FLUVOXAMINE MALEATE - fluvoxamine maleate tablet
Stat Rx USA

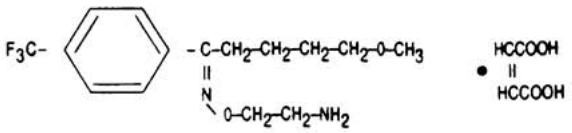
Insert

11. DESCRIPTION

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

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

The structural formula is:



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

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

12. CLINICAL PHARMACOLOGY12.1 Mechanism Of Action

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

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.
12.3 Pharmacokinetics

Absorption: 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: 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 **DRUG INTERACTIONS** [7].)

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 Fluvoxamine Maleate Tablets at 50 and 100 mg comparing elderly (ages 66-73) and young subjects (ages 19-35), mean maximum plasma concentrations in the elderly were 40% higher. The multiple dose elimination half-life of fluvoxamine was 17.4 and 25.9 hours in the elderly compared to 13.6 and 15.6 hours in the young subjects at steady state for 50 and 100 mg doses, respectively. In elderly patients, the clearance of fluvoxamine was reduced by about 50% and, therefore, Fluvoxamine Maleate Tablets should be slowly titrated during initiation of therapy. (See **DOSAGE AND ADMINISTRATION** [2.3].)

Pediatric Subjects: The multiple-dose pharmacokinetics of fluvoxamine were determined in male and female children (ages 6-11) and adolescents (ages 12-17). Steady-state plasma fluvoxamine concentrations were 2-3 fold higher in children than in adolescents. AUC and C_{max} in children were 1.5- to 2.7-fold higher than that in adolescents. (See Table 4.) As in adults, both children and adolescents exhibited nonlinear multiple-dose pharmacokinetics. Female children showed significantly higher AUC (0-12) and C_{max} compared to male children and, therefore, lower doses of Fluvoxamine Maleate Tablets may produce therapeutic benefit. (See Table 5.) No gender differences were observed in adolescents. Steady-state plasma fluvoxamine concentrations were similar in adults and adolescents at a dose of 300 mg/day, indicating that fluvoxamine exposure was similar in these two populations. (See Table 4.) Dose adjustment in adolescents (up to the adult maximum dose of 300 mg) may be indicated to achieve therapeutic benefit. (See **DOSAGE AND ADMINISTRATION** [2.2].)

Hepatic and Renal Disease: A cross study comparison (healthy subjects versus patients with hepatic dysfunction) suggested a 30% decrease in fluvoxamine clearance in association with hepatic dysfunction. The mean minimum plasma concentrations in renally impaired patients (creatinine clearance of 5 to 45 mL/min) after 4 and 6 weeks of treatment (50 mg b.i.d., N=13) were comparable to each other, suggesting no accumulation of fluvoxamine in these patients. (See **WARNINGS AND PRECAUTIONS** - ***Use in Patients with Concomitant Illness*** [5.13].)

1. INDICATIONS AND USAGE1.1 Obsessive-Compulsive Disorder

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

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 efficacy of Fluvoxamine Maleate Tablets was established in four trials in outpatients with OCD: two 10-week trials in adults, one 10-week trial in pediatric patients (ages 8-17), and one maintenance trial in adults. (See **CLINICAL STUDIES** [14].)

4. CONTRAINDICATIONS

Coadministration of tizanidine, thioridazine, alosetron, or pimozide with Fluvoxamine Maleate Tablets is contraindicated. (See **WARNINGS AND PRECAUTIONS** [5.3- 5.6].)

The use of MAOIs concomitantly with or within 14 days of treatment with Fluvoxamine Maleate Tablets is contraindicated. (See **WARNINGS AND PRECAUTIONS** [5.2].)

