PRODUCT MONOGRAPH

[Pr]FLUVOXAMINE

Fluvoxamine Maleate Tablets

50 mg and 100 mg

Antidepressant, Antiobsessional Agent

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Toronto, Ontario
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FLUVOXAMINE

Fluvoxamine Maleate

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	All Non-medicinal Ingredients
Oral	Tablet/ 50 mg and 100 mg	Carnauba wax, hydroxypropyl methylcellulose, magnesium stearate, mannitol, polydextrose, polyethylene glycol, titanium dioxide.

INDICATIONS AND CLINICAL USE

FLUVOXAMINE is indicated for:

- Depression:

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

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

- Obsessive-Compulsive Disorder:

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

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

Geriatrics (> 65 years of age):

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

Pediatrics (< 18 years of age):

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

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

- Coadministration of FLUVOXAMINE with monoamine oxidase (MAO) inhibitors, including methylene blue (intravenous dye) and linezolid (an antibiotic which is a reversible non-selective MAO inhibitor).

  In patients receiving selective serotonin reuptake inhibitors (SSRIs) in combination with a MAO inhibitor, there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have begun treatment on a MAO inhibitor. Some cases presented with features resembling serotonin syndrome or neuroleptic malignant syndrome.

  At least two weeks should elapse after discontinuation of MAO inhibitor therapy before FLUVOXAMINE treatment is initiated. MAO inhibitors should not be introduced within two weeks of cessation of therapy with FLUVOXAMINE (see **WARNINGS AND PRECAUTIONS**, **Neurologic, Serotonin Syndrome/Neuroleptic Malignant Syndrome** and **DRUG INTERACTIONS**).

- Coadministration of thioridazine, mesoridazine, pimozide, terfenadine, astemizole, or cisapride with FLUVOXAMINE. Each of these drugs alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsade de pointes-type arrhythmias and sudden death.

  Fluvoxamine maleate has been shown to increase plasma levels of thioridazine, mesoridazine and pimozide (See **DRUG INTERACTIONS**).

  Terfenadine, astemizole and cisapride plasma concentrations may also be increased when

coadministered with FLUVOXAMINE (See **DRUG INTERACTIONS**).

- Coadministration of tizanidine and FLUVOXAMINE (see **DRUG INTERACTIONS**).

- Coadministration of FLUVOXAMINE with ramelteon, a sleep medicine not available in Canada (See **DRUG INTERACTIONS**).

WARNINGS AND PRECAUTIONS

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

Pediatrics: Placebo-Controlled Clinical Trial Data

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

Adults and Pediatrics: Additional data

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

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

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

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

Discontinuation Symptoms:

Patients currently taking FLUVOXAMINE should NOT be discontinued abruptly, due to risk of discontinuation symptoms. At the time that a medical decision is made to discontinue an SSRI or other newer antidepressant drug, a gradual reduction in the dose rather an abrupt cessation is recommended (See WARNINGS AND PRECAUTIONS, Dependence/Tolerance, Discontinuation of Treatment with FLUVOXAMINE; ADVERSE REACTIONS, Adverse Reactions Following Discontinuation of Treatment (or Dose Reduction)).

Bone Fracture Risk:

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

General

Monoamine Oxidase Inhibitors

See **CONTRAINDICATIONS** and **DRUG INTERACTIONS.**

Potential Interactions with Thioridazine, Mesoridazine, Pimozide, Terfenadine, Astemizole and Cisapride

See **CONTRAINDICATIONS** and **DRUG INTERACTIONS.**

Potential Interaction with Tizanidine

See **CONTRAINDICATIONS** and **DRUG INTERACTIONS.**

Potential Interactions with Drugs with a Narrow Therapeutic Index

There may be a potential interaction between fluvoxamine maleate and drugs or prodrugs metabolized by CYP1A2, CYP3A4 and CYP2C that have a narrow therapeutic index [e.g., theophylline, tacrine, mexiletine, and clozapine (CYP1A2 substrates), carbamazepine, methadone, cyclosporine and sildenafil (CYP3A4 substrates), phenytoin and warfarin (CYP2C substrates)]. Patients administered these combinations should be carefully monitored and, if necessary, dose adjustment of these drugs is recommended (See **DRUG INTERACTIONS**).

Fluvoxamine is not recommended for patients taking prodrugs metabolized by CYP1A2 or

CYP2C19 to their active metabolites as clinical significant reduction in drug levels is expected, such as the antiplatelet agent clopidogrel.

There is a potential for CYP1A2 inhibitors (e.g., fluvoxamine) to affect the circulating levels of the antineoplastic agent bendamustine and its active metabolites. Caution should be used with FLUVOXAMINE, or alternative treatments considered in patients taking bendamustine.

Cardiovascular

Concomitant Illness

Fluvoxamine maleate has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from pre-marketing clinical studies.

Dependence/Tolerance

Discontinuation of Treatment with FLUVOXAMINE

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

If FLUVOXAMINE is used until or shortly before birth, discontinuation effects in the newborn may occur (See WARNINGS AND PRECAUTIONS, Special Populations, Fertility, Pregnant Women and Newborns).

Endocrine and Metabolism

Disturbance of Glycemic Control

Glycemic control may be disturbed, especially in the early stages of the treatment. Reported events include hyperglycemia, hypoglycemia, diabetes mellitus and decreased glucose tolerance; these have been reported in both patients with and without pre-existing disturbance of glycemic

control. Patients should therefore be monitored for signs and symptoms of glucose fluctuations. When FLUVOXAMINE is given to patients with a known history of diabetes mellitus, the dosage of anti-diabetic drugs may need to be adjusted.

Hematologic

Abnormal Bleeding

SSRIs and serotonin / norepinephrine reuptake inhibitors (SNRIs), including fluvoxamine maleate may increase the risk of bleeding events by causing abnormal platelet aggregation. Concomitant use of acetylsalicylic acid (ASA), nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin and other anticoagulants may add to the risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding or gynecological hemorrhage. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis and petechiae to life-threatening hemorrhages (See **ADVERSE REACTIONS**).

Patients should be cautioned about the risk of bleeding associated with the concomitant use of fluvoxamine maleate and NSAIDs, ASA, or other drugs that affect coagulation (See **DRUG INTERACTIONS**). Caution is advised in patients with a history of bleeding disorder or predisposing conditions (e.g. thrombocytopenia or coagulation disorders).

Hepatic/Biliary/Pancreatic

Hepatic Enzymes

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

Neurologic

Seizures

Seizures are a potential risk with antidepressant drugs. Convulsions have been reported rarely during fluvoxamine maleate administration, but fluvoxamine maleate has not been systematically evaluated in patients with a seizure disorder. Caution is recommended when the drug is administered to patients with a history of seizures. Fluvoxamine maleate 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. Seizures have also been reported as a discontinuation symptom (See **WARNINGS AND PRECAUTIONS**, **Discontinuation Symptoms**; **ADVERSE REACTIONS**, **Adverse Events Leading to Discontinuation of Treatment**).

Serotonin Syndrome/Neuroleptic Malignant Syndrome

On rare occasions development of a serotonin syndrome or neuroleptic malignant syndrome-like events have been reported in association with treatment of fluvoxamine maleate**,** particularly when given in combination with other serotonergic and / or neuroleptic/antipsychotic drugs. As these syndromes may result in potentially life-threatening conditions, treatment with FLUVOXAMINE should be discontinued if patients develop a combination of symptoms possibly including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma, and supportive symptomatic treatment should be initiated. Due to the risk of serotonergic syndrome FLUVOXAMINE should not be used in combination with MAO inhibitors [including linezolid, an antibiotic which is a reversible non-selective MAO inhibitor and methylthioninium chloride (methylene blue)] or serotonin precursors (such as L-tryptophan, oxitriptan) and should be used with caution in patients receiving other serotonergic drugs (e.g., triptans, lithium, tramadol, most tricyclic antidepressants), neuroleptics/antipsychotics or St. John's Wort (See **CONTRAINDICATIONS** and **DRUG INTERACTIONS**, **Serotonergic Drugs**).

