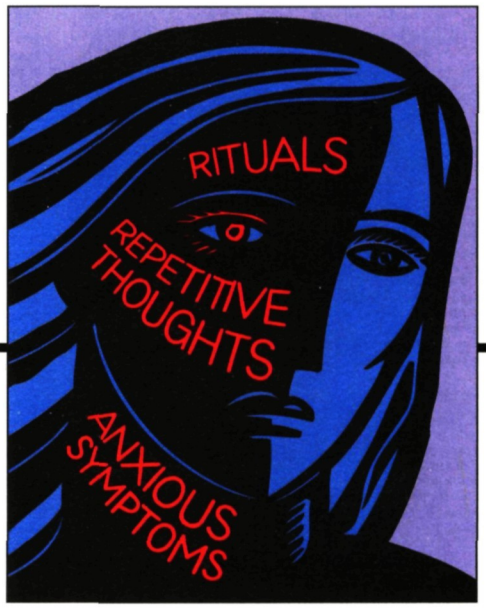
LUVOX®

fluvoxamine maleate 50mg & 100mg SCORED TABLETS



ESTABLISHED THERAPY FOR OBSESSIONS AND COMPULSIONS

- A selective serotonin reuptake inhibitor with a distinctive clinical profile
- Proven effective in controlling obsessive and compulsive symptoms
- Distinctive side effect, safety, and pharmacokinetic profiles

Pharmacia & Upjohn

Solvay Pharmaceuticals

1ED 4/96

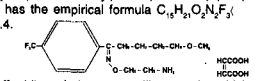
LUVOX™
fluvoxamine maleate

4E1252 Rev 9/95

DESCRIPTION

Fluvoxamine maleate is a selective serotonin (5-HT) reuptake inhibitor (SSRI) belonging to a new chemical series, the 2-aminoethyl oxime ethers of aralkylketones. It is chemically unrelated to other SSRIs and clomipramine. It is chemically designated as 5-methoxy-4'-(trifluoromethyl)valerophenone-(E)-O-(2-aminoethyl)oxime maleate (1:1) and has the empirical formula $C_{15}H_{21}O_2N_2F_3 \cdot C_4H_4O_4$. Its molecular weight is 434.4.

The structural formula is:



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

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

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of fluvoxamine maleate in Obsessive Compulsive Disorder is presumed to be linked to its specific serotonin reuptake inhibition in brain neurons. In preclinical studies, it was found that fluvoxamine inhibited neuronal uptake of serotonin.

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

Pharmacokinetics

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

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

Distribution/Protein Binding: The mean apparent volume of distribution for fluvoxamine is approximately 25 L/kg, suggesting extensive tissue distribution. Approximately 80% of fluvoxamine is bound to plasma protein, mostly albumin, over a concentration range of 20 to 2000 ng/mL.

Metabolism: Fluvoxamine maleate is extensively metabolized by the liver; the main metabolic routes are oxidative demethylation and deamination. Nine metabolites were identified following a 5 mg radiolabelled dose of fluvoxamine maleate, constituting approximately 85% of the urinary excretion products of fluvoxamine. The main human metabolite was fluvoxamine acid which, together with its N-acetylated analog, accounted for about 60% of the urinary excretion products. A third metabolite, fluvoxethanol, formed by oxidative deamination, accounted for about 10%. Fluvoxamine acid and fluvoxethanol were tested in an *in vitro* assay of serotonin and norepinephrine reuptake inhibition in rats; they were inactive except for a weak effect of the former metabolite on inhibition of serotonin uptake (1-2 orders of magnitude less potent than the parent compound). Approximately 2% of fluvoxamine was excreted in urine unchanged. (See PRECAUTIONS - Drug Interactions)

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

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

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

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

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

Clinical Trials

The effectiveness of LUVOX Tablets for the treatment of Obsessive Compulsive Disorder (OCD) was demonstrated in two 10-week multicenter, parallel group studies of adult outpatients. Patients in these trials were titrated to a total daily fluvoxamine maleate dose of 150 mg/day over the first two weeks of the trial, following which the dose was adjusted within a range of 100-300 mg/day (on a bid schedule), on the basis of response and tolerance. Patients in these studies had moderate to severe OCD (DSM-III-R), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), total score of 23. Patients receiving fluvoxamine maleate experienced mean reductions of approximately 4 to 5 units on the Y-BOCS total score, compared to a 2 unit reduction for placebo patients.