6. ADVERSE REACTIONS6.1 Adverse Reactions Leading to Treatment Discontinuation

Of the 1087 OCD and depressed patients treated with fluvoxamine maleate in controlled clinical trials in North America, 22% discontinued due to an adverse reaction. Adverse reactions that led to discontinuation in at least 2% of fluvoxamine maleate-treated patients in these trials were: nausea (9%), insomnia (4%), somnolence (4%), headache (3%), and asthenia, vomiting, nervousness, agitation, and dizziness (2% each).
6.2 Incidence in Controlled Trials

Commonly Observed Adverse Reactions in Controlled Clinical Trials: Fluvoxamine Maleate Tablets have been studied in 10-week short-term controlled trials of OCD (N=320) and depression (N=1350). In general, adverse reaction rates were similar in the two data sets as well as in the pediatric OCD study. The most commonly observed adverse reactions associated with the use of Fluvoxamine Maleate Tablets and likely to be drug-related (incidence of 5% or greater and at least twice that for placebo) derived from Table 2 were: *nausea, somnolence, insomnia, asthenia, nervousness, dyspepsia, abnormal ejaculation, sweating, anorexia, tremor,* and *vomiting.* In a pool of two studies involving only patients with OCD, the following additional reactions were identified using the above rule: *anorgasmia, decreased libido, dry mouth, rhinitis, taste perversion,* and *urinary frequency.* In a study of pediatric patients with OCD, the following additional reactions were identified using the above rule: *agitation, depression, dysmenorrhea, flatulence, hyperkinesia,* and *rash.*

Adverse Reactions Occuring at an Incidence of 1%: Table 2 enumerates adverse reactions 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 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 a reaction at some time during their treatment. Reported adverse reactions 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 Reactions in OCD Placebo Controlled Studies Which are Markedly Different (defined as at least a two-fold difference) in Rate from the Pooled Reaction Rates in OCD and Depression Placebo Controlled Studies: The reactions in OCD studies with a two-fold decrease in rate compared to reaction rates in OCD and depression studies were dysphagia and amblyopia (mostly blurred vision). Additionally, there was an approximate 25% decrease in nausea.

The reactions in OCD studies with a two-fold increase in rate compared to reaction rates in OCD and depression studies were: *asthenia, abnormal ejaculation (mostly delayed ejaculation), anxiety, rhinitis,*

anorgasmia (in males), depression, libido decreased, pharyngitis, agitation, impotence, myoclonus/twitch, thirst, weight loss, leg cramps, myalgia, and *urinary retention.* These reactions are listed in order of decreasing rates in the OCD trials.

6.3 Other Adverse Reactions in OCD Pediatric Population

In pediatric patients (N=57) treated with Fluvoxamine Maleate Tablets, the overall profile of adverse reactions was generally similar to that seen in adult studies, as shown in Table 2. However, the following adverse reactions, not appearing in Table 2, were reported in two or more of the pediatric patients and were more frequent with Fluvoxamine Maleate Tablets than with placebo: cough increase, dysmenorrhea, ecchymosis, emotional lability, epistaxis, hyperkinesia, manic reaction, rash, sinusitis, and weight decrease.

6.4 Male and Female Sexual Dysfunction with SSRIs

Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder and with aging, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRIs), can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence.

Table 3 displays the incidence of sexual side effects reported by at least 2% of patients taking Fluvoxamine Maleate Tablets in placebo-controlled trials in depression and OCD.
There are no adequate and well-controlled studies examining sexual dysfunction with fluvoxamine treatment.

Fluvoxamine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae and upon discontinuation of fluvoxamine.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

6.5 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.

6.6 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.

6.7 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.

6.8 Other Reactions 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 reactions 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 reactions without first grouping similar types of untoward reactions into a limited (i.e., reduced) number of standard reaction categories.

In the tabulations which follow, a standard COSTART-based Dictionary terminology has been used to classify reported adverse reactions. If the COSTART term for a reaction 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 a reaction of the type cited on at least one occasion while receiving fluvoxamine maleate. All reported reactions are included in the list below, with the following exceptions: 1) those reactions 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 reactions for which a drug cause was not considered likely are omitted; 3) reactions for which the COSTART term was too vague to be clinically meaningful and could not be replaced with a more informative term; and 4) reactions 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 reactions reported did occur during treatment with fluvoxamine maleate, a causal relationship to fluvoxamine maleate has not been established.

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

Body as a Whole – *Frequent:* malaise; *Infrequent:* photosensitivity reaction and suicide attempt.

Cardiovascular System – *Frequent:* syncope.

Digestive System – *Infrequent:* gastrointestinal hemorrhage and melena; *Rare:* hematemesis.

Hemic and Lymphatic Systems – *Infrequent:* anemia and ecchymosis; *Rare:* purpura.

Metabolic and Nutritional Systems – *Frequent:* weight gain and weight loss.