Cognitive and Motor Disturbances

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

Ophthalmologic

Angle-Closure Glaucoma

As with other antidepressants, FLUVOXAMINE can cause mydriasis, which may trigger an angle-closure attack in a patient with anatomically narrow ocular angles. Healthcare providers should inform patients to seek immediate medical assistance if they experience eye pain, changes in vision or swelling or redness in or around the eye.

Psychiatric

Suicide/Suicidal Thoughts or Clinical Worsening

The possibility of a suicide attempt is inherent in depression and other psychiatric disorders, and may persist until significant remission occurs. Patients with depression may experience worsening of their depressive symptoms and / or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications. Close supervision of patients should accompany drug therapy and consideration should be given to the need for hospitalization of high risk patients. Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at a greater risk of suicidal thoughts or suicide attempts and should receive careful monitoring during treatment.

Physicians should encourage patients of all ages, their families, and their caregivers to be alert to the emergence of any new or worsened distressing thoughts or feelings occurring at any time, and especially when initiating therapy or during any change in dose or dosage regimen. In order to minimize the risk of overdose, prescriptions for FLUVOXAMINE should be written for the smallest quantity of drug consistent with good patient management.

Because of the well established comorbidity between depression and other psychiatric disorders, the same precautions observed when treating patients with depression should be observed when treating patients with other psychiatric disorders, e.g. obsessive compulsive disorder (See **WARNINGS AND PRECAUTIONS**, **POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM**).

Mania/Hypomania
A major depressive episode may be the initial presentation of bipolar disorder. Patients with bipolar disorder may be at an increased risk of experiencing manic episodes when treated with antidepressants alone. Therefore, the decision to initiate symptomatic treatment of depression should only be made after patients have been adequately assessed to determine if they are at risk for bipolar disorder.

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

Electroconvulsive Therapy (ECT)
The safety and efficacy of concurrent administration of fluvoxamine maleate with electroshock therapy have not been studied and, therefore, caution is advisable.

Renal

Hyponatremia

As with other SSRIs, hyponatremia has been rarely reported and appeared to be reversible when fluvoxamine maleate was discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of reports were associated with older patients. Elderly patients, patient taking diuretics, and patients who are otherwise volume depleted may be at greater risk for this event. Discontinuation of FLUVOXAMINE should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Symptoms may include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls.

Sexual Function

See **ADVERSE REACTIONS.**

Special Populations

Fertility, Pregnant Women and Newborns

Fertility

Reproductive toxicity studies in rats have shown that fluvoxamine maleate impairs male and female fertility (See TOXICOLOGY, Reproduction and Teratology, Reproductive Studies). Animal data have shown that fluvoxamine maleate may affect sperm quality. Human case reports with some SSRI's have shown that an effect on sperm quality is reversible.

Impact on human fertility has not been observed so far.

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

Pregnant Women and Newborns

Safe use of fluvoxamine maleate during pregnancy has not been established. Therefore, FLUVOXAMINE should not be used during pregnancy or in women intending to become pregnant unless, in the opinion of the treating physician, the expected benefits to the patient outweigh the possible hazards to the fetus.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant. If FLUVOXAMINE is used until or shortly before birth, discontinuation symptoms in the newborn should be considered.

Complications following late third trimester exposure to SSRIs

Post-marketing reports indicate that some neonates exposed to fluvoxamine maleate, SSRIs (Selective Serotonin Reuptake Inhibitors), or other newer antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability and constant crying. These features are consistent with either a direct toxic effect of SSRIs and other newer antidepressants or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (See WARNINGS AND PRECAUTIONS, Neurologic, Serotonin Syndrome/Neuroleptic Malignant Syndrome). When treating a pregnant woman with FLUVOXAMINE the physician should carefully consider the benefit of the treatment to the mother and the potential risk to the fetus (See DOSAGE AND ADMINISTRATION).

Risk of PPHN and exposure to SSRIs:

Epidemiological studies on persistent pulmonary hypertension of the newborn (PPHN) have shown that the use of SSRIs (including fluvoxamine maleate) in pregnancy, particularly use in

late pregnancy, was associated with an increased risk of PPHN). PPHN occurs in 1 to 2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. A study of 831,324 infants born in Sweden in 1997 to 2005 found a PPHN risk ratio of 2.4 (95% CI 1.2 to 4.3) associated with patient-reported maternal use of SSRIs in "early pregnancy" and a PPHN risk ratio of 3.6 (95% CI 1.2 to 8.3) associated with a combination of patient-reported maternal use of SSRIs in "early pregnancy" and an antenatal SSRI prescription in "later pregnancy".

Nursing Women

Safe use of fluvoxamine maleate during lactation has not been established. Like other antidepressants, fluvoxamine maleate is excreted via human milk in small quantities. FLUVOXAMINE should not be administered to nursing mothers unless, in the opinion of the treating physician, the expected benefits to the patient outweigh the possible risk to the child, in which case the infant should be closely monitored.

Pediatrics (< 18 years of age)

Safety and efficacy in children under 18 years of age have not been established. FLUVOXAMINE is not indicated for use in patients below the age of 18 years (see **WARNINGS AND PRECAUTIONS, POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM**).

Geriatrics (> 65 years of age)

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

ADVERSE REACTIONS

Adverse Drug Reaction

Adverse event information for fluvoxamine maleate was collected from adult patients diagnosed with major depressive disorder (MDD) or obsessive compulsive disorder and treated with fluvoxamine maleate in controlled clinical trials.

Clinical Trial Adverse Drug Reactions

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

rates.

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

Adverse Events Leading to Discontinuation of Treatment

Of the 1087 patients with MDD or OCD that were treated with fluvoxamine maleate in controlled clinical trials, conducted 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 of Adverse Experiences

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

Table 1. Treatment-Emergent Adverse Experience Incidence (≥5%) In Placebo- Controlled Clinical Trials for Depression and Obsessive-Compulsive Disorder*

	Percentage of Patients Reporting Event			
	Depression		OCD	
Body System/ Adverse Events	**Fluvoxamine (N=222)**	**Placebo (N=192)**	**Fluvoxamine (N=160)**	**Placebo (N=160)**
Nervous System				
Somnolence	26	9	27	9
Agitation	16	9	4	0
Insomnia	14	10	31	15
Dizziness	15	14	9	4
Tremor	11	5	8	1
Hypokinesia	8	4	--	--
Hyperkinesia	7	9	--	--
Depression	4	4	6	4
Nervousness	2	2	16	5
Anxiety	2	2	9	7
Libido Decreased	--	--	8	2
Thinking Abnormal	--	--	7	4
Digestive System				
Nausea	37	11	29	7

Dry Mouth	26	24	12	3
Constipation	18	7	14	9
Anorexia	15	6	5	3
Diarrhea	6	6	12	9
Dyspepsia	3	0	14	9
Body as a Whole				
Headache	22	19	20	24
Pain	6	4	4	1
Asthenia	5	3	29	9
Infection	--	--	11	9
Abdominal pain	4	4	6	8
Flu syndrome	--	--	5	4
Skin				
Sweating Increased	11	13	7	2
Respiratory System				
Pharyngitis	-	-	6	5
Rhinitis	1	3	6	2
Special Senses				
Accommodation	6	6	-	-
Abnormal	3	3	5	0
Taste Perversion				
Urogenital				
Urinary frequency	2	2	5.0	1
Abnormal ejaculation	1	0	18[+]	0

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

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

NOTE: The results in this table have been rounded to whole numbers.

