mannitol, hypromellose, polyethylene glycol 6000, pregelatinized starch, sodium stearyl fumarate, talc and titanium dioxide.

There is no gluten, lactose, sulfite or tartrazine in LUVOX.

What dosage forms it comes in:
LUVOX is available as:
- 50 mg white to off-white tablets
- 100 mg white to off-white tablets

WARNINGS AND PRECAUTIONS

During treatment with these types of medications, it is important that you and your doctor have good ongoing communication about how you are feeling.

LUVOX is not for use in children under 18 years of age.

New or Worsened Emotional or Behaviour Problems
Particularly in the first few weeks or when doses are adjusted, a small number of patients taking drugs of this type may feel worse instead of better. They may experience new or worsened feelings of agitation, hostility, anxiety, impulsivity, or thoughts about suicide, self-harm or harm to others. Suicidal thoughts and actions can occur in any age group but may be more likely in patients 18 to 24 years old. Should this happen to you, or those in your care, **consult your doctor immediately**. Close observation by a doctor is necessary in this situation. **Do not discontinue your medication on your own.**

Bone Fracture Risk
Taking LUVOX may increase your risk of breaking a bone if you are elderly or have osteoporosis or have other major risk factors for breaking a bone. You should take extra care to avoid falls especially if you get dizzy or have low blood pressure.

BEFORE you use LUVOX tell your doctor or pharmacist:
- if you have had any allergic reaction to medications
- all your medical conditions, including a history of seizures, liver or kidney disease, heart problems or a history of any abnormal bleeding
- you have a bleeding disorder or have been told that you have low platelets
- you had a recent bone fracture or were told you have osteoporosis or risk factors for osteoporosis
- you have glaucoma or increased pressure in your eyes
- any medications (prescription or nonprescription) you are taking or have recently taken, especially monoamine oxidase (MAO) inhibitors (e.g., phenelzine sulphate, moclobemide), or any other antidepressants, tizanidine, thioridazine, pimozide, mesoridazine, neuroleptics, warfarin, propranolol, phenytoin, theophylline, lithium, tryptophan, terfenadine, astemizole, cisapride and drugs used to prevent seizures (anticonvulsants)
- if you have ever had any allergic reaction to medications, food, etc.
- any natural or herbal products you are taking (e.g., St. John's Wort)
- whether you are pregnant, or thinking about becoming pregnant, or if you are breast feeding
- your habits of alcohol and/or street drug consumption
- if you drive a vehicle or perform hazardous tasks during your work.

Effects on Pregnancy and Newborns
If you are already taking LUVOX and have just found out that you are pregnant, you should talk to your doctor immediately. You should also talk to your doctor if you are planning to become pregnant.

Some newborns whose mothers took an SSRI (Selective Serotonin Reuptake Inhibitor) or other newer antidepressants, such as LUVOX, during pregnancy have developed complications at birth requiring prolonged hospitalization, breathing support and tube feeding. Reported symptoms included: feeding and / or breathing difficulties, vomiting, seizures, tense or overly relaxed muscles, jitteriness, cyanosis (bluish skin), irritability, lethargy, drowsiness, difficulty in sleeping and constant crying.

In most cases, the newer antidepressant was taken during the third trimester of pregnancy. These symptoms are consistent with either a direct adverse effect of the antidepressant on the baby or possibly a discontinuation syndrome caused by sudden withdrawal from the drug. These symptoms normally resolve over time. However, if your baby experiences any of these symptoms, contact your doctor as soon as you can.

Persistent Pulmonary Hypertension (PPHN) and newer antidepressants:
When taken during pregnancy, particularly in the last 3 months of pregnancy, medicines like LUVOX may increase the risk of a serious lung condition in babies, called persistent pulmonary hypertension of the newborn (PPHN), that causes breathing difficulties in newborns soon after birth, making the baby breathe faster and appear bluish. These symptoms usually begin during the first 24 hours after the baby is born. If this happens to your baby you should contact your doctor immediately.

