PRODUCT MONOGRAPH

ratio-FLUVOXAMINE

fluvoxamine maleate

50 mg and 100 mg Film Coated, Scored Tablets

Antidepressant

Antiobsessional Agent

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ACTION

The antidepressant and antiobsessional actions of **ratio-FLUVOXAMINE** (fluvoxamine maleate) are believed to be related to its selective inhibition of presynaptic serotonin re-uptake in brain neurones.

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 $Alpha_1$, $Alpha_2$, $Beta_1$, $dopamine_2$, $histamine_1$, $serotonin_1$, $serotonin_2$ or muscarinic receptors.

PHARMACOKINETICS

In healthy volunteers, fluvoxamine maleate is well absorbed after oral administration. Following a single 100 mg oral dose, peak plasma levels of 31-87 ng/mL were attained 1.5 to 8 hours post-dose. Peak plasma levels and AUC's (0-72 hours) are directly proportionate to dose after single oral doses of 25, 50, and 100mg. Following single doses, the mean plasma half-life is 15 hours, and slightly longer (17-22 hours), during repeated dosing. Steady-state plasma levels are usually achieved within 10-14 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 3-8 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.

METABOLISM AND ELIMINATION

Fluvoxamine maleate undergoes extensive hepatic transformation, mainly via oxidative demethylation, to at least nine metabolites, which are excreted by the kidney. Ninety-four percent of an oral radioactive dose is recovered in the urine within 48 hours. The two major metabolites showed negligible pharmacological activity. *In vitro* binding of fluvoxamine maleate to human plasma proteins is about 77% at drug concentrations up to 4000 ng/mL.

INDICATIONS

DEPRESSION

ratio-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

ratio-FLUVOXAMINE (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 **ratio-FLUVOXAMINE** (fluvoxamine maleate) has been studied in double-blind, placebo-controlled clinical trials conducted in obsessive-compulsive outpatients. The usefulness of **ratio-FLUVOXAMINE** (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 **ratio-FLUVOXAMINE** (fluvoxamine maleate) for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

ratio-FLUVOXAMINE (fluvoxamine maleate) is contraindicated in patients with known hypersensitivity to fluvoxamine maleate or any of the excipients.

Fluvoxamine maleate should not be administered together with tizanidine or monoamine oxidase (MAO) inhibitors, including linezolid, an antibiotic which is a reversible non-selective MAO inhibitor. At least two weeks should elapse after discontinuation of MAO inhibitor therapy before fluvoxamine maleate treatment is initiated. MAO inhibitors should not be introduced within 2 weeks of cessation of therapy with **ratio-FLUVOXAMINE** (fluvoxamine maleate).

Co-administration of thioridazine, mesoridazine, terfenadine, astemizole, or cisapride with **ratio-FLUVOXAMINE** (fluvoxamine maleate) is contraindicated (see **WARNINGS** and **PRECAUTIONS**).

WARNINGS

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 anti-depressants suggests 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 anti-depressants, 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 with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than

25 years old.

Discontinuation Symptoms

Patients currently taking ratio-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 anti-depressant drug, a gradual reduction in the dose rather an abrupt cessation is recommended.

Potential Interaction with Thioridazine and Mesoridazine:

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

Thioridazine 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. It is likely that this experience underestimates the degree of risk that might occur with higher doses of thioridazine. Moreover, the effect of fluvoxamine may even be more pronounced when it is administered at higher doses.

Therefore **ratio-FLUVOXAMINE** (fluvoxamine maleate) and thioridazine or mesoridazine should not be co-administered (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

Potential Interaction with Terfenadine, Astemizole and Cisapride: Terfenadine, astemizole, and cisapride are all metabolized by CYP3A4. Since fluvoxamine maleate is known to inhibit the CYP3A4, theoretically, there may be a potential interaction with terfenadine, astemizole, or cisapride. Consequently, it is recommended that fluvoxamine maleate not be used in combination with terfenadine, astemizole, or cisapride (see **CONTRAINDICATIONS and PRECAUTIONS- Drug Interactions**).

Potential Interaction with Drugs with a Narrow Therapeutic Index

There may be a potential interaction between fluxovamine maleate and drugs metabolized by CYP3A4 that have a narrow therapeutic index (e.g., carbamazepine, methadone and cyclosporine). Patients administered these combinations should be carefully monitored and, if necessary, dose adjustment of these drugs is recommended (See **PRECAUTIONS – Drug Interactions**).

