For the use of a Psychiatrist or a Hospital or a Laboratory only

FLUVATOR

(Fluvoxamine Tablets I.P.)

COMPOSITION:

FLUVATOR-50

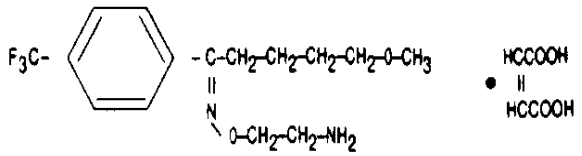
Each film coated tablet contains:
Fluvoxamine Maleate I.P. 50 mg
Excipients q.s.
Colour: Yellow Oxide of Iron

FLUVATOR-100

Each film coated tablet contains:
Fluvoxamine Maleate .P. 100 mg
Excipients q.s.
Colour: Yellow Oxide of Iron

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:



CLINICAL PHARMACOLOGY

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*.

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.

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 radiolabeled 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.

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.

Pediatric Subjects:
The multiple-dose pharmacokinetics of fluvoxamine were determined in male and female children (ages 6-11) and adolescents (ages 12-17). Steady-state plasma fluvoxamine concentrations were 2-3 fold higher in children than in adolescents. AUC and C_{max} in children were 1.5- to 2.7-fold higher than that in adolescents. (See Table 1) As in adults, both children and adolescents exhibited nonlinear multiple-dose pharmacokinetics. Female children showed significantly higher AUC (0-12) and C_{max} compared to male children and, therefore, lower doses of 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 1)

Dose adjustment in adolescents (up to the adult maximum dose of 300 mg) may be indicated to achieve therapeutic benefit.

TABLE 1
Comparison of mean (sd) fluvoxamine pharmacokinetic Parameters between children, adolescents, and adults

Pharmacokinetic Parameter (body weight corrected)	**Dose = 200 mg/day (100 mg b.i.d.)**		**Dose = 300 mg/day (150 mg b.i.d.)**	
	Children (N=10)	Adolescent (N=17)	Adolescent (N=13)	Adult (N=16)
AUC 0-12 (ng•h/mL/kg)	155.1 (160.9)	43.9 (27.9)	69.6 (46.6)	59.4 (40.9)
C_{max} (ng/mL/kg)	14.8 (14.9)	4.2 (2.6)	6.7 (4.2)	5.7 (3.9)
C_{min} (ng/mL/kg)	11.0 (11.9)	2.9 (2.0)	4.8 (3.8)	4.6 (3.2)

TABLE 2
Comparison of mean (sd) fluvoxamine pharmacokinetic Parameters between male and female children (6-11 years)

Pharmacokinetic Parameter (body weight corrected)	**Dose = 200 mg/day (100 mg b.i.d.)**	
	Male Children (N=7)	Female Children (N=3)
AUC 0-12 (ng•h/mL/kg)	95.8 (83.9)	293.5 (233.0)
C_{max} (ng/mL/kg)	9.1 (7.6)	28.1 (21.1)
C_{min} (ng/mL/kg)	6.6 (6.1)	21.2 (17.6)

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

INDICATIONS AND USAGE
1. The treatment of obsessive-compulsive disorder (OCD)
2. The treatment of depressive illness

DOSAGE AND ADMINISTRATION
For OCD and depression
Adults,including the elderly: The recommended starting dose is 50 mg per day at bedtime. The effective dosage usually lies between 100 mg and 200 mg, with some patients requiring up to 300 mg per day. The dose should be increased in 50 mg increments every 4 to 7 days, up to a maximum of 300 mg per day. A total daily dosage in excess of 100 mg should be given in divided doses. If the two divided doses are not equal, the larger dose should be given at bedtime. If no improvement of the OCD symptoms is observed within ten weeks, treatment with Fluvoxamine should be reconsidered.