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

OUTCOME CLASSIFICATION (%) ON CGI-GLOBAL IMPROVEMENT ITEM FOR COMPLETERS IN POOL OF TWO OCD STUDIES

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

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

INDICATIONS AND USAGE

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

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

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

The effectiveness of LUVOX Tablets for long-term use, i.e., for more than 10 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use LUVOX Tablets for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient. (See DOSAGE AND ADMINISTRATION)

CONTRAINDICATIONS

Co-administration of terfenadine, astemizole, or cisapride with LUVOX Tablets is contraindicated (see WARNINGS and PRECAUTIONS).

LUVOX Tablets are contraindicated in patients with a history of hypersensitivity to fluvoxamine maleate.

WARNINGS

Potential for Interaction with Monoamine Oxidase Inhibitors

In patients receiving another serotonin reuptake inhibitor drug in combination with monoamine oxidase inhibitors (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have discontinued that drug and have been started on a MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, it is recommended that LUVOX Tablets not be used in combination with a MAOI, or within 14 days of discontinuing treatment with a MAOI. After stopping LUVOX Tablets, at least 2 weeks should be allowed before starting a MAOI.

Potential Terfenadine, Astemizole, and Cisapride Interactions

Terfenadine, astemizole, and cisapride are all metabolized by the cytochrome P450IIIA4 isozyme, and it has been demonstrated that ketoconazole, a potent inhibitor of IIIA4, blocks the metabolism of these drugs, resulting in increased plasma concentrations of parent drug. Increased plasma concentrations of terfenadine, astemizole, and cisapride cause QT prolongation and have been associated with torsades de pointes-type ventricular tachycardia, sometimes fatal. As noted below, a substantial pharmacokinetic interaction has been observed for fluvoxamine in combination with alprazolam, a drug that is known to be metabolized by the IIIA4 isozyme. Although it has not been definitively demonstrated that fluvoxamine is a potent IIIA4 inhibitor, it is likely to be, given the substantial interaction of fluvoxamine with alprazolam. Consequently, it is recommended that fluvoxamine not be used in combination with either terfenadine, astemizole, or cisapride (see CONTRAINDICATIONS and PRECAUTIONS).

Other Potentially Important Drug Interactions

(Also see PRECAUTIONS - Drug Interactions)

Benzodiazepines: Benzodiazepines metabolized by hepatic oxidation (e.g., alprazolam, midazolam, triazolam, etc.) should be used with caution because the clearance of these drugs is likely to be reduced by fluvoxamine. The clearance of benzodiazepines metabolized by glucuronidation (e.g., lorazepam, oxazepam, temazepam) is unlikely to be affected by fluvoxamine.

Alprazolam - When fluvoxamine maleate (100 mg qd) and alprazolam (1 mg qid) were co-administered to steady state, plasma concentrations and other pharmacokinetic parameters (AUC, C_{max}, T.) of alprazolam were approximately *twice those observed when alprazolam was administered alone; oral clearance* was reduced by about 50%. The elevated plasma alprazolam concentrations resulted in decreased psychomotor performance and memory. This interaction, which has not been investigated using higher doses of fluvoxamine, may be more pronounced if a 300 mg daily dose is co-administered, particularly since fluvoxamine exhibits non-linear pharmacokinetics over the dosage range 100-300 mg. If alprazolam is co-administered with LUVOX Tablets, the initial alprazolam dosage should be at least halved and titration to the lowest effective dose is recommended. No dosage adjustment is required for LUVOX Tablets.

Diazepam - The co-administration of LUVOX Tablets and diazepam is generally not advisable. Because fluvoxamine reduces the clearance of both diazepam and its active metabolite, N-desmethyldiazepam, there is a strong likelihood of substantial accumulation of both species during chronic co-administration. Evidence supporting the conclusion that it is inadvisable to co-administer fluvoxamine and diazepam is derived from a study in which healthy volunteers taking 150 mg/day of fluvoxamine were administered a single oral dose of 10 mg of diazepam. In these subjects (N=8), the clearance of diazepam was reduced by 65% and that of N-desmethyldiazepam to a level that was too low to measure over the course of the 2 week long study.