Nervous System – *Frequent:* hyperkinesia, manic reaction, and myoclonus; *Infrequent:* abnormal dreams, akathisia, convulsion, dyskinesia, dystonia, euphoria, extrapyramidal syndrome, and twitching; *Rare:* withdrawal syndrome.

Respiratory System – *Infrequent:* epistaxis. *Rare:* hemoptysis and laryngismus.

Skin – *Infrequent:* urticaria.

Urogenital System* – *Infrequent:* hematuria, menorrhagia, and vaginal hemorrhage; *Rare:* hematospermia.

* Based on the number of males or females, as appropriate.

6.9 Postmarketing Reports

Voluntary reports of adverse reactions in patients taking Fluvoxamine Maleate Tablets that have been received since market introduction and are of unknown causal relationship to Fluvoxamine Maleate Tablets use include: acute renal failure, agranulocytosis, amenorrhea, anaphylactic reaction, angioedema, aplastic anemia, bullous eruption, Henoch-Schoenlein purpura, hepatitis, ileus, pancreatitis, porphyria, Stevens-Johnson syndrome, toxic epidermal necrolysis, vasculitis, and ventricular tachycardia (including torsades de pointes).

10. OVERDOSAGE10.1 Human Experience

Worldwide exposure to fluvoxamine includes over 45,000 patients treated in clinical trials and an estimated exposure of 50,000,000 patients treated during worldwide marketing experience (end of 2005). Of the 539 cases of deliberate or accidental overdose involving fluvoxamine reported from this population, there were 55 deaths. Of these, 9 were in patients thought to be taking fluvoxamine alone

and the remaining 46 were in patients taking fluvoxamine along with other drugs. Among non-fatal overdose cases, 404 patients recovered completely. Five patients experienced adverse sequelae of overdosage, to include persistent mydriasis, unsteady gait, hypoxic encephalopathy, kidney complications (from trauma associated with overdose), bowel infarction requiring a hemicolectomy, and vegetative state. In 13 patients, the outcome was provided as abating at the time of reporting. In the remaining 62 patients, the outcome was unknown. The largest known ingestion of fluvoxamine 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 gastrointestinal complaints (nausea, vomiting and diarrhea), coma, hypokalemia, hypotension, respiratory difficulties, somnolence, and tachycardia. Other notable signs and symptoms seen with fluvoxamine maleate overdose (single or multiple drugs) include bradycardia, ECG abnormalities (such as heart arrest, QT interval prolongation, first degree atrioventricular block, bundle branch block, and junctional rhythm), convulsions, dizziness, liver function disturbances, tremor, and increased reflexes.

10.2 Management of Overdosage

Treatment should consist of those general measures employed in the management of overdosage with any antidepressant.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for fluvoxamine are known.

A specific caution involves patients taking, or recently having taken, fluvoxamine who might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation. (See **DRUG INTERACTIONS** [7.2].)

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).

2. DOSAGE AND ADMINISTRATION2.1 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.

2.2 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. Physicians should consider age and gender differences when dosing pediatric patients. The maximum dose in children up to age 11 should not exceed 200 mg/day. Therapeutic effect in female children may be achieved with lower doses. Dose adjustment in adolescents (up to the adult maximum dose of 300 mg) may be indicated to achieve therapeutic benefit.

The dose should be increased in 25 mg increments every 4 to 7 days, as tolerated, until maximum therapeutic benefit is achieved. It is advisable that a total daily dose of more then 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.
2.3 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.
2.4 Pregnant Women During the Third Trimester

Neonates exposed to Fluvoxamine Maleate Tablets and other SSRIs or SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding and may be at risk for persistent pulmonary hypertension of the newborn (PPHN). (See **USE IN SPECIFIC POPULATIONS** [8.1].) When treating pregnant women with Fluvoxamine Maleate Tablets during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Fluvoxamine Maleate Tablets in the third trimester.
2.5 Switching Patients To or From a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Fluvoxamine Maleate Tablets. Similarly, at least 14 days should be allowed after stopping Fluvoxamine Maleate Tablets before starting an MAOI.
2.6 Maintenance/Continuation Extended Treatment

It is generally agreed that obsessive compulsive disorder requires several months or longer of sustained pharmacologic therapy. The benefit of maintaining patients with OCD on Fluvoxamine Maleate Tablets after achieving a response for an average duration of about 4 weeks in a 10-week single-blind phase during which patients were titrated to effect was demonstrated in a controlled trial [see CLINICAL TRIALS (14.2)]. The physician who elects to use Fluvoxamine Maleate Tablets for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.
2.7 Discontinuation of Treatment with Fluvoxamine Maleate Tablets