Paediatric population (children and adolescents): The recommended starting dose in paediatric populations (ages 8 to 17 years) is 25 mg administered as a single daily dose at bedtime. The dose should be increased in 25 mg increments every 4 to 7 days, as tolerated, until the maximum therapeutic benefit is achieved, not to exceed 200 mg per day. 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.

Whilst there are no systematic studies to answer the question of how long to continue Fluvoxamine treatment, OCD is a chronic condition and it is reasonable to consider continuation beyond ten weeks in responding patients. Dosage adjustments should be made carefully on an individual patient basis, to maintain the patient at the lowest effective dose. The need for treatment should be reassessed periodically.

The tablets should be swallowed with water, without chewing.

CONTRAINDICATIONS

Coadministration of tizanidine, thioridazine, alosetron, or pimozide with Fluvoxamine Maleate Tablets is contraindicated.

Serotonin Syndrome and Monoamine Oxidase Inhibitors (MAOIs)

The use of MAOIs intended to treat psychiatric disorders with Fluvoxamine Maleate Tablets or within 14 days of stopping treatment with Fluvoxamine Maleate Tablets is contraindicated because of an increased risk of serotonin syndrome. The use of Fluvoxamine Maleate Tablets within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated.

Starting Fluvoxamine Maleate Tablets in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome

WARNINGS AND PRECAUTIONS

Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of shortterm placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over

77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 3.

TABLE 3:
Drug-placebo differences in number of cases of suicidality per 1000 patients treated

Age Range	Increases Compared to Placebo
<18	14 Additional Cases
18-24	5 Additional Cases
Age Range	Decreases Compared to Placebo
25-64	1 Fewer Case
≥ 65	6 Fewer Cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about the drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for otherindications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in

behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Fluvoxamine Maleate Tablets should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder
A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Fluvoxamine Maleate Tablets are not approved for use in treating bipolar depression.

Serotonin Syndrome
The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including Fluvoxamine Maleate Tablets, alone but particularly with concomitant use of serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, busipirone, and St. John's Wort) and with drugs that impair metabolism of serotonin (in particular MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular aberrations (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of Fluvoxamine Maleate Tablets with MAOIs intended to treat psychiatric disorders is contraindicated. Fluvoxamine Maleate Tablets should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking Fluvoxamine Maleate Tablets. Fluvoxamine Maleate Tablets should be discontinued before initiating treatment with the MAOI.

If concomitant use of Fluvoxamine Maleate Tablets with other serotonergic drugs, including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

Treatment with Fluvoxamine Maleate Tablets and any concomitant serotonergic agents, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Angle Closure Glaucoma
The pupillary dilation that occurs following use of many antidepressant drugs including Fluvoxamine Maleate Tablets may trigger an angle closure attack in a patient with anatomically narrow angles who do not have a patent iridectomy.

Potential Thioridazine Interaction
The effect of fluvoxamine (25 mg b.i.d. for one week) on thioridazine steady-state concentrations was evaluated in 10 male inpatients with schizophrenia. Concentrations of thioridazine and its two active metabolites, mesoridazine and sulforidazine, increased threefold following coadministration of fluvoxamine.

Thioridazine administration produces a dose-related prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsades de pointes-type arrhythmias, and sudden death. It is likely that this experience underestimates the degree of risk that might occur with higher doses of thioridazine. Moreover, the effect of fluvoxamine may be even more pronounced when it is administered at higher doses.

Therefore, fluvoxamine and thioridazine should not be coadministered.

Potential Tizanidine Interaction
Fluvoxamine is a potent inhibitor of CYP1A2 and tizanidine is a CYP1A2 substrate. The effect of fluvoxamine (100 mg daily for 4 days) on the pharmacokinetics and pharmacodynamics of a single 4 mg dose of tizanidine has been studied in 10 healthy male subjects. Tizanidine Cmax was increased approximately 12-fold (range 5-fold to 32-fold), elimination half-life was increased by almost 3-fold, and AUC increased 33-fold (range 14-fold to 103-fold). The mean maximal effect on blood pressure was a 35 mm Hg decrease in systolic blood pressure, a 20 mm Hg decrease in diastolic blood pressure, and a 4 beat/min decrease in heart rate. Drowsiness was significantly increased and performance on the psychomotor task was significantly impaired. Fluvoxamine and tizanidine should not be used together.