It is likely that this experience significantly underestimates the degree of accumulation that might occur with repeated diazepam administration. Moreover, as noted with alprazolam, the effect of fluvoxamine may even be more pronounced when it is administered at higher doses.

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

Theophylline: The effect of steady-state fluvoxamine (50 mg bid) on the pharmacokinetics of a single dose of theophylline (375 mg as 442 mg aminophylline) was evaluated in 12 healthy non-smoking, male volunteers. The clearance of theophylline was decreased approximately 3-fold. Therefore, if *theophylline is co-administered with fluvoxamine maleate, its dose should be* reduced to one third of the usual daily maintenance dose and plasma concentrations of theophylline should be monitored. No dosage adjustment is required for LUVOX Tablets.

Warfarin: When fluvoxamine maleate (50 mg tid) was administered concomitantly with warfarin for two weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Thus patients receiving oral anticoagulants and LUVOX Tablets should have their prothrombin time monitored and their anticoagulant dose adjusted accordingly. No dosage adjustment is required for LUVOX Tablets.

PRECAUTIONS

General

Activation of Mania/Hypomania: During premarketing studies involving primarily depressed patients, hypomania or mania occurred in approximately 1% of patients treated with fluvoxamine. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. As with all antidepressants, LUVOX Tablets should be used cautiously in patients with a history of mania.

Seizures: During premarketing studies, seizures were reported in 0.2% of fluvoxamine-treated patients. LUVOX Tablets should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Suicide: The possibility of a suicide attempt is inherent in patients with depressive symptoms, whether these occur in primary depression or in association with another primary disorder such as OCD. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for LUVOX Tablets should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness: Closely monitored clinical experience with LUVOX Tablets in patients with concomitant systemic illness is limited. Caution is advised in administering LUVOX Tablets to patients with diseases or conditions that could affect hemodynamic responses or metabolism. LUVOX Tablets have not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from many clinical studies during the product's premarketing testing. Evaluation of the electrocardiograms for patients with depression or OCD who participated in premarketing studies revealed no differences between fluvoxamine and placebo in the emergence of clinically important ECG changes.

In patients with liver dysfunction, fluvoxamine clearance was decreased by approximately 30%. LUVOX Tablets should be slowly titrated in patients with liver dysfunction during the initiation of treatment.

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe LUVOX Tablets:

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

Pregnancy: Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy with LUVOX Tablets.

Nursing: Patients receiving LUVOX Tablets should be advised to notify their physicians if they are breast feeding an infant. (See PRECAUTIONS - Nursing Mothers)

Concomitant Medication: Patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for clinically important interactions with LUVOX Tablets.

Alcohol: As with other psychotropic medications, patients should be advised to avoid alcohol while taking LUVOX Tablets.

Allergic Reactions: Patients should be advised to notify their physicians if they develop a rash, hives, or a related allergic phenomenon during therapy with LUVOX Tablets.

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

Potential Interactions with Drugs that Inhibit or are Metabolized by Cytochrome P450 Isozymes: Multiple hepatic cytochrome P450 (CYP450) enzymes are involved in the oxidative biotransformation of a large number of structurally different drugs and endogenous compounds. The available knowledge concerning the relationship of fluvoxamine and the CYP450 enzyme system has been obtained mostly from pharmacokinetic interaction studies conducted in healthy volunteers, but some preliminary *in vitro* data are also available. Based on a finding of substantial interactions of fluvoxamine with certain of these drugs (see later parts of this section and also WARNINGS for details) and limited *in vitro* data for the IIIA4 isozyme, it appears that fluvoxamine inhibits the following isozymes that are known to be involved in the metabolism of the listed drugs:

IA2	IIC9	IIIA4
Warfarin	Warfarin	Alprazolam
Theophylline		
Propranolol		

In vitro data suggest that fluvoxamine is a relatively weak inhibitor of the IID6 isozyme.

None of the drugs studied for drug interactions significantly affected the pharmacokinetics of fluvoxamine. However, the metabolism of fluvoxamine has not been fully characterized and the effects of potent inhibitors of IID6, such as quinidine, or of IIIA4 such as ketoconazole, on fluvoxamine metabolism have not been studied.