Additional AEs (with common [>1% and <10%] frequency) include: Malaise, palpitation and vomiting.

Adverse Reactions Following Discontinuation of Treatment (or Dose Reduction)

There have been reports of adverse reactions upon the discontinuation of fluvoxamine maleate particularly when abrupt, including but not limited to the following: dizziness, abnormal dreams, sensory disturbances (including paresthesias and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation, irritability, anxiety, fatigue, confusion, emotional instability, headache, tremor, nausea, vomiting, diarrhea, sweating, palpitations or other symptoms which may be of clinical significance. Isolated cases of withdrawal symptoms in the newborn child have been described after the use of fluvoxamine maleate at the end of pregnancy (See **WARNINGS AND PRECAUTIONS** Dependence/Tolerance, **Discontinuation of Treatment with fluvoxamine maleate and Special Populations, Pregnant Women and Newborns).** Generally these events are mild to moderate and are self-limiting; however in some patients they may be severe and/or

prolonged. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose.

Patients should be monitored for these or any other symptoms. A gradual reduction in the dosage over several weeks, rather than abrupt cessation, is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response. (See **DOSAGE AND ADMINISTRATION**).

Less Common Clinical Trial Adverse Events (<1%)

During pre-marketing and post-marketing studies, multiple doses of fluvoxamine maleate were administered to approximately 34,587 patients. All events with an incidence of > 0.01% and < 1% are listed, regardless of relation to drug, except those in terms so general as to be uninformative.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent (occurring on 1 or more occasions in at least 1/100 patients), infrequent (occurring in less than 1/100, but at least 1/1000 patients) or rare (occurring in less than 1/1000 but at least in 1/10,000 patients). Multiple events may have been reported by a single patient. It is important to emphasize that although the events reported did occur during treatment with fluvoxamine maleate, they were not necessarily caused by it.

Blood and Lymphatic System Disorders:	Rare: Anemia, cyanosis, ecchymosis, lymphadenopathy, thrombocytopenia.
Cardiac Disorders:	Infrequent: Angina pectoris, syncope, tachycardia. Rare: Arrhythmia, bradycardia, ,extrasystoles, hemorrhage, myocardial infarct, shock.
Ear and Labyrinth Disorders:	Infrequent: Hyperacusis. Rare: Deafness, ear pain
Eye Disorders:	Infrequent: Abnormal vision, amblyopia Rare: Abnormality of accommodation, blepharitis, conjunctivitis, diplopia, dry eyes, eye pain, lacrimation disorder, mydriasis, photophobia.

Gastrointestinal Disorders:	Infrequent: Colitis, dysphagia, eructation, flatulence, gastritis, gastroenteritis, thirst. Rare: Abdomen enlarged, esophagitis, fecal incontinence, gastrointestinal carcinoma, gastrointestinal hemorrhage, gingivitis, glossitis, halitosis, hematemesis, hernia, melena, mouth ulceration, rectal hemorrhage, stomatitis, tenesmus, tongue discoloration, tongue edema, tooth disorder.
General Disorders and Administration Site Conditions:	Infrequent: Accidental injury, allergic reaction, chest pain, chills, fever, flu syndrome, pain, pallor, peripheral edema. Rare: Chills, edema, fever, face edema, hangover effect, neck rigidity, overdose, pelvic pain, parosmia, taste loss.
Hepatobiliary Disorders	Rare: Biliary pain, hepatitis, jaundice, liver function tests abnormal, hepatic function abnormal.
Infections and Infestations	Infrequent: Bronchitis, herpes simplex, herpes zoster, infection, pneumonia, sinusitis.
Metabolism and Nutrition Disorders:	Infrequent: Increased appetite, weight loss. Rare: Alcohol intolerance, dehydration, obesity.
Musculoskeletal and Connective Tissue Disorders:	Infrequent: Arthralgia, arthrosis, back pain, myalgia, myasthenia, neck pain, tetany. Rare: Arthritis, bone pain, leg cramps, pathological fracture, rheumatoid arthritis.
Neoplasms	Rare: CNS neoplasia.
Nervous System Disorders:	Infrequent: Abnormal gait, akathisia, amnesia, apathy, ataxia, confusion, cerebrovascular accident, hyperkinesia, hypertonia, hypoesthesia, hypokinesia,

	incoordination, increased salivation, migraine, paraesthesia, stupor, twitching. Rare: Akinesia, CNS stimulation, coma, convulsion, dysarthria, dyskinesia, dystonia, extrapyramidal syndrome, hemiplegia, hyperesthesia, hypotonia, myoclonus, neuralgia, neuropathy, paralysis, reflexes decreased, torticollis, trismus.
Psychiatric Disorders:	Infrequent: Abnormal dreams, aggression, apathy, depersonalization, depression, drug dependence, emotional lability, euphoria, hallucinations, hostility, manic reaction, neurosis, psychotic depression, libido decreased, libido increased, suicide attempt. Rare: Anorgasmia, delirium, delusions, hysteria, paranoid reaction, psychosis, schizophrenic reaction, screaming syndrome.
Renal and Urinary Disorders:	Infrequent: Dysuria, urinary frequency, urinary incontinence. Rare: Cystitis, hematuria, kidney pain, leukorrhea, nocturia, polyuria, prostatic disorder, urinary retention, urinary tract infection, urinary urgency.
Reproductive system and breast disorders:	Infrequent: Abnormal ejaculation, impotence, metrorrhagia. Rare: Amenorrhea, breast pain, dysmenorrhea, female lactation, menorrhagia, vaginitis.
Respiratory, Thoracic and Mediastinal Disorders:	Infrequent: Dyspnea, pharyngitis, rhinitis. Rare: Asthma, cough increased, epistaxis, hiccup, hyperventilation, laryngismus, laryngitis, voice alteration, yawn.
Skin and Subcutaneous Tissue Disorders:	Infrequent: Cutaneous hypersensitivity reactions (including rash, pruritis, angioedema)

	Rare: Acne, alopecia, dry skin, eczema, furunculosis, maculopapular rash, psoriasis, urticaria.
Vascular Disorders:	Infrequent: Hypertension, hypotension, peripheral vascular disorder, postural hypotension, vasodilata tion.

Post-Market Adverse Drug Reactions
Spontaneous reports, from the marketplace, but not from clinical trials, have been collected for the following adverse experiences: galactorrhoea, photosensitivity, Stevens Johnson Syndrome/Toxic Epidermal Necrolysis, alopecia, taste perversion, tinnitus, psychomotor restlessness, hyperprolactinemia, micturition disorder (including pollakiuria and enuresis), menstrual disorders (such as amenorrhea, hypomenorrhea, metrorrhagia, menorrhagia), glaucoma, bone fractures, drug withdrawal syndrome (including drug withdrawal syndrome neonatal), weight gain and hemorrhagic manifestations e.g. ecchymoses, purpura, gastrointestinal bleeding and gynecological hemorrhage (See **WARNINGS AND PRECAUTIONS, Dependence/Tolerance, Discontinuation of Treatment with FLUVOXAMINE and Hematologic, Abnormal Bleeding**).