Symptoms associated with discontinuation of other SSRIs or SNRIs have been reported. (See **WARNINGS AND PRECAUTIONS** [5.8].) Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

16. HOW SUPPLIED/STORAGE AND HANDLING16.1 How Supplied

Fluvoxamine Maleate Tablets are available in the following strengths, colors, imprints, and presentations:

Tablets 25 mg: unscored, white, elliptical, film-coated (debossed “1222” on one side)

Bottles of 100.....NDC 42769-1222-0

Tablets 50 mg: scored, yellow, elliptical, film-coated (debossed “1225” on one side and scored on the other)

Bottles of 100.....NDC 42769-1225-0

Tablets 100 mg: scored, beige, elliptical, film-coated (debossed “1221” on one side and scored on the other)

Bottles of 100.....NDC 42769-1221-0
16.2 Storage

Keep out of reach of children.

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

Dispense in tight containers.

17. PATIENT COUNSELING INFORMATION

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

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Fluvoxamine Maleate Tablets.

17.1 Clinical Worsening and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate the need for very close monitoring and possibly changes in the medication (see **Boxed Warning** and **WARNINGS AND PRECAUTIONS** [5.1]).

17.2 Serotonin Syndrome

Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of fluvoxamine and triptans, tramadol, or other serotonergic agents (see **WARNINGS AND PRECAUTIONS-Serotonergic Drugs** [5.7]).

17.3 Interference with Cognitive or Motor Performance

Since any psychoactive drug may impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are certain that Fluvoxamine Maleate Tablets therapy does not adversely affect their ability to engage in such activities.

17.4 Pregnancy

Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy with Fluvoxamine Maleate Tablets (see **USE IN SPECIFIC POPULATIONS** [8.1]).

17.5 Nursing

Patients receiving Fluvoxamine Maleate Tablets should be advised to notify their physicians if they are breast-feeding an infant. (See **USE IN SPECIFIC POPULATIONS - Nursing Mothers** [8.3].)

17.6 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 Fluvoxamine Maleate Tablets.

Patients should be cautioned about the concomitant use of fluvoxamine and NSAIDs, aspirin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin

reuptake and these agents has been associated with an increased risk of bleeding (see ***WARNINGS AND PRECAUTIONS-Warfarin and Other Drugs That Interfere With Hemostasis*** [5.7]).

Because of the potential for the increased risk of serious adverse reactions including severe lowering of blood pressure and sedation when fluvoxamine and tizanidine are used together, fluvoxamine should not be used with tizanidine (see **WARNINGS AND PRECAUTIONS** [5.4]).

Because of the potential for the increased risk of serious adverse reactions when fluvoxamine and alosetron are used together, fluvoxamine should not be used with Lotronex™ (alosetron) (see **WARNINGS AND PRECAUTIONS** [5.6]).

17.7 Alcohol

As with other psychotropic medications, patients should be advised to avoid alcohol while taking Fluvoxamine Maleate Tablets.

17.8 Allergic Reactions

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

Lotronex™ is a registrered trademark of GlaxoSmithKline.

Manufactured for

BayPharma, Inc.

Baltimore, MD 21244

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Fluvoxamine Maleate Tablets or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Fluvoxamine Maleate Tablets are not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD). (See **WARNINGS AND PRECAUTIONS-Clinical Worsening and Suicide Risk** [5.1].)

fluvoxamine 25mg

FLUVOXAMINE MALEATE

fluvoxamine maleate tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:16590-270(NDC:42769-1222)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
FLUVOXAMINE MALEATE (UNII: 5LGN83G74V) (FLUVOXAMINE - UNII:O4L1XPO44W)	FLUVOXAMINE MALEATE	25 mg

Product Characteristics			
Color	white	**Score**	2 pieces
Shape	OVAL	**Size**	9mm
Flavor		**Imprint Code**	1222
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:16590-270-30	30 in 1 BOTTLE, PLASTIC		
2	NDC:16590-270-60	60 in 1 BOTTLE, PLASTIC		
3	NDC:16590-270-90	90 in 1 BOTTLE, PLASTIC		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA022235	04/14/2008	

Labeler - Stat Rx USA (786036330)

Revised: 10/2009 Stat Rx USA