Potential Pimozide Interaction
Pimozide is metabolized by the cytochrome P4503A4 isoenzyme, and it has been demonstrated that ketoconazole, a potent inhibitor of CYP3A4, blocks the metabolism of this drug, resulting in increased plasma concentrations of parent drug. An increased plasma concentration of pimozide causes QT prolongation and has been associated with torsades de pointes-type ventricular tachycardia, sometimes fatal. As noted below, a substantial pharmacokinetic interaction has been observed for fluvoxamine in combination with alprazolam, a drug that is known to be metabolized by CYP3A4. Although it has not been definitively demonstrated that fluvoxamine is a potent CYP3A4 inhibitor, it is likely to be, given the substantial interaction of fluvoxamine with alprazolam. Consequently, it is recommended that fluvoxamine not be used in combination with pimozide.

Potential Alosetron Interaction
Because alosetron is metabolized by a variety of hepatic CYP drug metabolizing enzymes, inducers or inhibitors of these enzymes may change the clearance of alosetron. Fluvoxamine

is a known potent inhibitor of CYP1A2 and also inhibits CYP3A4, CYP2C9, and CYP2C19. In a pharmacokinetic study, 40 healthy female subjects received fluvoxamine in escalating doses from 50 mg to 200 mg a day for 16 days, with coadministration of alosetron 1 mg on the last day. Fluvoxamine increased mean alosetron plasma concentration (AUC) approximately 6-fold and prolonged the half-life by approximately 3-fold

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

Alprazolam
When fluvoxamine maleate (100 mg q.d.) and alprazolam (1 mg q.i.d.) were coadministered to steady state, plasma concentrations and other pharmacokinetic parameters (AUC, C_{max}, T½) 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 coadministered, particularly since fluvoxamine exhibits non-linear pharmacokinetics over the dosage range 100-300 mg. If alprazolam is coadministered with Fluvoxamine Maleate 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 Fluvoxamine Maleate Tablets.

Diazepam
The coadministration of Fluvoxamine Maleate 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 coadministration.

Evidence supporting the conclusion that it is inadvisable to coadminister 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 coadministered.

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 coadministered. Patients should be closely monitored when fluvoxamine maleate and clozapine are used concurrently.

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.

Mexiletine:
The effect of steady-state fluvoxamine (50 mg b.i.d. for 7 days) on the single dose pharmacokinetics of mexiletine (200 mg) was evaluated in 6 healthy Japanese males. The clearance of mexiletine was reduced by 38% following coadministration with fluvoxamine compared to mexiletine alone. If fluvoxamine and mexiletine are coadministered, serum mexiletine levels should be monitored.

Ramelteon:
When fluvoxamine 100 mg twice daily was administered for 3 days prior to single-dose coadministration of ramelteon 16 mg and fluvoxamine, the AUC for ramelteon increased approximately 190-fold and the C_{max} increased approximately 70-fold compared to ramelteon administered alone. Ramelteon should not be used in combination with fluvoxamine**.**

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 coadministered 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 Fluvoxamine Maleate Tablets.

Warfarin and other drugs that interfere with hemostasis (nsaids, aspirin, etc.):
Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with fluvoxamine.

Warfarin
When fluvoxamine maleate (50 mg t.i.d.) 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 Fluvoxamine Maleate Tablets should have their prothrombin time monitored and their anticoagulant dose adjusted accordingly. No dosage adjustment is required for Fluvoxamine Maleate Tablets.

Dicontinuation of Treatment with Fluvoxamine Maleate Tablets
During marketing of Fluvoxamine Maleate Tablets and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse

events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias, such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with Fluvoxamine Maleate Tablets. 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.