Cases of suicidal ideation and suicidal behaviours have been reported during fluvoxamine maleate therapy or early after treatment discontinuation. Rarely, serotonin syndrome, neuroleptic malignant syndrome-like events, hyponatremia and SIADH have been reported (See **WARNINGS AND PRECAUTIONS, Neurologic, Serotonin Syndrome/Neuroleptic Malignant Syndrome; and DRUG INTERACTIONS, Serotonergic Drugs**).

DRUG INTERACTIONS

Serious Drug Interactions

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

Overview

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

Effect of fluvoxamine on the oxidative metabolism of other drugs
Fluvoxamine maleate can inhibit the metabolism of drugs or prodrugs metabolized by certain cytochrome P450 isoenzymes (CYPs). A strong inhibition of CYP1A2 and CYP2C19 has been demonstrated *in vitro* and *in vivo*. CYP2C9, CYP2D6 and CYP3A4 are inhibited to a lesser extent.

Drugs which are largely metabolized via these isoenzymes are eliminated slower and may have higher plasma concentrations when coadministered with fluvoxamine maleate. Concomitant therapy of fluvoxamine maleate and these drugs should be initiated at or adjusted to the low end of their dose range. Plasma concentrations, effects or adverse effects of co-administered drugs should be monitored and their dosage should be reduced if necessary.

For some drugs coadministration may not be recommended. This is particularly relevant for drugs with a narrow therapeutic index (**Table 2**), as well as for prodrugs metabolized by CYP1A2 or CYP2C19 to their active metabolites since a reduction in drug levels is expected, such as for bendamustine and clopidogrel (See **WARNINGS AND PRECAUTIONS, General**).

Monoamine oxidase inhibitors (MAOIs)
FLUVOXAMINE should not be used in combination with MAOIs, including linezolid (an antibiotic which is a reversible non-selective MAO inhibitor) and the thiazine dye methylthioninium chloride (methylene blue), due to risk of serotonin syndrome. Fluvoxamine maleate should not be used in combination with a MAOI within 14 days of discontinuing treatment with a MAOI. At least 14 days should elapse after discontinuing FLUVOXAMINE treatment before starting a MAOI (See **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Neurologic Serotonin Syndrome/Neuroleptic Malignant Syndrome**).

Potential Interaction with Thioridazine and Mesoridazine
Thioridazine and mesoridazine administration produces a dose-related prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsade de pointes-type arrhythmias and sudden death.

The effect of fluvoxamine maleate (25 mg twice daily for one week) on thioridazine steady-state concentrations was evaluated in 10 male inpatients with schizophrenia. Concentrations of thioridazine and its two active metabolites, mesoridazine and sulforidazine, increased threefold following coadministration of fluvoxamine maleate. The effect of fluvoxamine maleate may be more pronounced when it is administered at higher doses. Isolated cases of cardiac toxicity have been reported when fluvoxamine maleate was combined with thioridazine. Therefore, FLUVOXAMINE and thioridazine or mesoridazine should not be coadministered (See **CONTRAINDICATIONS**).

Potential Interaction with Pimozide
Elevation of pimozide blood concentration may result in QTc interval prolongation and severe arrhythmias including torsade de pointes. Fluvoxamine maleate has been shown to increase plasma pimozide levels. Therefore, coadministration of pimozide with FLUVOXAMINE is contraindicated (See **CONTRAINDICATIONS**).

Potential Interactions with Terfenadine, Astemizole, and Cisapride
Elevations in terfenadine, astemizole or cisapride plasma concentrations may result in QTc interval prolongation and severe arrhythmias including torsade de pointes. Terfenadine, astemizole and cisapride are all metabolized by CYP3A4. Because fluvoxamine maleate is known to inhibit CYP3A4, there is the potential for the plasma concentrations of these drugs to be elevated when coadministered with fluvoxamine maleate. Therefore, coadministration of fluvoxamine maleate with terfenadine, astemizole or cisapride is contraindicated (See **CONTRAINDICATIONS**).

Potential Interaction with Tizanidine
Tizanidine exposure (AUC) was shown to be significantly elevated during coadministration with fluvoxamine maleate. Coadministration of FLUVOXAMINE with tizanidine is contraindicated due to the risk of clinically significant hypotension during coadministration (See **CONTRAINDICATIONS**).

Ramelteon
When fluvoxamine maleate tablets 100 mg twice daily were administered for three days prior to single-dose coadministration of ramelteon 16 mg and fluvoxamine maleate tablets, the AUC for ramelteon increased approximately 190-fold and the C_{max} increased approximately 70-fold compared to ramelteon administered alone. Coadministration of fluvoxamine maleate and ramelteon is contraindicated due to significant increases in ramelteon plasma concentration and exposure (AUC) during coadministration with fluvoxamine Maleate (See **CONTRAINDICATIONS**).

Serotonergic Drugs
Based on the mechanism of action of fluvoxamine maleate and the potential for serotonin syndrome, caution is advised when fluvoxamine maleate is coadministered with other drugs or agents that may affect the serotonergic neurotransmitter systems, such as tryptophan, triptans, serotonin reuptake inhibitors, MAOIs, lithium, fentanyl and its analogues, dextromethorphan, tramadol, tapentadol, meperidine, methadone, pentazocine and St. John's Wort (See **WARNINGS AND PRECAUTIONS, Neurologic Serotonin Syndrome/Neuroleptic Malignant Syndrome**).

Triptans ($5HT_1$ agonists)
Cases of life-threatening serotonin syndrome have been reported during combined use of SSRIs/SNRIs and triptans. If concomitant treatment with fluvoxamine maleate and a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (See **WARNINGS AND PRECAUTIONS, Neurologic Serotonin Syndrome/Neuroleptic Malignant Syndrome**).

Drugs Affecting Platelet Function (e.g. NSAIDs, ASA and other anticoagulants)
Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper

gastrointestinal bleeding have also shown that concurrent use of an NSAID, ASA or other anticoagulants may potentiate the risk of bleeding.

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

Drugs Lowering the Seizure Threshold
Antidepressants with serotonergic effect can lower the seizure threshold. Caution is advised when concomitantly using other medicinal products capable of lowering the seizure threshold [e.g. antidepressants (tricyclics, SSRIs, SNRIs), neuroleptics (phenothiazines, thioxanthenes and butyrophenones), mefloquin, bupropion and tramadol] (See **WARNINGS AND PRECAUTIONS, Neurologic, Seizures**).

Lithium and tryptophan
Lithium, and possibly tryptophan, may enhance the serotonergic effects of FLUVOXAMINE. This may, on rare occasions, result in a serotonergic syndrome. Therefore, combinations of fluvoxamine maleate with lithium or tryptophan should be used with caution.