A clinically significant fluvoxamine interaction is possible with drugs having a narrow therapeutic ratio such as terfenadine, astemizole, or cisapride, warfarin, theophylline, certain benzodiazepines and phenytoin. If LUVOX Tablets are to be administered together with a drug that is eliminated via oxidative metabolism and has a narrow therapeutic window, plasma levels and/or pharmacodynamic effects of the latter drug should be monitored closely, at least until steady-state conditions are reached (See CONTRAINDICATIONS and WARNINGS).

CNS Active Drugs:

Monoamine Oxidase Inhibitors: See WARNINGS

Alprazolam: See WARNINGS

Diazepam: See WARNINGS

Lorazepam: A study of multiple doses of fluvoxamine maleate (50 mg bid) in healthy male volunteers (N=12) and a single dose of lorazepam (4 mg single dose) indicated no significant pharmacokinetic interaction. On average, both lorazepam alone and lorazepam with fluvoxamine produced substantial decrements in cognitive functioning; however, the co-administration of fluvoxamine and lorazepam did not produce larger mean decrements compared to lorazepam alone.

Lithium: As with other serotonergic drugs, lithium may enhance the serotonergic effects of fluvoxamine and, therefore, the combination should be used with caution. Seizures have been reported with the co-administration of fluvoxamine maleate and lithium.

Tryptophan: Tryptophan may enhance the serotonergic effects of fluvoxamine, and the combination should, therefore, be used with caution. Severe vomiting has been reported with the co-administration of fluvoxamine maleate and tryptophan.

Clozapine: Elevated serum levels of clozapine have been reported in patients taking fluvoxamine maleate and clozapine. Since clozapine related seizures and orthostatic hypotension appear to be dose related, the risk of these adverse events may be higher when fluvoxamine and clozapine are co-administered. Patients should be closely monitored when fluvoxamine maleate and clozapine are used concurrently.

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

Tricyclic Antidepressants (TCAs): Significantly increased plasma TCA levels have been reported with the co-administration of fluvoxamine maleate and amitriptyline, clomipramine or imipramine. Caution is indicated with the co-administration of LUVOX Tablets and TCAs.

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

Methadone: Significantly increased methadone (plasma level:dose) ratios have been reported when fluvoxamine maleate was administered to patients receiving maintenance methadone treatment, with symptoms of opioid intoxication in one patient. Opioid withdrawal symptoms were reported following fluvoxamine maleate discontinuation in another patient.

Other Drugs:

Theophylline: See WARNINGS

Propranolol and Other Beta-Blockers: Co-administration of fluvoxamine maleate 100 mg per day and propranolol 160 mg per day in normal volunteers resulted in a mean five-fold increase (range 2 to 17) in minimum propranolol plasma concentrations. In this study, there was a slight potentiation of the propranolol-induced reduction in heart rate and reduction in the exercise diastolic pressure. One case of bradycardia and hypotension and a second case of orthostatic hypotension have been reported with the co-administration of fluvoxamine and metoprolol.

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

Co-administration of fluvoxamine maleate 100 mg per day with atenolol 100 mg per day (N=6) did not affect the plasma concentrations of atenolol. Unlike propranolol and metoprolol which undergo hepatic metabolism, atenolol is eliminated primarily by renal excretion.

Warfarin: See WARNINGS

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

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

Effects of Smoking on Fluvoxamine Metabolism: Smokers had a 25% increase in the metabolism of fluvoxamine compared to nonsmokers.

Electroconvulsive Therapy (ECT): There are no clinical studies establishing the benefits or risks of combined use of ECT and fluvoxamine maleate.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: There is no evidence of carcinogenicity, mutagenicity or impairment of fertility with fluvoxamine maleate.

There was no evidence of carcinogenicity in rats treated orally with fluvoxamine maleate for 30 months or hamsters treated orally with fluvoxamine maleate for 20 (females) or 26 (males) months. The daily doses in the high dose groups in these studies were increased over the course of the study from a minimum of 160 mg/kg to a maximum of 240 mg/kg in rats, and from a minimum of 135 mg/kg to a maximum of 240 mg/kg in hamsters. The maximum dose of 240 mg/kg is approximately 6 times the maximum human daily dose on a mg/m^2 basis.

