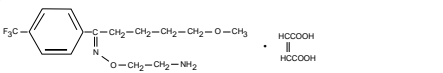




FLUVOXAMINE MALEATE TABLETS Rx only

DESCRIPTION Fluvoxamine maleate is a selective serotonin (5-HT) reuptake inhibitor (SSRI) belonging to a new chemical series, the 2-aminoethoxy oxime ethers of trifluoromethoxy...



C15H21O2N2F3C4H4O4 M.W. 434.4

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.

FLUVOXAMINE MALEATE TABLETS Each tablet contains the following inactive ingredients: hydroxypropyl methylcellulose, mannitol, microcrystalline cellulose, pregelatinized starch, polyethylene glycol, polysorbate 80, sodium starch glycolate, sodium stearyl fumarate 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.

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

Elimination Following a 14C-labelled oral dose of fluvoxamine maleate (5 mg), an average of 94% of drug-related products was recovered in the urine within 21 hours.

Metabolism Fluvoxamine maleate is extensively metabolized by the liver; the main metabolic routes are oxidative demethylation and deamination.

Hepatic and Renal Disease A cross study comparing healthy subjects vs. patients with hepatic dysfunction suggested a 30% decrease in fluvoxamine clearance in association with hepatic dysfunction.

Adult OCD Studies The effectiveness of fluvoxamine maleate tablets for the treatment of Obsessive Compulsive Disorder (OCD) was demonstrated in two 10-week multicenter, parallel group studies of adult outpatients.

Pediatric OCD Study The effectiveness of fluvoxamine maleate tablets for the treatment of OCD was also demonstrated in a 10-week multicenter, parallel group study in a pediatric outpatient population (children and adolescents, ages 8-17).

Outcome Classification (%) on CGI-Global Improvement Item for Completers in Trial of Two Adult OCD Studies

Table with 3 columns: Outcome Classification, Fluvoxamine (N=120), Placebo (N=134)

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

Pediatric OCD Study The effectiveness of fluvoxamine maleate tablets for the treatment of OCD was also demonstrated in a 10-week multicenter, parallel group study in a pediatric outpatient population (children and adolescents, ages 8-17).

Outcome Classification (%) on CGI-Global Improvement Item for Completers in Pediatric Study

Table with 3 columns: Outcome Classification, Fluvoxamine (N=38), Placebo (N=38)

Post hoc exploratory analyses for gender effects on outcomes did not suggest any differential responsiveness on the basis of gender.

INDICATIONS AND USAGE Fluvoxamine Maleate Tablets are indicated for the treatment of obsessions and compulsions in patients with Obsessive Compulsive Disorder (OCD), as defined in the DSM-III-R.

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.

CONTRAINDICATIONS Co-administration of chlorazepate, terfenadine, astemizole, cisapride, or pimozide with fluvoxamine maleate tablets is contraindicated (see WARNINGS and PRECAUTIONS).

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, rhabdomyolysis, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma.

Potential Interaction with Thioridazine The effect of fluvoxamine (25 mg bid for one week) on thioridazine steady-state concentrations was evaluated in 10 male inpatients with schizophrenia.

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.

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, Cmax, T1/2) of alprazolam were approximately twice those observed when alprazolam was administered alone.

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.

Atenolol Co-administration of fluvoxamine maleate 100 mg per day and atenolol 100 mg per day did not affect the plasma concentrations of atenolol. Unlike propranolol and metoprolol which undergo hepatic metabolism, atenolol is eliminated

Diagnosis The co-administration of fluvoxamine maleate tablets and diazepam is generally not advisable. Because fluvoxamine reduces the clearance of both diazepam and its active metabolite, desmethyldiazepam, there is a strong likelihood of substantial accumulation of both species during chronic co-administration.

Mexiletine The effect of steady state fluvoxamine (50 mg BID for 7 days) on the single dose pharmacokinetics of mexiletine (200 mg) was evaluated in 6 healthy Japanese males.

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.

Warfarin When fluvoxamine maleate (50 mg tid) was administered concomitantly with warfarin for two weeks, warfarin plasma concentrations increased 38% and prothrombin times were prolonged.

Activation of Mania/Hypomania During premarketing studies involving primarily depressed patients, hypomania or mania occurred in approximately 1% of patients treated with fluvoxamine.

Seizures During premarketing studies, seizures were reported in 0.2% of fluvoxamine-treated patients.