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

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

Drug-Drug Interactions

Table 2. Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical recommendations
Benzodiazepines (oxidatively metabolized benzodiazepines [e.g., triazolam, midazolam, alprazolam and diazepam])	CT (for alprazolam, diazepam)	The plasma levels of oxidatively metabolized benzodiazepines are likely to be increased when co-administered with fluvoxamine maleate. Alprazolam and diazepam (see CYP3A4 Substrates in this table).	The dosage of these benzodiazepines should be reduced during co-administration with fluvoxamine maleate.
Benzodiazepines (metabolized by glucuronidation [e.g.,		The clearance of benzodiazepines metabolized by glucuronidation (e.g.,	

lorazepam, oxazepam, temazepam])		*lorazepam, oxazepam, temazepam*) is unlikely to be affected by fluvoxamine maleate.	
CYP1A2 substrates Tricyclic antidepressants (e.g., clomipramine, imipramine, amitriptyline) and neuroleptics (e.g., clozapine, olanzapine, quetiapine)		An increase in previously stable plasma levels of those tricyclic antidepressants and neuroleptics, which are largely metabolized through CYP1A2, has been reported in patients taking fluvoxamine maleate concomitantly.	Coadministration of FLUVOXAMINE and CYP1A2 substrates should be carefully monitored. A decrease in dose of such drugs should be considered if treatment with FLUVOXAMINE is initiated.
CYP1A2 substrates with narrow therapeutic index (e.g., tacrine, theophylline, mexiletine, clozapine)	CT (tacrine)	A clinically significant interaction is possible with CYP1A2 substrates with a narrow therapeutic index. When a single 40 mg dose of tacrine was added to fluvoxamine maleate 100 mg/day administered at steady state, an associated 5 and 8-fold increase in tacrine C_{max} and AUC, respectively, were observed.	Coadministration of FLUVOXAMINE and drugs with a narrow therapeutic index should be carefully monitored (plasma levels and/or pharmacodynamic effects of coadministered drugs) when these drugs are metabolized exclusively or by a combination of CYPs inhibited by fluvoxamine. If necessary, dose adjustment of these drugs is recommended.
CYP2C substrates with narrow therapeutic index (e.g. diazepam, phenytoin, warfarin)	C (phenytoin)	Fluvoxamine maleate is believed to inhibit CYP2C and thus may interact with CYP2C substrates. A clinically significant interaction is possible with CYP2C substrates with a narrow therapeutic index, such as phenytoin or warfarin.	Coadministration of FLUVOXAMINE and drugs with a narrow therapeutic index should be carefully monitored (plasma levels and/or pharmacodynamic effects of coadministered drugs) when these drugs are metabolized exclusively or by a combination of CYPs inhibited by fluvoxamine. If necessary, dose adjustment of these drugs is recommended.

		Clearance of both diazepam and its active metabolite N-desmethyldiazepam were reduced with concurrent administration of fluvoxamine maleate. Warfarin (see Warfarin in this table).	The dosage of diazepam should be reduced during co-administration with fluvoxamine.
CYP3A4 substrates (e.g. alprazolam, diltiazem)	CT (alprazolam, diltiazem)	Fluvoxamine maleate is known to inhibit CYP3A4 and thus may interact with CYP3A4 substrates. Bradycardia has been reported with coadministration of fluvoxamine maleate and diltiazem. When fluvoxamine maleate and alprazolam were coadministered to steady state, plasma concentrations and other pharmacokinetic parameters (AUC, C_{max}, T1/2) of alprazolam were approximately twice those observed when alprazolam was administered alone; clearance was reduced by about 50%.	Coadministration of FLUVOXAMINE and CYP3A4 substrates should be carefully monitored. A decrease in dose of such drugs should be considered if treatment with FLUVOXAMINE is initiated. The initial alprazolam dosage should be reduced by half and titration to the lowest effective dose is recommended during coadministration with FLUVOXAMINE.
CYP3A4 substrates with a narrow therapeutic index (carbamazepine, methadone, cyclosporine and sildenafil)	C (cyclosporine, carbamazepine, methadone) CT (sildenafil)	A clinically significant interaction is possible with CYP3A4 substrates that have a narrow therapeutic index. A significantly increased methadone plasma level / dose ratio was seen during concurrent administration of fluvoxamine maleate.	Coadministration of FLUVOXAMINE and drugs with a narrow therapeutic index should be carefully monitored (plasma levels and/or pharmacodynamic effects of coadministered drugs) when these drugs are metabolized exclusively or by a combination of CYPs inhibited by fluvoxamine. If necessary, dose adjustment of these drugs is recommended.

Digoxin	C	Fluvoxamine maleate does not influence plasma concentrations of digoxin.	No dosage adjustment is required.
Lansoprazole	CT	Inhibitors of CYP2C19 such as fluvoxamine would likely increase the systemic exposure of lansoprazole.	The use of FLUVOXAMINE should be discouraged in patients taking lansoprazole.
Omeprazole	T	The multi-P450 inhibitor fluvoxamine, which inhibits both CYP3A4 and CYP2C19, resulted in 5.6- (CYP2C19 EMs) and 6.3-fold (genotype not known) increases in omeprazole AUC, respectively.	The use of FLUVOXAMINE should be discouraged in patients taking omeprazole.
Prodrug: Clopidogrel	CT, T	Since clopidogrel is metabolized to its active metabolite mostly by CYP2C19, use of drugs that inhibit the activity of this enzyme (e.g., fluvoxamine) would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain.	The use of FLUVOXAMINE should be discouraged in patients taking clopidogrel.
Prodrug: Bendamustine	T	Potential to affect the circulating levels of bendamustine and its active metabolites with CYP1A2 inhibitors (e.g., fluvoxamine).	Caution should be used with FLUVOXAMINE or alternative treatments considered, in patients taking bendamustine.
Propranolol and other beta-blockers	C (propranolol) CT (atenolol)	Plasma concentrations of propranolol are increased when coadministered with fluvoxamine maleate; a 5-fold increase in plasma levels of propranolol was seen in interaction studies. Fluvoxamine maleate does not influence plasma concentrations of	A reduction in the initial propranolol dose and more cautious dose titration are recommended. No dosage adjustment is required for atenolol.

		atenolol. Unlike propranolol, which undergoes hepatic metabolism, atenolol is eliminated primarily by renal excretion.	
Ropinirole		Plasma concentrations of ropinirole may be increased in combination with fluvoxamine maleate thus increasing the risk of overdose.	Careful monitoring and reduction in the dosage of ropinirole during treatment with FLUVOXAMINE and after its withdrawal may be required.
Valproate / Valproic acid	T	Since valproate / valproic acid are metabolized almost entirely by the liver, use of fluvoxamine, inhibiting cytochromes CYP2C19, 1A2, 2C9 and 3A4 may result in increased drug levels.	Caution should be used if concomitant treatment with FLUVOXAMINE is needed.
Warfarin	CT	Warfarin plasma concentrations were significantly increased and prothrombin times prolonged during concurrent administration of fluvoxamine maleate; in interaction studies a 65% increase in warfarin plasma levels was seen (See Drugs Affecting Platelet Function (e.g. NSAIDS, ASA and other anticoagulants). Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are co-administered with warfarin.	Patients receiving warfarin therapy should be carefully monitored when FLUVOXAMINE is initiated or discontinued. **(See WARNINGS AND PRECAUTIONS, Hematologic, Abnormal Bleeding.)**

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Drug-Food Interactions

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

Drug-Herb Interactions

St. John's Wort

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

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

- **Discontinuation of FLUVOXAMINE Treatment**

  Symptoms associated with the discontinuation or dosage reduction of fluvoxamine maleate have been reported. Patients should be monitored for these and other symptoms when discontinuing treatment or during dosage reduction.

  A gradual reduction in the dose over several weeks rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response **(See WARNINGS AND PRECAUTIONS, Dependence/Tolerance, Discontinuation of Treatment with FLUVOXAMINE** and **ADVERSE REACTIONS, Adverse Reactions Following Discontinuation of Treatment (or Dose Reduction)**.

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

- **Treatment of Pregnant Women During the Third Trimester**

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

- **Use in Geriatrics**

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

Recommended Dose and Dosage Adjustment

Depression

Adult Dosage

Treatment should be initiated at the lowest possible dose (50 mg) given once daily at bedtime and then increased to 100 mg daily at bedtime after a few days, as tolerated. The effective daily dose usually lies between 100 mg and 200 mg and should be adjusted gradually according to the patient's individual response and tolerability, up to a maximum of 300 mg. Dosage increases should be made in 50 mg increments. Doses above 150 mg should be divided so that a maximum of 150 mg is given in the bedtime dose.