Mutagenesis: No evidence of mutagenic potential was observed in a mouse micronucleus test, an *in vitro* chromosome aberration test, or the Ames microbial mutagen test with or without metabolic activation.

Impairment of Fertility: In fertility studies of male and female rats, up to 80

mg/kg/day orally of fluvoxamine maleate, (approximately 2 times the maximum human daily dose on a mg/m² basis) had no effect on mating performance, *duration of gestation, or pregnancy rate.*

Pregnancy

Teratogenic Effects - Pregnancy Category C: In teratology studies in rats and rabbits, daily oral doses of fluvoxamine maleate of up to 80 and 40 mg/kg, respectively (approximately 2 times the maximum human daily dose on a mg/m² *basis) caused no fetal malformations. However, in other reproduction studies in* which pregnant rats were dosed through weaning there was (1) an increase in pup mortality at birth (seen at 80 mg/kg and above but not at 20 mg/kg), and (2) decreases in postnatal pup weights (seen at 160 but not at 80 mg/kg) and survival (seen at all doses; lowest dose tested = 5 mg/kg). (Doses of 5, 20, 80, *and 160 mg/kg are approximately 0.1, 0.5, 2, and 4 times the maximum human* daily dose on a mg/m² basis.) While the results of a cross-fostering study implied that at least some of these results likely occurred secondarily to maternal toxicity, the role of a direct drug effect on the fetuses or pups could not be ruled out. There are no adequate and well-controlled studies in pregnant *women. Fluvoxamine maleate should be used during pregnancy only if the* potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of fluvoxamine on labor and delivery in humans is unknown.

Nursing Mothers

As for many other drugs, fluvoxamine is secreted in human breast milk. The decision of whether to discontinue nursing or to discontinue the drug should take into account the potential for serious adverse effects from exposure to fluvoxamine in the nursing infant as well as the potential benefits of LUVOX™ (fluvoxamine maleate) Tablets therapy to the mother.

Pediatric Use

Safety and effectiveness of LUVOX Tablets in individuals below 18 years of age have not been established.

Geriatric Use

Approximately 230 patients participating in controlled premarketing studies with LUVOX Tablets were 65 years of age or over. No overall differences in safety were observed between these patients and younger patients. Other reported clinical experience has not identified differences in response between the elderly and younger patients. However, the clearance of fluvoxamine is decreased by about 50% in elderly compared to younger patients (see *Pharmacokinetics* under CLINICAL PHARMACOLOGY), and greater sensitivity of some older individuals also cannot be ruled out. Consequently, LUVOX Tablets should be slowly titrated during initiation of therapy.

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Of the 1087 OCD and depressed patients treated with fluvoxamine maleate in controlled clinical trials conducted in North America, 22% discontinued treatment due to an adverse event. The most common events (⊕1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate at least twice that of placebo) included:

Table 1: ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATION OF TREATMENT IN OCD AND DEPRESSION POPULATIONS

BODY SYSTEM/ ADVERSE EVENT	PERCENTAGE OF PATIENTS FLUVOXAMINE	PLACEBO
BODY AS A WHOLE		
Headache	3%	1%
Asthenia	2%	<1%
Abdominal Pain	1%	0%
DIGESTIVE		
Nausea	9%	1%
Diarrhea	1%	<1%
Vomiting	2%	<1%
Anorexia	1%	<1%
Dyspepsia	1%	<1%
NERVOUS SYSTEM		
Insomnia	4%	1%
Somnolence	4%	<1%
Nervousness	2%	<1%
Agitation	2%	<1%
Dizziness	2%	<1%
Anxiety	1%	<1%
Dry Mouth	1%	<1%

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials: LUVOX Tablets have been studied in controlled trials of OCD (N=320) and *depression (N=1350). In general, adverse event rates were similar in the two* data sets. The most commonly observed adverse events associated with the use of LUVOX Tablets and likely to be drug-related (incidence of 5% or greater and at least twice that for placebo) derived from Table 2 were: *somnolence, insomnia, nervousness, tremor, nausea, dyspepsia, anorexia, vomiting, abnormal ejaculation, asthenia, and sweating. In a pool of two studies involving* only patients with OCD, the following additional events were identified using the above rule: *dry mouth, decreased libido, urinary frequency, anorgasmia, rhinitis and taste perversion.*