Hyponatremia Cases of hyponatremia have been reported. In cases where the outcome was known, the hyponatremia appeared to be reversible when fluvoxamine was discontinued.

Use in Patients with Concomitant Illnesses Fluvoxamine maleate tablets have not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease.

Interference with Cognitive or Motor Performance Since fluvoxamine maleate is a psychoactive drug, it may impair judgement, thinking, or motor skills.

Pregnancy Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy with fluvoxamine maleate tablets.

Nursing Patients receiving fluvoxamine maleate tablets should be advised to notify their physicians if they are breast feeding an infant.

Alcohol As with other psychotropic medications, patients should be advised to avoid alcohol while taking fluvoxamine maleate tablets.

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.

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FLUVOXAMINE MALEATE TABLETS



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primarily by renal excretion.  
**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<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> basis.) While the results of a cross-fostering study indicate that some of these results likely occurred secondary to maternal toxicity, the role of 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 fluvoxamine to the mother.

**Pediatric Use**  
 The efficacy of fluvoxamine maleate for the treatment of Obsessive Compulsive Disorder was demonstrated in a 10-week multicenter placebo controlled study with 120 outpatients ages 7-17. The adverse event profile observed in this study was generally similar to that observed in adult studies with fluvoxamine (see **ADVERSE REACTIONS AND DOSAGE AND ADMINISTRATION**).

Decreased appetite and weight loss have been observed in association with the use of fluvoxamine as well as other SSRIs. Consequently, regular monitoring of weight and growth is recommended if treatment of a child with an SSRI is to be continued long term.

The risks, if any, that may be associated with fluvoxamine's extended use in children and adolescents with OCD have not been systematically assessed. The prescriber should be mindful that the evidence relied upon to conclude that fluvoxamine is safe for use in children and adolescents derives from relatively short term clinical studies and from extrapolation of experience gained with adult patients. In particular, there are no studies that directly evaluate the effects of long term fluvoxamine use on the growth, development, and maturation of children and adolescents. Although there is no affirmative finding to suggest that fluvoxamine possesses a capacity to adversely affect growth, development or maturation, the absence of findings is not compelling evidence of the absence of the potential of fluvoxamine to have adverse effects in chronic use.

**Geriatric Use**  
 Approximately 230 patients participating in controlled premarketing studies with fluvoxamine maleate 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, fluvoxamine has been associated with several cases of clinically significant hyponatremia in elderly patients (see **PRECAUTIONS, General**). Furthermore, the clearance of fluvoxamine is decreased by about 50% in elderly compared to younger patients (see **Pharmacokinetics under CLINICAL PHARMACOLOGY**), and greater sensitivity of some older individuals also cannot be ruled out. Consequently, fluvoxamine maleate 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:

Body System/ Adverse Event	Percentage Of Patients	
	Fluvoxamine	Placebo
<b>Body As A Whole</b>		
Headache	3%	1%
Asthenia	2%	<1%
Abdominal Pain	1%	0%
<b>Digestive</b>		
Nausea	9%	1%
Diarrhea	1%	<1%
Vomiting	2%	<1%
Anorexia	1%	<1%
Dyspepsia	1%	<1%
<b>Nervous System</b>		
Somnolence	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**  
 Fluvoxamine maleate 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 as well as in the pediatric OCD study. The most commonly observed adverse events associated with the use of fluvoxamine maleate tablets and likely to be drug-related (incidence of 4% or greater or 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, urticaria, pruritus, anorexia, rhinitis and taste perversion*. In a study of pediatric patients with OCD, the following additional events were identified using the above rule: *agitation, depression, dysmenorrhea, fatigue, hyperkinesia, and rash*.

**Adverse Events Occurring at an Incidence of 1% or More**  
 Table 2 enumerates adverse events that occurred in adults at a frequency of 1% or more, and were more frequent than in the placebo group, among patients treated with fluvoxamine maleate tablets in two short-term placebo controlled OCD trials (10 weeks) and depression trials (6 weeks) 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, or investigators. The cited rates, 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.