If you are pregnant and taking an SSRI, or other newer antidepressants, you should discuss the risks and benefits of the various treatment options with your doctor. It is very important that you do NOT stop taking these medications without first consulting your doctor. See **SIDE EFFECTS AND WHAT TO DO ABOUT THEM** section for more information.

INTERACTIONS WITH THIS MEDICATION

Do not use LUVOX if you are taking or have recently taken monoamine oxidase (MAO) inhibitors, methylene blue (intravenous), linezolid, thioridazine or pimozide.

LUVOX should not be used with tizanidine, terfenadine, astemizole and cisapride.

You should tell your doctor if you are taking or have recently taken any medications (prescription, nonprescription or natural / herbal), especially:

- other antidepressants, such as SSRIs and certain tricyclics
- other drugs that affect serotonin such as lithium, linezolid, tramadol, tryptophan, St. John's Wort and triptans (used to treat migraines)
- certain medicines used to treat schizophrenia
- certain medicines used to treat bipolar depression such as lithium
- certain medicines used to treat epilepsy
- certain medicines which may affect blood clotting and increase bleeding, such as oral anticoagulants (e.g. warfarin, dabigatran), acetylsalicylic acid (e.g. Aspirin) and other nonsteroidal anti-inflammatory drugs (e.g. ibuprofen)
- propranolol or other medications used to treat high blood pressure
- certain medicines used to treat patients with irregular heart beats
- certain drugs used to treat diabetes
- certain medicines used to treat some respiratory conditions such as chronic obstructive pulmonary disease (COPD) or asthma (e.g., theophylline)
- certain medicines used to treat pain, such as fentanyl (used in anesthesia or to treat chronic pain), tramadol, tapentadol, meperidine, methadone, pentazocine
- certain medicines used to treat cough such as dextromethorphan
- sedatives such as benzodiazapines

In general, drinking alcoholic beverages should be kept to a minimum or avoided completely while taking LUVOX.

PROPER USE OF THIS MEDICATION

Usual dose:

- It is very important that you take LUVOX exactly as your doctor has instructed. Generally most people take between 100 mg to 200 mg per day for depression and between 100 mg and 300 mg for obsessive compulsive disorder.
- LUVOX is usually taken once a day at bedtime. However, doses above 150 mg per day may be divided so that a maximum of 150 mg is taken at bedtime. Swallow the tablets whole with water. Do not chew them.
- Establishing an effective dosage level will vary from one person to another. For this reason, your doctor may adjust your dosage gradually during treatment.
- Never increase or decrease the amount of LUVOX you are taking unless your doctor tells you to change your dosage.
- Do not stop taking this medication without consulting your doctor.
- As with all antidepressants, improvement with LUVOX is gradual. You should continue to take your medication even if you do not feel better, as it may take a number of weeks for your medicine to work.
- Talk to your doctor before you stop taking your medication on your own.
- You should avoid taking St. John's Wort if you are taking LUVOX.

Reminder: This medicine has been prescribed only for you. Do not give it to anybody else as they may experience undesirable effects, which may be serious. If you have further questions, please ask your doctor or pharmacist.

Missed Dose:
If you miss a dose, do not try to make up for it by doubling up on the dose the next time. Just take your next regularly scheduled dose and try not to miss any more.

Overdose:
In case of an overdose contact your doctor, the regional Poison Control Centre, or the nearest hospital emergency department, even if you do not feel sick. Take your medicine with you.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medications, LUVOX can cause some side effects. You may not experience any of them. For most patients, side effects are likely to be minor and temporary. However some may be serious. Some of these side effects may be dose related. Consult your doctor if you experience these or other side effects, as the dose may have to be adjusted.

If you experience an allergic reaction (including red skin, hives, itching, swelling of the lips, face tongue, throat, trouble breathing, wheezing, shortness of breath, skin rashes, blisters of the skin, sores or pain in the mouth or eyes) or any severe or unusual side effects, stop taking the drug and contact your doctor immediately.