Adverse Events Occurring at an Incidence of 1%: Table 2 enumerates *adverse events that occurred at a frequency of 1% or more, and were more* frequent than in the placebo group, among patients treated with LUVOX Tablets in two short-term placebo controlled OCD trials (10 week) and depression trials (6 week) in which patients were dosed in a range of generally 100 to 300 mg/day. This table shows the percentage of patients in each group who had at *least one occurrence of an event at some time during their treatment.* Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

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

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

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

Vital Sign Changes

Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression trials on (1) median change from baseline on various vital signs variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various vital signs variables revealed no important differences between fluvoxamine maleate and placebo.

Laboratory Changes

Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression trials on (1) median change from baseline on various serum chemistry, hematology, and urinalysis variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various serum chemistry, hematology, and urinalysis variables revealed no important differences between fluvoxamine maleate and placebo.

ECG Changes

Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression trials on (1) mean change from baseline on various ECG variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various ECG variables revealed *no important differences between fluvoxamine maleate and placebo.*

Table 2: TREATMENT-EMERGENT ADVERSE EVENT INCIDENCE RATES BY BODY SYSTEM IN OCD AND DEPRESSION POPULATIONS COMBINED[1]

BODY SYSTEM/ ADVERSE EVENT	Percentage of Patients Reporting Event FLUVOXAMINE N = 892	PLACEBO N = 778
BODY AS WHOLE		
Headache	22	20
Asthenia	14	6
Flu Syndrome	3	2
Chills	2	1
CARDIOVASCULAR		
Palpitations	3	2
DIGESTIVE SYSTEM		
Nausea	40	14
Diarrhea	11	7
Constipation	10	8
Dyspepsia	10	5
Anorexia	6	2
Vomiting	5	2
Flatulence	4	3
Tooth Disorder[2]	3	1
Dysphagia	2	1
NERVOUS SYSTEM		
Somnolence	22	8
Insomnia	21	10
Dry Mouth	14	10
Nervousness	12	5
Dizziness	11	6
Tremor	5	1
Anxiety	5	3
Vasodilatation[3]	3	1
Hypertonia	2	1
Agitation	2	1
Decreased Libido	2	1
Depression	2	1
CNS Stimulation	2	1
RESPIRATORY SYSTEM		
Upper Respiratory Infection	9	5
Dyspnea	2	1
Yawn	2	0
SKIN		
Sweating	7	3
SPECIAL SENSES		
Taste Perversion	3	1
Amblyopia[4]	3	2
UROGENITAL		
Abnormal Ejaculation[5,6]	8	1
Urinary Frequency	3	2
Impotence[6]	2	1
Anorgasmia	2	0
Urinary Retention	1	0

[1] Events for which fluvoxamine maleate incidence was equal to or less than placebo are not listed in the table above, but include the following: abdominal pain, abnormal dreams, appetite increase, back pain, chest pain, confusion, dysmenorrhea, fever, infection, leg cramps, migraine, myalgia, pain, paresthesia, pharyngitis, postural hypotension, pruritus, rash, rhinitis, thirst and tinnitus.

[2] Includes "toothache," "tooth extraction and abscess," and "caries."

[3] Mostly feeling warm, hot, or flushed.

[4] Mostly "blurred vision."

[5] Mostly "delayed ejaculation."

[6] Incidence based on number of male patients.

Other Events Observed During the Premarketing Evaluation of LUVOX Tablets

During premarketing clinical trials conducted in North America and Europe, multiple doses of fluvoxamine maleate were administered for a combined total of 2737 patient exposures in patients suffering OCD or Major Depressive Disorder. Untoward events associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing.

Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a limited (i.e., reduced) number of standard event categories.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[1] *Based on the number of females.*

[2] Based on the number of males.