Body System/ Adverse Event	Percentage of Patients Reporting Event	
	Fluvoxamine N=892	Placebo N=778
<b>Body As A Whole</b>		
Headache	22	20
Asthenia	14	6
Flu syndrome	3	2
Chills	3	2
<b>Cardiovascular</b>		
Palpitations	2	2
<b>Digestive System</b>		
Nausea	40	14
Diarrhea	11	7
Constipation	10	2
Dyspepsia	10	5
Anorexia	6	2
Vomiting	4	3
Flatulence	4	3
Tooth disorder <sup>2</sup>	3	1
Dysphagia	3	1
<b>Nervous System</b>		
Somnolence	22	8
Insomnia	21	10
Dry mouth	14	10
Nervousness	15	5
Dizziness	11	6
Tremor	5	3
Anxiety	5	3
Vasodilation <sup>3</sup>	3	3
Hypertonia	2	1
Agitation	2	1
Decreased libido	2	1
Depression	2	1
CNS stimulation	2	1
<b>Respiratory System</b>		
Upper respiratory infection	9	5
Dyspnea	2	0
Rhinitis	2	0
<b>Skin</b>		
Sweating	7	3
<b>Special Senses</b>		
Taste perversion	3	1
Amblyopia <sup>4</sup>	3	2
<b>Urogenital</b>		
Abnormal ejaculation <sup>5,6</sup>	8	1
Urinary frequency	3	2
Impotence <sup>7</sup>	3	0
Anorgasmia	2	0
Urinary retention	1	0

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

<sup>2</sup>Includes "toothache," "tooth extraction and abscess," and "caries".

<sup>3</sup>Mostly feeling warm, hot, or flushed.

<sup>4</sup>Mostly "blurred vision".

<sup>5</sup>Mostly "delayed ejaculation".

<sup>6</sup>Incidence based on number of male patients.

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

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

**Other Adverse Events in OCD Pediatric Population**  
 In pediatric patients (N=57) treated with fluvoxamine maleate tablets, the overall profile of adverse events was generally similar to that seen in adult studies, as shown in Table 2. However, the following adverse events were not reported in Table 2, were reported in two or more of the pediatric patients and were more frequent with fluvoxamine maleate tablets than

with placebo: abnormal thinking, cough increase, dysmenorrhea, ecchymosis, emotional lability, epistaxis, hyperkinesia, infection, manic reaction, rash, sinusitis, and weight decrease.

**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) median change from baseline on various ECG variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various ECG variables revealed no important differences between fluvoxamine maleate and placebo.

**Other Events Observed During the Premarketing Evaluation of Fluvoxamine Maleate 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 excluded; and (3) events which occurred 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:** Myocardial infarction, stroke, 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:** Esophageal cancer, cholecystitis, cholelithiasis, fecal incontinence, hematemesis, intestinal obstruction, jaundice

**Endocrine System**  
**Frequent:** Hypothyroidism  
**Rare:** Goiter

**Hemic and Lymphatic Systems**  
**Infrequent:** Anemia, ecchymosis, leukocytosis, lymphadenopathy, thrombocytopenia  
**Rare:** Leukopenia

**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**  
**Frequent:** 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, hemiparesis, hostility, hyperreflexia, hyperreflexia, hyperreflexia, hyperreflexia, hyperreflexia, hyperreflexia, hyperreflexia, increased libido, neuralgia, paralysis, paranoid reaction, phobia, psychosis, sleep disorder, stupor, twitching, vertigo  
**Rare:** Akinesia, coma, fibrillations, mutism, obsessions, reflexes decreased, stirred speech, tardive dyskinesia, torticollis, tic, 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 dull, visual field defect  
**Rare:** Corneal ulcer, retinal detachment

**Urogenital System**  
**Infrequent:** Amenorrhea, breast pain, cystitis, delayed menstruation<sup>1</sup>, dysuria, female lactation<sup>1</sup>, hematuria, menopause<sup>1</sup>, menorrhagia<sup>1</sup>, metrorrhagia<sup>1</sup>, nocturia, polyuria, premenstrual syndrome<sup>1</sup>, urinary incontinence, urinary tract infection, urinary urgency, urination impaired, vaginal hemorrhage<sup>1</sup>, vaginitis<sup>1</sup>  
**Rare:** Kidney calculus, hematuria<sup>1</sup>, oliguria

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

**Premarketing Reports**  
 Voluntary reports of adverse events in patients taking fluvoxamine maleate tablets that have been received since market introduction and are of unknown causal relationship to fluvoxamine maleate tablets include: ventricular tachycardia (including torsades de pointes), epidermal necrolysis, Stevens-Johnson syndrome, Henoch-Schönlein purpura, bullous eruption, priapism, agranulocytosis, aplastic anemia, anaphylactic reaction, angioedema, vasculitis, hyponatremia, acute renal failure, hepatitis, pancreatitis, ileus, serotonin syndrome, neuropathy, laryngismus, and severe drug-induced allergic reactions. Fluvoxamine maleate was co-administered with antipsychotic medication.