PRECAUTIONS

DISCONTINUATION SYMPTOMS

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), agitation, anxiety, fatigue, confusion, headache, tremor, nausea, vomiting, and sweating or other symptoms which may be of clinical significance (see **ADVERSE REACTIONS**)]. 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** and **DOSAGE and ADMINISTRATION**). If fluvoxamine is used until or shortly before birth, discontinuation effects in the newborn may occur (see also **PRECAUTIONS**, Use in Pregnancy and Lactation).

SUICIDE / SUICIDAL THOUGHTS OR CLINICAL WORSENING

The possibility of a suicide attempt is inherent in depression 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 high-risk patients should accompany drug therapy and consideration should be given to

the possible need for hospitalization. Physicians should encourage patients of all ages to report any new or worsened distressing thoughts or feelings occurring at any time. In order to minimize the opportunity for overdosage, prescriptions for **ratio-FLUVOXAMINE** (fluvoxamine maleate) should be written for the smallest quantity of drug consistent with good patient management.
Obsessive compulsive disorders can also be associated with an increased risk of suicide-related events.

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. Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Because of the well established co-morbidity 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: POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM)**.

AKATHISIA/ PSYCHOMOTOR RESTLESSNESS
The use of fluvoxamine 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.

SEIZURES

Convulsions have been reported rarely during **ratio-FLUVOXAMINE** (fluvoxamine maleate) administration. 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 maleate should be discontinued if seizures occur or if seizure frequency increases. Seizures have also been reported as a discontinuation symptom (see also **PRECAUTIONS**, DISCONTINUATION SYMPTOMS; **ADVERSE EVENTS**, DISCONTINUATION SYMPTOMS; **DOSAGE AND ADMINISTRATION**, Discontinuation of **ratio-FLUVOXAMINE** TREATMENT) .

DISTURBANCE OF GLYCEMIC CONTROL

Glycemic control may be disturbed, especially in the early stages of the treatment. Reported events include hyperglycemia, hypoglycaemia, diabetes mellitus and decreased glucose tolerance; these have been reported in both patients with and without pre-existing disturbance of glycemic control. The dosage of anti-diabetic drugs may need to be adjusted.

ECT

Concurrent administration with electroshock therapy should be avoided because of the absence of experience in this area.

HEPATIC ENZYMES

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

COMBINATION WITH ALCOHOL

Fluvoxamine maleate may potentiate the effects of alcohol and increase the level of psychomotor impairment.

SEROTONIN SYNDROME

On rare occasions, development of a serotonin syndrome or neuroleptic malignant syndrome-like events have been reported in association with treatment of fluvoxamine, particularly when given in combination with other serotonergic and /or neuroleptic drugs. As these syndromes may result in potentially life-threatening conditions, treatment with fluvoxamine maleate should be discontinued and supportive treatment initiated, if characteristic events occur i.e., clusters of symptoms such as 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 (See also **PRECAUTIONS**, DRUG INTERACTIONS, Serotonergic Drugs).

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. The majority of reports were associated with older patients.

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 co-ordination - such as driving an automobile or performing hazardous tasks - until they are reasonably certain that treatment with **ratio-FLUVOXAMINE** (fluvoxamine maleate) does not affect them adversely.

CONCOMITANT ILLNESS

ratio-FLUVOXAMINE (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 premarketing clinical studies.

HAEMORRHAGE

SSRIs and serotonin/norepinephrine reuptake inhibitors (SNRIs), including LUVOX (fluvoxamine maleate), may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. There have been reports of bleeding events ranging from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening haemorrhages, associated with treatment with SSRIs and SNRIs.

Caution is advised in patients taking SSRIs and SNRIs, particularly in concomitant use with drugs known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, anticoagulants, platelet aggregation inhibitors, acetylsalicylic acid and NSAIDs), as well as in patients with a history of bleeding disorders.

USE IN PREGNANCY AND LACTATION

Safe use of fluvoxamine maleate during pregnancy and lactation has not been established. Like other antidepressants, fluvoxamine maleate is excreted via human milk in small quantities. Therefore, it should not be administered to women of childbearing potential or nursing mothers unless, in the opinion of the treating physician, the expected benefits to the patient outweigh the possible hazards to the child or fetus.