Abnormal Bleeding
SSRIs and SNRIs, including Fluvoxamine Maleate Tablets, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of Fluvoxamine Maleate Tablets and NSAIDs, aspirin, or other drugs that affect coagulation.

Activation of Mania/Hypomania
During premarketing studies involving primarily depressed patients, hypomania or mania occurred in approximately 1% of patients treated with fluvoxamine. In a ten week pediatric OCD study, 2 out of 57 patients (4%) treated with fluvoxamine experienced manic reactions, compared to none of 63 placebo patients. 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, Fluvoxamine Maleate Tablets should be used cautiously in patients with a history of mania.

Siezures
During premarketing studies, seizures were reported in 0.2% of fluvoxamine-treated patients. Caution is recommended when the drug is administered to patients with a history of convulsive disorders. Fluvoxamine should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Treatment with fluvoxamine should be discontinued if seizures occur or if seizure frequency increases.

Hyponatremia
Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Fluvoxamine Maleate Tablets. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk. Discontinuation of Fluvoxamine Maleate

Tablets should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

Use in Patients with Concomitant Illness
Closely monitored clinical experience with Fluvoxamine Maleate Tablets in patients with concomitant systemic illness is limited. Caution is advised in administering Fluvoxamine Maleate Tablets to patients with diseases or conditions that could affect hemodynamic responses or metabolism.

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. 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.

Patients with Hepatic Impairment - In patients with liver dysfunction, fluvoxamine clearance was decreased by approximately 30%. Patients with liver dysfunction should begin with a low dose of Fluvoxamine Maleate Tablets and increase it slowly with careful monitoring.

DRUG INTERACTIONS
Potential Interactions with Drugs that inhibit or are metabolized by Cytochrome P450 Isoenzymes
Multiple hepatic cytochrome P450 isoenzymes 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 cytochrome P450 isoenzyme 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 and limited *in vitro* data for CYP3A4, it appears that fluvoxamine inhibits several cytochrome P450 isoenzymes that are known to be involved in the metabolism of other drugs such as: CYP1A2 (e.g., warfarin, theophylline, propranolol, tizanidine), CYP2C9 (e.g., warfarin), CYP3A4 (e.g., alprazolam), and CYP2C19 (e.g., omeprazole).

In vitro data suggest that fluvoxamine is a relatively weak inhibitor of CYP2D6.

Approximately 7% of the normal population has a genetic code that leads to reduced levels of activity of CYP2D6. Such individuals have been referred to as "poor metabolizers" (PM) of drugs such as debrisoquin, dextromethorphan, and tricyclic antidepressants. While none of the drugs studied for drug interactions significantly affected the pharmacokinetics of fluvoxamine, an *in vivo* study of fluvoxamine single-dose pharmacokinetics in 13 PM subjects demonstrated altered pharmacokinetic properties compared to 16 "extensive metabolizers" (EM): mean C_{max}, AUC, and half-life were increased by 52%, 200%, and 62%, respectively, in the PM compared to the EM group. This suggests that fluvoxamine is

metabolized, at least in part, by CYP2D6. Caution is indicated in patients known to have reduced levels of CYP2D6 activity and those receiving concomitant drugs known to inhibit this cytochrome P450 isoenzyme (e.g., quinidine).

The metabolism of fluvoxamine has not been fully characterized and the effects of potent cytochrome P450 isoenzyme inhibition, such as the ketoconazole inhibition of CYP3A4, on fluvoxamine metabolism have not been studied.

A clinically significant fluvoxamine interaction is possible with drugs having a narrow therapeutic ratio such as pimozide, warfarin, theophylline, certain benzodiazepines, omeprazole and phenytoin. If Fluvoxamine Maleate 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.