Obsessive-Compulsive Disorder

Adult Dosage

Treatment should be initiated at the lowest possible dose (50 mg) given once daily at bedtime and then increased to 100 mg daily at bedtime after a few days, as tolerated. The effective daily dose usually lies between 100 mg and 300 mg and should be adjusted gradually according to the patient's individual response and tolerability, up to a maximum of 300 mg. If no improvement is observed within 10 weeks, treatment with FLUVOXAMINE should be reassessed. Dosage increases should be made in 50 mg increments. Doses above 150 mg should be divided so that a maximum of 150 mg is given in the bedtime dose.

Use in Hepatic or Renal Insufficiency

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

Missed Dose
If a dose is forgotten, the next dose should be taken at the normal time.

Administration
FLUVOXAMINE should be swallowed whole with water and without chewing.

OVERDOSAGE

Symptoms
Since market introduction, reports of overdose have been rare and reports of death attributed to overdose with fluvoxamine maleate alone have been extremely rare.

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

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

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

Treatment

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

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

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

Pharmacodynamics

See **DETAILED PHARMACOLOGY**.

Pharmacokinetics

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

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

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

active in serotonergic or noradrenergic processes.

Absorption

Fluvoxamine is completely absorbed following oral administration. Maximum plasma concentrations occur within 3 to 8 hours of dosing. The mean absolute bioavailability is 53%, due to first-pass metabolism.

The pharmacokinetics of fluvoxamine maleate is not influenced by concomitant food intake.

Distribution
In vitro binding of fluvoxamine maleate to human plasma proteins is approximately 80% over a concentration range of 20 to 2000 ng/mL. Volume of distribution in humans is 25 L/kg.

Metabolism

Fluvoxamine maleate undergoes extensive hepatic transformation, mainly via oxidative demethylation, to at least nine metabolites, which are excreted by the kidney. The two major metabolites showed negligible pharmacological activity. Fluvoxamine is a potent inhibitor of CYP1A2 and CYP2C19. A moderate inhibition was found for CYP2C9, CYP2D6 and CYP3A4.

Excretion
Following a ^{14}C-labelled oral dose of fluvoxamine maleate an average of 94% of the radioactive dose was recovered in the urine within 48 hours.

Special Populations and Conditions

Pediatrics

FLUVOXAMINE is not indicated for use in patients below the age of 18 years (see **INDICATIONS AND CLINICAL USE** and **WARNINGS AND PRECAUTIONS**).

Geriatrics

Since there is limited clinical experience in the geriatric age group, caution is recommended when administering FLUVOXAMINE to elderly patients (see **INDICATIONS AND CLINICAL USE)**.

Hepatic Insufficiency

The metabolism of fluvoxamine is impaired in patients with liver disease. Patients with hepatic insufficiency should begin treatment with a low dose and be carefully monitored (see **DOSAGE AND ADMINISTRATION**).

Renal Insufficiency

Patients with renal insufficiency should begin treatment with a low dose and be carefully monitored (see **DOSAGE AND ADMINISTRATION**).

STORAGE AND STABILITY

Preserve in well-closed containers. Store in a dry place at room temperature (15^{O}C to 30^{O}C). Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

FLUVOXAMINE (fluvoxamine maleate) 50 mg Tablets: Each round, white, biconvex, filmcoated tablet, engraved "NU" on one side, and "50" on the other, contains fluvoxamine maleate 50 mg. Available in bottles of 100.

FLUVOXAMINE 100 mg Tablets: Each oval, white, biconvex, film-coated tablet, scored and engraved "NU " on one side, and “100” on the other, contains fluvoxamine maleate 100 mg. Available in bottles of 100.

Listing of Non-Medicinal Ingredients

Each FLUVOXAMINE 50 mg tablet contains 50 mg fluvoxamine maleate with the following non-medicinal ingredients: Carnauba wax, hydroxypropyl methylcellulose, magnesium stearate, mannitol, polydextrose, polyethylene glycol, titanium dioxide.

Each FLUVOXAMINE 100 mg tablet contains 100 mg fluvoxamine maleate with the following non-medicinal ingredients: Carnauba wax, hydroxypropyl methylcellulose, magnesium stearate, mannitol, polydextrose, polyethylene glycol, titanium dioxide.

PART II: SCIENTIFIC INFORMATION

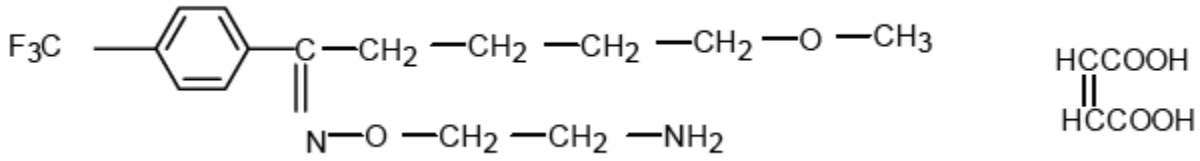
PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common Name: Fluvoxamine maleate

Chemical Name(s): 5-methoxy-4'-(trifluoromethyl)-valerophenone(*E*)-0-(2-amino-ethyl)oxime maleate (1:1).

Structural Formula:



Molecular Formula: $C_{15}H_{21}F_3N_2O_2.C_4H_4O_4$

Molecular Weight: 434.4 g/mol

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

CLINICAL TRIALS

Comparative Bioavailability

A standard, randomized, two-way crossover study was conducted in 18 healthy, adult, male volunteers to evaluate the relative bioavailability of single oral doses (one 100 mg tablet) of FLUVOXAMINE manufactured by Nu-Pharm Inc. and Luvox® manufactured by Solvay Kingswood. The mean pharmacokinetic parameters of the 16 subjects completing the study are listed in the following table:

Summary Table of the Comparative Bioavailability Data
Fluvoxamine (Dose: 1 x 100 mg) From Measured Data

Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)
	Fluvoxamine	Luvox®†	
AUC_T (ng•hr/mL)	652.6 774.2 (57.6)	612.8 780.7 (67.1)	106
AUC_I (ng•hr/mL)	751.4 883.3 (55.8)	735.8 904.6 (63.0)	102
C_{max} (ng/mL)	31.69 34.44 (41.0)	29.73 32.44 (42.0)	107
T_{max} (hr)*	5.00 (22.59)	5.00 (26.94)	-
$t_{1/2}$ (hr)*	15.81 (26.38)	16.37 (29.20)	-

* Arithmetic means (CV%). For t_{max} these are medians

† Luvox® is manufactured by Solvay Kingswood Inc. and was purchased in Canada.

DETAILED PHARMACOLOGY

Animal

Pharmacodynamics

In a series of *in vitro* and animal *in vivo* experiments, fluvoxamine maleate demonstrated as its primary pharmacological effect serotonin potentiating properties due to blockade of the membrane pump mechanism responsible for neuronal serotonin reuptake. Fluvoxamine was effective in inhibiting serotonin uptake by blood platelets and brain synaptosomes. The drug prevented serotonin depletion by tyramine derivatives through its membrane-pump inhibiting properties. As a result of this interference with the neuronal serotonin reuptake mechanism,

fluvoxamine produced a decreased serotonin turnover in the brain. The effects of 5-hydroxytryptophan in mice and rabbits were potentiated. Fluvoxamine, in combination with MAO inhibitors (in rats together with tryptophan), induced serotonin-like behaviour in mice and rats. In receptor binding studies, fluvoxamine is practically devoid of affinity towards cholinergic, histaminergic, adrenergic, dopaminergic and serotonergic receptors.