Complications following late third trimester exposure to SSRIs:

Post-marketing reports indicate that some neonates exposed to **ratio-FLUVOXAMINE**, SSRIs (Selective Serotonin Reuptake Inhibitors), or other newer anti-depressants 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 anti-depressants, or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see PRECAUTIONS – SEROTONIN SYNDROME). When treating a pregnant woman with **ratio-FLUVOXAMINE** the physician should carefully consider the potential risks and benefits of treatment (see **DOSAGE AND ADMINISTRATION**).

Risk of PPHN and exposure to SSRIs:

In one epidemiological case-control study on persistent pulmonary hypertension (PPHN) with n = 377 infants with PPHN and n = 836 matched control infants, PPHN was six times more common in babies whose mothers took an SSRI antidepressant after the 20th week of pregnancy compared to babies whose mothers did not take an antidepressant. The study was too small to determine relative risks among the specific SSRIs. This information is considered to be preliminary at this time. The absolute risk of PPHN in the general population is reported to be 1 – 2 per 1000.

USE IN CHILDREN

Safety and efficacy in children under 18 years of age have not been established.

DRUG INTERACTIONS

ratio-FLUVOXAMINE (fluvoxamine maleate) is contraindicated in combined use with tizanidine, MAO inhibitors, linezolid (an antibiotic which is a reversible non-selective MAO inhibitor), thioridazine, or mesoridxazine (see **CONTRAINDICATIONS** and **WARNINGS**). Isolated cases of cardiac toxicity have been reported when fluvoxamine was combined with thioridazine (See **CONTRAINDICATIONS** and **WARNINGS**).

CYTOCHROME P450 ENZYMES

Fluvoxamine maleate is a potent inhibitor of CYP1A2, and to a lesser extent of CYP2C and CY93A4. Drugs which are largely metabolised via these isoenzymes are eliminated slower and may have higher plasma concentrations when co-administered with fluvoxamine maleate. This is particularly relevant for drugs with a narrow therapeutic index. Patients should be carefully monitored and, if necessary, dose adjustment of these drugs is recommended.

CYP1A2

An increase in previously stable plasma levels of those tricyclic antidepressants (e.g., clomipramine, imipramine, amitriptyline) and neuroleptics (e.g., clozapine, olanzapine) which are largely metabolized through CYP1A2", has been reported in patients taking fluvoxamine maleate concomitantly. Thus, the combination of these drugs with fluvoxamine is not recommended.

Patients co-administered fluvoxamine maleate and CYP1A2 metabolized drugs with a narrow therapeutic index (such as tacrine, theophylline, methadone, mexiletine, clozapine, warfarin) should be carefully monitored and, if necessary, dose adjustment of these drugs is recommended.

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.

As plasma concentrations of propranolol are increased in combination with fluvoxamine maleate, the propranolol dose may need to be lowered; a 5-fold increase in plasma levels of propranolol was seen in interaction studies.

When a single 40 mg dose of tacrine was added to fluvoxamine maleate 100 mg/day administered at steady-state, an associated five and eight fold increase in tacrine C_{max} and AUC, respectively, were observed.

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

As plasma concentrations of ropinirole may be increased in combination with fluvoxamine maleate thus increasing the risk of overdose, surveillance and reduction in the dosage of ropinirole during fluvoxamine maleate treatment and after its withdrawal may be required.

CYP2C

Fluvoxamine maleate is also believed to inhibit CYP2C and thus may interact with CYP2C substrates like diazepam. Clearance of both diazepam and its active metabolite N-desmethyldiazepam were reduced with concurrent administration of fluvoxamine maleate.

Patients co-administered fluvoxamine maleate and CYP2C metabolised drugs with a narrow therapeutic index (such as phenytoin) should be carefully monitored and, if necessary, dose adjustment of these drugs is recommended.