CNS Active Drugs
Antipsychotics: see warnings and precautions
Benzodiazepines: see warnings and precautions
Alprazolam: see warnings and precautions
Diazepam: see warnings and precautions

Lorazepam*:*
A study of multiple doses of fluvoxamine maleate (50 mg b.i.d.) 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 coadministration of fluvoxamine and lorazepam did not produce larger mean decrements compared to lorazepam alone.

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 b.i.d.) revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of the other. As with other psychotropic medications, patients should be advised to avoid alcohol while taking Fluvoxamine Maleate Tablets.

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

Clozapine: see warnings and precautions

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 coadministration of fluvoxamine maleate and lithium.

Methadone: see warnings and precautions

Monoamine Oxidase Inhibitors: See dosage and administration contraindications, and warnings and precautions.

Pimozide: See contraindications and warnings and precautions

Ramelteon: See warnings and precautions

Serotonergic Drugs: See dosage and administration, contraindications and warnings and precautions.

Tacrine: In a study of 13 healthy, male volunteers, a single 40 mg dose of tacrine added to fluvoxamine 100 mg/day administered at steady-state was associated with five- and eight-fold increases in tacrine C_{max} and AUC, respectively, compared to the administration of tacrine alone. Five subjects experienced nausea, vomiting, sweating, and diarrhea following coadministration, consistent with the cholinergic effects of tacrine.

Thioridazine: See contraindications and warnings and precautions.

Tizanidine: See contraindications and warnings and precautions.

Tricyclic Antidepressants (TCAs): Significantly increased plasma TCA levels have been reported with the coadministration of fluvoxamine maleate and amitriptyline, clomipramine or imipramine. Caution is indicated with the coadministration of Fluvoxamine Maleate Tablets and TCAs; plasma TCA concentrations may need to
be monitored, and the dose of TCA may need to be reduced.

Triptans: There have been rare post-marketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of fluvoxamine with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Sumatriptan: There have been rare post-marketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) is clinically warranted, appropriate observation of the patient is advised.

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 coadministration of fluvoxamine maleate and tryptophan.

Other Drugs
Alosetron: see contraindications, warnings and precautions,

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 coadministration of fluvoxamine maleate and diltiazem.

Mexiletine: see warnings and precautions.

Propranolol and Other Beta-Blockers: Coadministration 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 coadministration of fluvoxamine maleate and metoprolol.

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

Coadministration 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.

Theophylline: see warnings and precautions.

Warfarin and other drugs that interfere with hemostasis (NSAIDS, aspirin, etc.): see warnings and precautions.

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.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects

Pregnancy Category C: When pregnant rats were given oral doses of fluvoxamine (60, 120, or 240 mg/kg) throughout the period of organogenesis, developmental toxicity in the form of increased embryofetal death and increased incidences of fetal eye abnormalities (folded retinas) was observed at doses of 120 mg/kg or greater. Decreased fetal body weight was seen at the high dose. The no effect dose for developmental toxicity in this study was 60 mg/kg (approximately 2 times the MRHD on a mg/m^2 basis).

In a study in which pregnant rabbits were administered doses of up to 40 mg/kg (approximately 2 times the MRHD on a mg/m^2 basis) during organogenesis, no adverse effects on embryofetal development were observed.

In other reproduction studies in which female rats were dosed orally during pregnancy and lactation (5, 20, 80, or 160 mg/kg), increased pup mortality at birth was seen at doses of 80 mg/kg or greater and decreases in pup body weight and survival were observed at all doses (low effect dose approximately 0.1 times the MRHD on a mg/m^2 basis).

Nonteratogenic Effects: Neonates exposed to Fluvoxamine Maleate Tablets and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome.

Infants exposed to SSRIs in pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 – 2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. Several recent epidemiologic studies suggest a positive statistical association between SSRI use (including Fluvoxamine Maleate Tablets) in pregnancy and PPHN.
Other studies do not show a significant statistical association.