The most common side effects of LUVOX are:
- nausea (sometimes with vomiting)
- constipation
- diarrhea
- loss of appetite
- upset stomach
- sleep disturbances
- dry mouth
- tremor (uncontrolled shaking)
- dizziness
- headache
- anxiety
- nervousness
- excessive sweating
- sexual problems
- urinating problems.

LUVOX does not usually affect people's normal activities. However, some people feel sleepy while taking it, in which case they should not drive or operate machinery.

Although psychiatric disorders may be associated with decreases in sexual desire, performance and satisfaction, treatment with this medication may also affect sexual functioning.

LUVOX can raise your levels of a hormone called "prolactin" (measured with a blood test). Symptoms of high prolactin may include: (in men) breast swelling, sexual dysfunction; (in women) breast discomfort, leakage of milk from the breasts, missed menstrual periods, or other problems with your cycle.

Discontinuation Symptoms
Contact your doctor before stopping or reducing your dosage of LUVOX. Symptoms such as dizziness, abnormal dreams, unusual skin sensations (burning, prickling, tingling), sleep disturbances (including insomnia and intense dreams) confusion, fatigue, agitation, irritability, anxiety, emotional instability, difficulty concentrating, headache, tremor, nausea, vomiting, diarrhea, sweating, palpitations (faster heartbeat) or other symptoms may occur after stopping or reducing the dosage of LUVOX. Such symptoms may also occur if a dose is missed. These symptoms usually disappear without needing treatment. Tell your doctor immediately if you have these or any other symptoms. Your doctor may adjust the dosage of LUVOX to alleviate the symptoms. Discontinuation symptoms may occur in an infant if the mother is taking antidepressants at, or shortly before, the time of birth or while nursing.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Seek immediate emergency medical assistance
		Only if severe	In all cases	
Common	Uncontrollable movements of the body or face		✓	
Uncommon	**Allergic reactions:** red and lumpy skin rash, hives, swelling, trouble breathing			✓
	Akathisia: feeling restless and unable to sit or stand still		✓	
	Hallucinations: strange visions or sounds		✓	
Unknown	**Low platelets:** Bruising or unusual bleeding from the skin or other areas		✓	
Rare	**Low sodium level in the blood:** tiredness, weakness, confusion, combined with achy, stiff or uncoordinated muscles		✓	
	Gastrointestinal bleeding: vomiting blood or passing blood in stools			✓
	Seizures: loss of consciousness with uncontrollable shaking			✓
	Liver disorder: nausea, vomiting, loss of appetite combined with itching, yellowing of the skin or eyes, dark urine			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Seek immediate emergency medical assistance
		Only if severe	In all cases	
	Serotonin syndrome: a combination of most or all of the following: confusion, restlessness, sweating, shaking, shivering, hallucinations, sudden jerking of the muscles, fast heartbeat			✓
	Glaucoma: increased pressure in the eyes, eye pain and blurred vision		✓	
See Warnings & Precautions	New or Worsened Emotional or Behavioural Problems		✓	
	Increased blood sugar: frequent urination, thirst and hunger		✓	
	Low blood sugar: symptoms of dizziness, lack of energy, drowsiness		✓	

This is not a complete list of side effects. For any unexpected effects while taking LUVOX, contact your doctor or pharmacist.

HOW TO STORE IT

Store in a dry place at temperatures between 15 – 25ºC. Protect from light. Keep LUVOX out of reach and sight of children. Keep container tightly closed. If your doctor tells you to stop taking LUVOX, please return any leftover medicine to your pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

http://www.hc-sc.gc.ca (Drug Product Database) or at www.abbott.ca or by contacting the sponsor, Abbott Laboratories, Limited at: 1-800-699-9948

This leaflet was prepared by Abbott Laboratories, Limited.

Last revised: March 6, 2013