CYP3A4

Fluvoxamine maleate is also known to inhibit the CYP3A4 and thus may interact with CYP3A4 substrates like diltiazem and alprazolam. A clinically significant interaction is possible with CYP3A4 substrates that have a narrow therapeutic index such as carbamazepine, methadone, and cyclosporine. Such combinations should therefore be administered with caution, and consideration be given to lowering the dose of the

concomitant agent. A significantly increased methadone plasma level/dose ratio was seen during concurrent administration of fluvoxamine maleate. When fluvoxamine maleate and alprazolam were co-administered to steady state, plasma concentrations and other pharmacokinetic parameters (AUC, Cmax, $T_{1/2}$) of alprazolam were approximately twice those observed when alprazolam was administered alone; clearance was reduced by about 50%. Since terfenadine, astemizole, and cisapride, are metabolized by the CYP3A4, theoretically there may be a potential interaction with fluvoxamine maleate that could result in an increased risk for QT prolongation/ Torsades de Pointes. Thus, it is recommended that fluvoxamine maleate not be used in combination with either terfenadine, astemizole, or cisapride (see **CONTRAINDICATIONS**).

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.

Oxidative Metabolism

The plasma levels of oxidatively metabolised benzodiazepines (e.g., triazolam, midazolam, alprazolam, and diazepam) are likely to be increased when co-administered with fluvoxamine. The dosage of these benzodiazepines should be reduced during co-administration with fluvoxamine.

Glucuronidation

Fluvoxamine maleate does not influence plasma concentrations of digoxin. The clearance of benzodiazepines metabolized by glucuronidation (e.g., lorazepam, oxazepam, temazepam) is unlikely to be affected by fluvoxamine maleate.

Renal excretion

Fluvoxamine maleate does not influence plasma concentrations of atenolol.

Pharmacodynamic interactions

CNS Active Drugs

The serotonergic effects of fluvoxamine may be enhanced when used in combination with other serotonergic agents (including triptans, tramodol, SSRIs and St. John's Wort preparations).

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.

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

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

Oral Anti-Coagulants

In patients on oral anticoagulants and fluvoxamine, the risk for haemorrhage may increase and these patients should therefore be closely monitored.

Metabolism of Fluvoxamine

The specific CYP isoenzymes involved in the metabolism of fluvoxamine maleate remains to be identified.

ADVERSE REACTIONS

COMMONLY OBSERVED

In clinical trials, the most commonly observed adverse events associated with **ratio-FLUVOXAMINE** (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 Approximately 14% (14.4%) of 34,587 patients who received **ratio-FLUVOXAMINE** (fluvoxamine maleate) in clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation from depression trials included nausea and vomiting, insomnia, agitation, headache, abdominal pain, somnolence, dizziness, asthenia and anorexia. The most common events causing discontinuation in patients suffering from obsessive compulsive disorder included insomnia, asthenia and somnolence.

INCIDENCE OF ADVERSE EXPERIENCES

Adverse events with an incidence of $\geq$ 5% reported in double-blind, placebo-controlled clinical trials in depression and in obsessive compulsive disorder are presented in the following table for each indication.

TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE (≥ 5%) IN PLACEBO-CONTROLLED CLINICAL TRIALS FOR DEPRESSION AND OBSESSIVE COMPULSIVE DISORDER*

Percentage of Patients Reporting Event				
	Depression		OCD	
BodySystem/AdverseEvent	Fluvoxamine (N=222)	Placebo (N=1 92)	Fluvoxamine (N=1 60)	Placebo (N=1 60)
NervousSystem				
Somnolence	26.2	9.0	26.9	9.4
Agitation	15.7	8.9	3.8	0
Insomnia	14.4	10.4	31.3	15.0
Dizziness	14.8	13.5	9.4	4.4
Tremor	10.8	4.7	8.1	0.6
Hypokinesia	8.1	3.6	-	-
Hyperkinesia	6.7	8.9	-	-
Depression	4.0	4.2	6.3	4.4
Nervousness	2.2	1.6	15.6	5.0
Anxiety	2.3	2.1	9.4	6.9
Libido Decreased	-	-	7.5	1.9
Thinking Abnormal	-	-	6.9	3.8
Digestive System				
Nausea	36.5	10.9	28.8	6.9
Dry Mouth	25.7	23.9	11.9	3.1
Constipation	18.0	6.8	14.4	8.8
Anorexia	14.9	6.3	5.0	3.1
Diarrhea	5.9	6.3	11.9	8.8
Dyspepsia	3.2	0	13.8	9.4
Body as a Whole				
Headache	21.6	18.7	20.0	23.8
Pain	5.9	3.7	4.4	1.3
Asthenia	4.9	3.2	28.8	9.4
Infection	-	-	11.3	9.4
Abdominal Pain	3.6	3.6	5.6	8.1
Flu Syndrome	-	-	5.0	3.8
Skin				
Sweating Increased	11.2	12.5	6.9	1.9
Respiratory System				
Pharyngitis	-	-	6.3	5.0
Rhinitis	1.3	2.6	5.6	1.9
Special Senses				
Accommodation Abnormal	6.3	6.3	-	-
Taste Perversion	3.2	3.1	5.0	0
Urogenital				
Urinary Frequency	2.2	1.6	5.0	1.3
Abnormal Ejaculation	1.4	0	17.9+	0