Physicians should also note the results of a prospective longitudinal study of 201 pregnant women with a history of major depression, who were either on antidepressants or had received antidepressants less than 12 weeks prior to their last menstrual period, and were in remission. Women who discontinued antidepressant medication during pregnancy showed a significant increase in relapse of their major depression compared to those women who remained on antidepressant medication throughout pregnancy.

When treating a pregnant woman with Fluvoxamine Maleate Tablets, the physician should carefully consider both the potential risks of taking an SSRI, along with the established benefits of treating depression with an antidepressant. This decision can only be made on a case by case basis**.**

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 Maleate Tablets therapy 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 8-17. In addition, 99 of these outpatients continued open-label fluvoxamine maleate treatment for up to another one to three years, equivalent to 94 patient years. The adverse event profile observed in that study was generally similar to that observed in adult studies with fluvoxamine.

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, cognitive behavioral 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 such findings is not compelling evidence of the absence of the potential of fluvoxamine to have adverse effects in chronic use.

Safety and effectiveness in the pediatric population other than pediatric patients with OCD have not been established. Anyone considering the use of Fluvoxamine Maleate Tablets in a child or adolescent must balance the potential risks with the clinical need.

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, SSRIs and SNRIs, including Fluvoxamine Maleate Tablets, have been associated with several cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event. Furthermore, the clearance of fluvoxamine is decreased by about 50% in elderly compared to younger patients, and greater sensitivity of some older individuals also cannot be ruled out. Consequently, a lower starting dose should be considered in elderly patients and Fluvoxamine Maleate Tablets should be slowly titrated during initiation of therapy.

ADVERSE REACTIONS

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).

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 Occurring 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.

TABLE 4
Treatment-emergent adverse reaction incidence rates by body system in adult OCD and depression populations combined[1]

BODY SYSTEM/ ADVERSE REACTION	**Percentage of patients reporting reaction**	
	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] Reactions for which fluvoxamine maleate incidence was equal to or less than placebo are not listed in the table above
[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

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.

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.

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.

Table 5
Percentage of patients reporting sexual adverse reactions in adult placebo-controlled trials in OCD and depression

	Fluvoxamine Maleate Tablets N=892	**Placebo N=778**
Abnormal Ejaculation*	8%	1%
Impotence*	2%	1%
Decreased Libido	2%	1%
Anorgasmia	2%	0%

*Based on the number of male patients.

There are no adequate and well-controlled studies examining sexual dysfunction with fluvoxamine treatment.
Fluvoxamine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae and upon discontinuation of fluvoxamine.

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

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

Laboratory Changes
Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression trials on (1) median change from baseline on various serum chemistry,

hematology, and urinalysis variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various serum chemistry, hematology, and urinalysis variables revealed no important differences between fluvoxamine maleate and placebo.

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

Other 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.

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).

DRUG ABUSE AND DEPENDENCE
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 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 at risk for drug dependency were systematically excluded from investigational studies of fluvoxamine maleate. Generally, it is not possible to predict on the basis of preclinical or premarketing clinical experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of fluvoxamine maleate misuse or abuse (i.e., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE
Human Experience
Worldwide exposure to fluvoxamine includes over 45,000 patients treated in clinical trials and an estimated exposure of 50,000,000 patients treated during worldwide marketing experience (end of 2005). Of the 539 cases of deliberate or accidental overdose involving fluvoxamine reported from this population, there were 55 deaths. Of these, 9 were in patients thought to be taking fluvoxamine alone and the remaining 46 were in patients taking fluvoxamine along with other drugs. Among non-fatal overdose cases, 404 patients recovered completely. Five patients experienced adverse sequelae of 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.

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.

EXPIRY DATE:
Do not use later than expiry date

STORAGE:
Store below 25^{o}C, protected from light & moisture.

PRESENTATION:
FLUVATOR - 50 and FLUVATOR - 100 tablets are available in strips of 10 tablets.

MARKETED BY:


TORRENT PHARMACEUTICALS LTD.
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