Non-US Postmarketing Reports

Voluntary reports of adverse events in patients taking LUVOX Tablets that have been received since market introduction and are of unknown causal relationship *to LUVOX Tablets use include: toxic epidermal necrolysis, Stevens-Johnson* syndrome, Henoch-Schoenlein purpura, bullous eruption, priapism, agranulocytosis, neuropathy, aplastic anemia, anaphylactic reaction, hyponatremia, acute renal failure, and severe akinesia with fever when fluvoxamine was co-administered with antipsychotic medication.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

LUVOX Tablets are not controlled substances.

Physical and Psychological Dependence

The potential for abuse, tolerance and physical dependence with fluvoxamine *maleate has been studied in a nonhuman primate model.* No evidence of dependency phenomena was found. The discontinuation effects of LUVOX Tablets were not systematically evaluated in controlled clinical trials. LUVOX Tablets were not systematically studied in clinical trials for potential for abuse, but there was no indication of drug-seeking behavior in clinical trials. It should be noted, however, that patients at risk for drug dependency were systematically excluded from investigational studies of fluvoxamine maleate. Generally, it is not possible to predict on the basis of preclinical or premarketing clinical experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of fluvoxamine maleate misuse or abuse (i.e., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

Worldwide exposure to fluvoxamine maleate includes over 37,000 patients treated in clinical trials and an estimated exposure of 4,500,000 patients treated during foreign marketing experience (circa 1992). Of the 354 cases of deliberate or accidental overdose involving fluvoxamine maleate reported from this population, there were 19 deaths. Of the 19 deaths, 2 were in patients taking fluvoxamine maleate alone and the remaining 17 were in patients taking fluvoxamine maleate along with other drugs. In the remaining 335 patients, 309 had complete recovery after gastric lavage or symptomatic treatment. One patient had persistent mydriasis after the event, and a second patient had a bowel infarction requiring a hemicolectomy. In the remaining 24 patients the outcome was unknown. The highest reported overdose of fluvoxamine maleate involved a non-lethal ingestion of 10,000 mg (equivalent of 1-3 months' dosage). The patient fully recovered with no sequelae.

Commonly observed adverse events associated with fluvoxamine maleate overdose included drowsiness, vomiting, diarrhea, and dizziness. Other notable signs and symptoms seen with fluvoxamine maleate overdose (single or mixed drugs) included coma, tachycardia, bradycardia, hypotension, ECG abnormalities, liver function abnormalities, convulsions, and symptoms such as aspiration pneumonitis, respiratory difficulties or hypokalemia that may occur secondary to loss of consciousness or vomiting.

Management of Overdose

1. An unobstructed airway should be established with maintenance of respiration as required. Vital signs and ECG should be monitored.
2. Administration of activated charcoal may be as effective as emesis or lavage and should be considered in treating overdose. Since absorption with overdose may be delayed, measures to minimize absorption may be necessary for up to 24 hours post-ingestion.
3. Maintain close observation as clinically indicated.
4. There are no specific antidotes for LUVOX Tablets.
5. In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdosage.
6. Dialysis is not believed to be beneficial.

DOSAGE AND ADMINISTRATION

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

Dosage for Elderly or Hepatically Impaired Patients

Elderly patients and those with hepatic impairment have been observed to have a decreased clearance of fluvoxamine maleate. Consequently, it may be appropriate to modify the initial dose and the subsequent dose titration for these patient groups.

Maintenance/Continuation Extended Treatment

Although the efficacy of LUVOX Tablets beyond 10 weeks of dosing for OCD has not been documented in controlled trials, OCD is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

HOW SUPPLIED

Tablets 50 mg: scored, yellow, elliptical, film-coated (debossed "SOLVAY" and "4205" on one side and scored on the other)

Bottles of 100 ..... NDC 0032-4205-01
Bottles of 1000 ..... NDC 0032-4205-10
Unit dose pack of 100 ..... NDC 0032-4205-11

Tablets 100 mg: scored, beige, elliptical, film-coated (debossed "SOLVAY" and "4210" on one side and scored on the other)

Bottles of 100 ..... NDC 0032-4210-01
Bottles of 1000 ..... NDC 0032-4210-10
Unit dose pack of 100 ..... NDC 0032-4210-11

LUVOX Tablets should be protected from high humidity and stored at controlled room temperature, 15°-30° C (59°-86° F).

Dispense in tight containers.

CAUTION: Federal law prohibits dispensing without prescription.

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