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

\+ Corrected for gender (males: n=78)

Additional Adverse Events Reported in Clinical Trials

During premarketing and postmarketing studies, multiple doses of **ratio-FLUVOXAMINE** (fluvoxamine maleate) were administered to approximately 34,587 patients. All events with an incidence of > 0.01% 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 **ratio-FLUVOXAMINE** (fluvoxamine maleate), they were not necessarily caused by it.

NERVOUS SYSTEM

Frequent: Agitation, anxiety, dizziness, insomnia, nervousness, somnolence, thinking abnormal, tremor, vertigo.

Infrequent: Abnormal dreams, abnormal gait, akathisia, amnesia, apathy , ataxia, confusion, depersonalization, depression, drug dependence, emotional lability, euphoria, hallucinations, hostility, hyperkinesia , hypertonia , hypoesthesia, hypokinesia, incoordination , increased salivation, libido decreased, libido increased, manic reaction, neurosis, paraesthesia, psychotic depression, stupor, twitching, vasodilatation.

Rare: Akinesia, CNS neoplasia, CNS stimulation, coma, convulsion, delirium, delusions, dysarthria , dyskinesia, dystonia, extrapyramidal syndrome, hemiplegia, hyperesthesia, hypotonia, hysteria, myoclonus, neuralgia, neuropathy, paralysis, paranoid reaction, psychosis, reflexes decreased, schizophrenic reaction, screaming syndrome, torticollis , trismus.

DIGESTIVE SYSTEM
Frequent: Anorexia, constipation, diarrhea, dry mouth, dyspepsia, nausea, vomiting.

Infrequent: Colitis, dysphagia, eructation, flatulence, gastritis, gastroenteritis, increased appetite, thirst.

Rare Biliary pain, esophagitis, fecal incontinence, gastrointestinal carcinoma, gastrointestinal haemorrhage, gingivitis, glossitis, hematemesis, hepatitis, jaundice, liver function tests abnormal, melena, mouth ulceration, rectal haemorrhage, stomatitis, tenesmus, tongue discoloration , tongue edema, tooth disorder.

CARDIOVASCULAR SYSTEM
Frequent: Palpitation.

Infrequent: Angina pectoris, hypertension, hypotension, migraine, postural hypotension, syncope, tachycardia.

Rare**:** Arrhythmia, bradycardia, cerebrovascular accident, extrasystoles, haemorrhage, myocardial infarct, pallor, peripheral vascular disorder, shock.

BODY AS A WHOLE
Frequent: Abdominal pain, asthenia, headache, malaise.

Infrequent: Accidental injury, allergic reaction, back pain, chest pain, chills, fever, flu syndrome, infection, neck pain, pain, suicide attempt.

Rare: Abdomen enlarged, chills and fever, face edema, halitosis, hangover effect, hernia, neck rigidity, overdose, pelvic pain.

SKIN

Frequent: Sweating increased.

Infrequent: Cutaneous hypersensitivity reactions (including rash, pruritis, angioedema)

Rare: Acne, alopecia, dry skin, eczema, furunculosis, Herpes simplex, Herpes zoster, maculopapular rash, psoriasis, urticaria.

RESPIRATORY SYSTEM

Infrequent: Dyspnea, pharyngitis, rhinitis.

Rare: Asthma, bronchitis, cough increased, epistaxis, hiccup, hyperventilation, laryngismus, laryngitis, pneumonia, sinusitis, voice alteration, yawn.

SPECIAL SENSES

Infrequent: Abnormal vision, amblyopia, hyperacusis.

Rare: Abnormality of accommodation, blepharitis, conjunctivitis, deafness, diplopia, dry eyes, ear pain, eye pain, lacrimation disorder, mydriasis, parosmia, photophobia, taste loss.

MUSCULOSKELETAL SYSTEM

Infrequent: Arthralgia, arthrosis, myalgia, myasthenia, tetany.