**DRUG ABUSE AND DEPENDENCE**  
**Controlled Substance Class**  
 Fluvoxamine maleate 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 the discontinuity effects of fluvoxamine maleate tablets were not systematically evaluated in controlled clinical trials. Fluvoxamine maleate 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 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 be alert to patients with 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 45,000 patients treated in clinical trials and an estimated exposure of 23,000 to patients treated during worldwide marketing experience (circa 1998). Of the 462 cases of deliberate or accidental overdose involving fluvoxamine maleate reported from this population, there were 44 deaths. Of these, six were in patients taking fluvoxamine maleate alone and the remaining 38 were in patients taking fluvoxamine maleate along with other drugs. The largest known overdose cases, 372 patients had complete recovery; four patients experienced adverse sequelae of overdosage, to include persistent mydriasis, unsteady gait, kidney complications (from trauma associated with overdose), and bowel intarction requiring a hemicolectomy. In the remaining 41 patients, the outcome was unknown. The largest known overdose cases involving fluvoxamine maleate involved 12,000 mg (equivalent to 2 to 3 months dosage). The patient fully recovered. However, ingestions as low as 1,400 mg have been associated with lethal outcome, indicating considerable prognostic variability.

Commonly (≥5%) observed adverse events associated with fluvoxamine maleate overdose include coma, hypokalemia, hypotension, nausea, respiratory difficulties, somnolence, tachycardia and vomiting. Other notable signs and symptoms seen with fluvoxamine maleate overdose (single or multiple doses) include: bradycardia, ECG abnormalities (such as heart block, QT interval prolongation), first degree atrioventricular block, bundle branch block, and junctional rhythm, convulsions, tremor, diarrhea, and increased reflexes.

**Management of Overdose**  
 Treatment should consist of those general measures employed in the management of overdose with any antidepressant. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for fluvoxamine are known. A specific caution involves patients taking, or recently having taken, fluvoxamine who might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (see **Tricyclic Antidepressants (TCAs) under PRECAUTIONS**).

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified Poison Control Centers are listed in the Physicians' Desk Reference (PDR).

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

**Dosage for Pediatric Population (children and adolescents)**  
 The recommended starting dose for fluvoxamine maleate tablets in pediatric populations (ages 8-17 years) is 25 mg, administered as a single daily dose at bedtime. In a controlled clinical trial establishing the effectiveness of fluvoxamine maleate tablets in OCD, pediatric patients (ages 8-17) were titrated within a dose range of 50 to 200 mg/day. The dose should be increased in 25 mg increments every 4 to 7 days, as tolerated, until maximum therapeutic benefit is achieved. It is advisable that a total daily dose of more than 50 mg should be given in two divided doses. If the two divided doses are not equal, the larger dose should be given at bedtime.

**Dosage for Elderly or Hepatically Impaired Patients**  
 In elderly patients and in patients with hepatic impairment, there has 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 fluvoxamine maleate 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 of a responding patient. Dose adjustment should be made to maintain the patient on the lowest effective dose, and patients should be periodically reassessed to determine the need for continued treatment.

**HOW SUPPLIED**  
 Fluvoxamine maleate tablets are available as white, round, film-coated tablets, debossed "X" and "4399" on one side and plain on the other side containing 25 mg fluvoxamine maleate, packaged in bottles of 100 and 500 unit-dose boxes of 100 tablets.

Fluvoxamine maleate tablets are available as yellow, round, film-coated tablets, debossed "X" and "4391" on one side and scored on the other side containing 50 mg fluvoxamine maleate, packaged in bottles of 100, 500 and 1000 unit-dose boxes of 100 tablets.

Fluvoxamine maleate tablets are available as beige, round, film-coated tablets, debossed "X" and "4392" on one side and scored on the other side containing 100 mg fluvoxamine maleate, packaged in bottles of 100, 500 and 1000 unit-dose boxes of 100 tablets.

**PHARMACIST:** Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).  
**PROTECT FROM HIGH HUMIDITY**  
 Store at controlled room temperature 15° to 30°C (59° to 86°F) (See USP).

**MANUFACTURED BY**  
 JANSSEN-CILAG PHARMACEUTICALS, INC.  
 MIAMI, FL 33137

**FLUVOXAMINE MALEATE TABLETS**

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