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

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

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

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

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

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

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

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

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

Pharmacokinetics

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

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

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

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

TOXICOLOGY

Acute Toxicity

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

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

	F	I.V.	68.1 (46.4-100.0)
Dog	M & F	Oral	> 464

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

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

Subacute Toxicity

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

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

The second study, in which hamsters were administered oral doses of 0, 9, 36, 142 and 432 mg/kg/day fluvoxamine, was of 30 days duration. Body weight gain and food consumption were significantly lower in the high-dose group and in male hamsters receiving 142 mg/kg/day. There was a significant treatment-related decrease in serum lipid levels in all treatment groups. However, after the 30-day recovery period, no treatment-related differences were evident except for a lower phospholipid level in the males of the high-dose group.

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

The effects of fluvoxamine (100, 200 mg/kg), imipramine and amitriptyline (25, 50, 100 mg/kg) on serum lipids were also compared in groups of mice given daily oral doses of each drug for two weeks. All three drugs exerted similar effects, with amitriptyline showing the strongest and

fluvoxamine the mildest. In mice treated with 200 mg/kg fluvoxamine, there was a dose-related decrease in body weight gain and food consumption and an increase in the weights of the liver and spleen. Slight histological changes were observed in the liver, lung, spleen and mesenteric lymph nodes. In addition, a dose-related hypolipidemia and, in the high-dose group, a significant increase in liver lipids was found. However, there was no evidence of phospholipidosis.

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

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

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

The toxic effects of orally administered fluvoxamine were further evaluated in mice in two additional 4-week studies involving doses ranging from 200 to 1600 mg/kg/day. In one study, mice received 0, 200, 300 or 400 mg/kg/day. Changes observed were a decrease in the body weight gain in male mice of the high-dose group and a dose-related accentuation of hepatic lobular pattern.

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

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

Long-Term Toxicity

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

Hamsters

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

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

Mouse

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

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

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

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

Two hours following autoradiography, radioactivity was detected within the hepatocellular

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

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

Rat

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

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

Fluvoxamine was administered to the diet of rats at dose levels of 0, 10, 40, 160 mg/kg/day for 81 weeks with the high-dose level increased to 200 mg/kg at week 40, then further increased to 240 mg/kg at week 47. Drug-related changes were primarily confined to the high-dose group and included decreases in body weight gain (males only), food and water consumption, the absolute weights of the brain and increases in urine concentration, the relative weights of the lung and liver (males only), the relative and absolute weights of the ovaries, lymphocytic infiltrations in the kidneys, the incidence of vacuolation of hepatocytes and the incidence of macrophage aggregations in the lungs. In the mid-dose group there was a decrease in body weight gain (females only) and an increase in the incidence of vacuolation of hepatocytes (males only). No drug-related changes were observed in the low-dose group. However, there was a significant decrease in the absolute and relative weights of the thyroid in females in this group. The biological significance of this finding is not known.

Dog

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

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

In a second study involving beagle dogs, fluvoxamine was administered orally via capsules for 53 weeks at dose levels of 0, 10, 25 or 62.5 mg/kg/day for 53 weeks. Clinical signs following drug treatment included moderate mydriasis at all dose levels, reduced weight gain and anorexia in the high-dose group, periodic reduction in water and food consumption and slight increase in the incidence of diarrhea in males in the mid- and high-dose groups. In addition, there was an increase in the levels of plasma alkaline phosphatase, an increase in the incidence of glomerular atrophy (also present in the control group) and occasional increases in plasma urea, creatinine and urine volume in the high-dose animals. Kidney weight was increased in male dogs in the mid- and high-dose groups. A foam-cell reaction in the reticuloendothelial system was observed in the mid- and high-dose groups and the lipid content of these cells was predominantly phospholipid.

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

Mutagenicity and Carcinogenicity

Mutagenicity

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

Carcinogenicity

Rats were given fluvoxamine as a day/diet mixture at dosage levels of 0, 10, 40 and 160 to 240

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

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

Reproduction and Teratology

Reproductive Studies

Reproductive studies in rats revealed impaired fertility and developmental toxicity.

In a study in which male and female rats were administered fluvoxamine (60, 120, or 240 mg/kg) prior to and during mating and gestation, fertility was impaired at oral doses of 120 mg/kg or greater, as evidenced by increased latency to mating, decreased sperm count, decreased epididymal weight, and decreased pregnancy rate. In addition, the numbers of implantations and embryos were decreased at the highest dose. The no effect dose for fertility impairment was 60 mg/kg (approximately 2 times the maximum recommended human dose [MRHD] on a mg/m2 basis).

When pregnant rats were given oral doses of fluvoxamine (60, 120, or 240 mg/kg) throughout the period of organogenesis, increased embryofetal death, decreased fetal body weight and increased incidences of fetal eye abnormalities (folded retina) were observed in fluvoxamine exposures exceeding by about 4 times human exposures at maximum recommended human doses. The no-effect dose for developmental toxicity in this study was 60 mg/kg (approximately 2 times the maximum recommended human dose on a mg/m2 basis).

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

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

Teratology

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

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

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PART III: CONSUMER INFORMATION

PrFLUVOXAMINE
fluvoxamine maleate

This leaflet is PART III of a three-part "Product Monograph" published when FLUVOXAMINE was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about FLUVOXAMINE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
FLUVOXAMINE has been prescribed by your doctor to relieve your symptoms of:

- depression (feeling sad, a change in appetite or weight, difficulty concentrating or sleeping, feeling tired, headaches, unexplained aches and pain), or
- obsessive-compulsive disorder (recurrent and intrusive thoughts, feelings, ideas or sensations; recurrent pattern of behaviour, or unwanted thoughts or actions)

What it does:
FLUVOXAMINE belongs to a group of medicines called selective serotonin reuptake inhibitor (SSRI) antidepressants. Depression is thought to be caused, in part, by low levels of a chemical that occurs naturally in the brain, called serotonin. FLUVOXAMINE is thought to work by increasing the levels of serotonin in the brain.

When it should not be used:
Do not use FLUVOXAMINE if you are:

- allergic to it or any of the components of its formulation (See **What the non-medicinal ingredients are:**).
- currently taking or have recently taken monoamine oxidase (MAO) inhibitor antidepressants (e.g. phenelzine sulphate, moclobemide) or a MAO inhibitor antibiotic (e.g. linezolid).
- going to have, or recently had, a medical procedure that involved the use of methylene blue (an intravenous dye).
- currently taking or have recently taken thioridazine, mesoridazine, pimozide, terfenadine, astemizole, or cisapride.
- currently taking or have recently taken tizanidine.
- taking ramelteon, a sleep medicine not available in Canada.

What the medicinal ingredient is:
Fluvoxamine maleate.

What the non-medicinal ingredients are:
Carnauba wax, hydroxypropyl methylcellulose, magnesium stearate, mannitol, polydextrose, polyethylene glycol, titanium dioxide.

What dosage forms it comes in:
FLUVOXAMINE is available as:

- Each round, white, biconvex, film-coated tablet, engraved "NU" on one side, and "50" on the other, contains fluvoxamine maleate 50 mg.
- Each oval, white, biconvex, film-coated tablet, scored and engraved "NU" on one side, and "100" on the other, contains fluvoxamine maleate 100 mg.

WARNING AND PRECAUTION

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

During treatment with FLUVOXAMINE or any type of antidepressant medication, it is important that you and your doctor have good ongoing communication about how you are feeling. Treatment with antidepressant medications is most safe and effective when you and your doctor have good communication about how you are feeling.

Changes in Feelings and Behaviour:
It is important that you have good communication with your doctor about how you feel. Discussing your feelings and treatment with a friend or relative who can tell you if they think you are getting worse is also useful.