Rare: Arthritis, bone pain, leg cramps, pathological fracture, rheumatoid arthritis.

UROGENITAL SYSTEM

Infrequent: Abnormal ejaculation, dysuria, impotence, metrorrhagia, urinary frequency, urinary incontinence.

Rare: Amenorrhea, anorgasmia, breast pain, cystitis, dysmenorrhea, female lactation, hematuria, kidney pain, leukorrhea, menorrhagia, nocturia, polyuria, prostatic disorder, urinary retention, urinary tract infection, urinary urgency, vaginitis.

METABOLIC AND NUTRITIONAL SYSTEM
Frequent: Weight gain
Infrequent: Peripheral edema, weight loss.

Rare: Alcohol intolerance, dehydration, edema, obesity.

HEMATIC AND LYMPH SYSTEMS
Rare: Anemia, cyanosis, ecchymosis, lymphadenopathy, thrombocytopenia.

HAEMORRAHAGE
See “PRECAUTIONS”**.**

ADVERSE REACTIONS FOLLOWING DISCONTINUATION OF TREATMENT (OR DOSE REDUCTION)
There have been reports of adverse reactions upon the discontinuation of **ratio-FLUVOXAMINE** (fluvoxamine maleate) (particularly when abrupt), including but not limited to the following : dizziness, abnormal dreams, sensory disturbances (including paresthesias and electric shock sensations), agitation, anxiety, fatigue, confusion, headache, tremor, nausea, vomiting and sweating or other symptoms which may be of clinical significance (see **PRECAUTIONS** and **DOSAGE and ADMINISTRATION**).

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. These events are generally self-limiting. Symptoms associated with discontinuation have been reported for other selective serotonin reuptake inhibitors. Isolated cases of withdrawal symptoms in the newborn child have been described after the use of fluvoxamine maleate at the end of pregnancy (see **PRECAUTIONS** and **DOSAGE and ADMINISTRATION**). Some newborns experience feeding and/or respiratory difficulties, seizures, temperature instability, hypoglycemia, tremor, abnormal muscle tone, jitteriness, and constant crying after third trimester exposure to SSRIs and may require prolonged hospitalization.

Anecdotal spontaneous reports, from the marketplace, but not from clinical trials, have been collected for the following adverse experiences: galactorrhoea, photosensitivity, Stevens Johnson Syndrome, alopecia, taste perversion, tinnitus, psychomotor restlessness, micturition disorder (including enuresis), drug withdrawal syndrome (including drug withdrawal syndrome neonatal) and haemorrhagic manifestations e.g. eccyhmoses, purpura, gastrointestinal bleeding (see **WARNINGS** and **PRECAUTIONS**). Cases of suicidal ideation and suicidal behaviours have been reported during fluvoxamine therapy or early after treatment discontinuation. Rarely, serotonin syndrome, neuroleptic malignant syndrome-like events, hyponatremia and SIADH have been reported (see **PRECAUTIONS**, Serotonin Syndrome; and **PRECAUTIONS**, DRUG INTERACTIONS, CNS Active Drugs).

SYMPTOMS AND TREATMENT OF OVERDOSE

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

SYMPTOMS

ratio-FLUVOXAMINE (fluvoxamine maleate) received its first marketing authorization worldwide in 1983 therefore it has been on the market for more than 25 years. In the cumulative post-marketing experience for fluvoxamine, there are over 700 cases in the safety database associated with the adverse drug reaction, overdose (or a similarly–

related term). In the majority of these cases, the patients were taking multiple drugs in addition to fluvoxamine. In such cases, it is difficult to differentiate the additive drug effects or drug interactions that may have impacted patient outcome. The smallest estimated dose of fluvoxamine alone associated with a fatal outcome is approximately 1800 mg.

The most common symptoms of overdosage include gastrointestinal complaints (nausea, vomiting, and diarrhoea), 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.

DOSAGE AND ADMINISTRATION

ratio-FLUVOXAMINE (fluvoxamine maleate) is not indicated for use in children under 18 years of age (see WARNINGS: POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM).

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 individual response of the patient, 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. Tablets should be swallowed with water and without chewing.

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 individual response of the patient, up to a maximum of 300 mg. If no improvement is observed within 10 weeks, treatment with **ratio-FLUVOXAMINE** (fluvoxamine maleate) should be reconsidered. 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. **ratio-FLUVOXAMINE** (fluvoxamine maleate) should be swallowed with water and without chewing.