Some patients may feel worse when first starting or changing the dose of drugs such as FLUVOXAMINE. You may feel more anxious, agitated, hostile, or impulsive, or may have thoughts about suicide, self-harm or harm to others. These changes in feelings can happen in patients treated with drugs like FLUVOXAMINE for any condition, and at any age, but it may be more likely in patients 18 to 24 years old. If this happens, see your doctor

immediately. Do not stop taking FLUVOXAMINE on your own.

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

Medicines like FLUVOXAMINE may affect your sperm. Fertility in some men may be reduced while taking FLUVOXAMINE. This effect is reversible. Full impact on fertility in men is not yet known.

Angle-closure Glaucoma: FLUVOXAMINE can cause an acute attack of glaucoma. Having your eyes examined before you take FLUVOXAMINE could help identify if you are at risk of having angle-closure glaucoma. Seek immediate medical attention if you experience:

- eye pain.
- changes in vision.
- swelling or redness in or around the eye.

Talk to your doctor or pharmacist before using FLUVOXAMINE:

- if you have had any allergic reaction to medications, food, etc.
- about all your medical conditions, including a history of seizures, liver or kidney disease, heart problems or a history of any abnormal bleeding.
- about any medications (prescription or over-the-counter) you are taking or have recently taken, especially monoamine oxidase (MAO) inhibitors (e.g., phenelzine sulphate, moclobemide), any other antidepressants, tizanidine, thioridazine, pimozide, mesoridazine, neuroleptics, clopidogrel, warfarin, propranolol, phenytoin, theophylline, lithium, tryptophan, terfenadine, astemizole, cisapride, triptans used to treat migraines, lithium, tramadol, drugs containing tryptophan, drugs used to prevent seizures (anticonvulsants).
- about any natural or herbal products you are taking (e.g., St. John's Wort).
- if you have a history or family history of mania/hypomania or bipolar disorder.
- if you have high or low blood sugar, or diabetes mellitus.
- if you have a bleeding disorder or a tendency to easily develop bruises, have been told that you have low platelets.
- if you have been told you have a low sodium level in the blood.
- if you had a recent bone fracture or were told you have osteoporosis or risk factors for osteoporosis.
- if you are pregnant, or are thinking about becoming pregnant, or if you are breast feeding.
- about your habits of alcohol and/or street drug consumption.
- if you drive a vehicle or perform hazardous tasks during your work.

Effects on Pregnancy and Newborns
FLUVOXAMINE should not be used during pregnancy unless the benefit outweighs the risk.

If you are already taking FLUVOXAMINE and have just found out that you are pregnant, you should talk to your doctor immediately. You should also talk to your doctor if you are planning to become pregnant. It is very important that you do NOT stop taking FLUVOXAMINE without first talking to your doctor.

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

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

Persistent Pulmonary Hypertension (PPHN) and newer antidepressants:
When taken during pregnancy, particularly in the last 3 months of pregnancy, medicines like FLUVOXAMINE may increase the risk of a serious

lung condition in babies, called persistent pulmonary hypertension of the newborn (PPHN), that causes breathing difficulties in newborns soon after birth, making the baby breathe faster and appear bluish. These symptoms usually begin during the first 24 hours after the baby is born. If this happens to your baby you should contact your doctor immediately.

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

INTERACTIONS WITH THIS MEDICATION

Do not use FLUVOXAMINE if you are taking or have recently taken monoamine oxidase (MAO) inhibitors, methylene blue (intravenous), linezolid, thioridazine, mesoridazine, pimozide, terfenadine, astemizole, cisapride, tizanidine or ramelteon (a sleep drug, not available in Canada).

Drugs that may interact with FLUVOXAMINE include:

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

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

PROPER USE OF THIS MEDICATION

Usual dose:

- It is very important that you take FLUVOXAMINE exactly as your doctor has instructed. Generally most people take between 100 mg to 200 mg per day for depression and between 100 mg and 300 mg for obsessive compulsive disorder.
- FLUVOXAMINE is usually taken once a day at bedtime. However, doses above 150 mg per day may be divided so that a maximum of 150 mg is taken at bedtime. Swallow the tablets whole with water. Do not chew them.
- Establishing an effective dosage level will vary from one person to another. For this reason, your doctor may adjust your dosage gradually during treatment.
- As with all antidepressants, improvement with FLUVOXAMINE is gradual. You should continue to take your medication even if you do not feel better, as it may take a number of weeks for your medicine to work. Continue to take FLUVOXAMINE for as long as your doctor recommends.
- Never increase or decrease the amount of FLUVOXAMINE you are taking unless your doctor tells you to change your dosage.
- Do not suddenly stop taking this medication without talking to your doctor first. Suddenly stopping treatment or changing the dose may cause unpleasant side effects (see SIDE EFFECTS AND WHAT TO DO ABOUT THEM).
- You should avoid taking St. John's Wort if you are taking FLUVOXAMINE.

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

Overdose:

If you think you have taken too much FLUVOXAMINE, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

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

The most common side effects of FLUVOXAMINE are:

- nausea (sometimes with vomiting)
- constipation
- diarrhea
- loss of appetite
- upset stomach
- sleep disturbances
- dry mouth
- tremor (uncontrolled shaking)
- dizziness
- headache
- anxiety
- nervousness
- excessive sweating
- sexual problems
- urinating problems.

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

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

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

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

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

Symptom / effect		Talk with your healthcare professional		Seek immediate emergency medical assistance
		Only if severe	In all cases	
Common	Uncontrollable movements of the body or face		✓	
Uncommon	**Allergic reactions:** red and lumpy skin rash, hives,			✓

	swelling, trouble breathing			
	Akathisia: feeling restless and unable to sit or stand still		✓	
	Hallucinations: strange visions or sounds		✓	
Unknown	**Low platelets:** Bruising or unusual bleeding from the skin or other areas		✓	
	Stevens Johnson Syndrome/Toxic Epidermal Necrolysis: Severe skin reactions, like skin rashes or redness, including widespread rash with blisters and peeling skin, particularly occurring around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome), extensive peeling of the skin (more than 30% of the body surface – toxic epidermal necrolysis)			✓
Rare	**Low sodium level in the blood:** tiredness, weakness, confusion, combined with achy, stiff or uncoordinated muscles		✓	
	Gastrointestinal bleeding: vomiting blood or passing blood in stools			✓
	Seizures: loss of consciousness with uncontrollable shaking			✓
	Liver disorder: nausea, vomiting, loss of appetite combined with itching, yellowing of the skin or eyes, dark urine			✓
	Serotonin syndrome/ Neuroleptic Malignant Syndrome: a combination of most or all of the following: confusion, restlessness, sweating, shaking, shivering, nausea, diarrhea, vomiting, hallucinations, sudden jerking of the muscles, fast heartbeat, changes in blood pressure			✓
	Glaucoma: Eye pain, change in vision, swelling or redness in or around the eye			✓
See Warnings & Precautions	Changes in feelings or behaviour (anger, anxiety, agitation, hostility)		✓	
	Thoughts of death or suicide			✓
	Increased blood sugar: frequent urination, thirst and hunger		✓	
	Low blood sugar: symptoms of dizziness, lack of energy, drowsiness		✓	

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

HOW TO STORE IT

Preserve in well-closed containers. Store in a dry place at room temperature (15 ^{O}C to 30^{O}C). Keep FLUVOXAMINE out of reach and sight of children. Keep container tightly closed. If your doctor tells you to stop taking FLUVOXAMINE, please return any leftover medicine to your pharmacist.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about FLUVOXAMINE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp). Find the Consumer Information on the manufacturer's website (http://www.apotex.ca/products) or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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