DISCONTINUATION OF ratio-FLUVOXAMINE TREATMENT
Symptoms associated with the discontinuation or dosage reduction **of ratio-FLUVOXAMINE** (fluvoxamine maleate) have been reported. Patients should be monitored for these and other symptoms when discontinuing treatment or during dosage reduction (see **PRECAUTIONS** and **ADVERSE REACTIONS**).

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 **PRECAUTIONS** and **ADVERSE REACTIONS**).

USE IN HEPATIC OR RENAL INSUFFICIENCY

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

USE IN CHILDREN

The safety and effectiveness of fluvoxamine maleate in children under 18 years of age have not been established **(see WARNINGS: 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 ratio-FLUVOXAMINE** (fluvoxamine maleate), SSRIs, or other newer anti-depressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see PRECAUTIONS). When treating pregnant women with **ratio-FLUVOXAMINE** (fluvoxamine maleate) the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering **ratio-FLUVOXAMINE** (fluvoxamine maleate) in the third trimester.

USE IN GERIATRICS

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

PHARMACEUTICAL INFORMATION

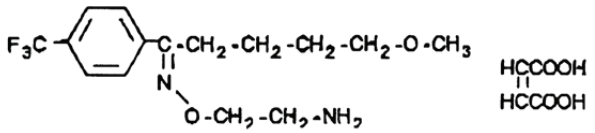
DRUG SUBSTANCE

Trade name: **ratio-FLUVOXAMINE**

Proper Name: Fluvoxamine maleate

Chemical Name: 5-methoxy-4'-(trifluoromethyl) valerophenone(E)-0-(2-aminoethyl) oxime maleate (1:1)

Structural Formula:



Molecular Weight: 434.4

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

STORAGE CONDITIONS

Store in a dry place at temperatures between 15 and 25°C. Protect from light.

AVAILABILITY

Each round, biconvex, scored, white, film-coated 50 mg tablet, stamped “291” twice on one side and a stylized “S” on the other, contains 50 mg fluvoxamine maleate. Non-medicinal ingredients: colloidal anhydrous silica, maize starch, mannitol, hypromellose, polyethylene glycol 6000, pregelatinized starch, sodium stearyl fumarate, talc and titanium dioxide. Bottles of 100.

Each oval, biconvex, scored, white, film-coated 100 mg tablet, stamped “313” twice on one side and a stylized “S” on the other, contains 100 mg fluvoxamine maleate. Non- medicinal ingredients: colloidal anhydrous silica, maize starch, mannitol, hypromellose, polyethylene glycol 6000, pregelatinized starch, sodium stearyl fumarate, talc and titanium dioxide. Bottles of 100.

Fluvoxamine maleate is a Schedule F drug.

PHARMACOLOGY

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 i.v. bolus injection in cats, a dose-dependent, transient blood pressure reduction was observed; infusions of fluvoxamine over 2 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 sulfate) 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 alpha-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 1 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 3 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, and autopsy of rats which succumbed to the treatment revealed marked erosion and haemorrhage 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 awareness. Haemoglobinuria at a concentrations of $\geq$10 mg/mL was indicative of an haemolytic 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, and 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 1 male mouse died during week 4. 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 intra-cellular 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 2 years.

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.

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-Beta 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.

Daily oral doses of 0, 5, 20 and 80 mg/kg/day fluvoxamine were administered to rats for 6 months, with the 80 mg/kg dose increased to 100 mg/kg after 9 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.

Dogs were treated with fluvoxamine 0, 5, 15 or 45 mg/kg/day (capsules) for 7 months, with the high dose increased to 60 mg/kg/day after 7 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 6 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, and 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.

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 six-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 unclear.

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 2 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.

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*.

TERATOLOGY

The teratologic effects of fluvoxamine were studied in both rats and rabbits. When fluvoxamine was administered to rats from day 6 to day 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.

REPRODUCTIVE STUDIES

Reproductive studies in rats revealed impaired fertility (Note: at doses exceeding about 4 times the maximum recommended human dosage), increased embryofetal death, decreased fetal body weight and increased incidences of fetal eye abnormalities (folded retina) in fluvoxamine doses which markedly exceed maximum recommended human dose. The potential risk for humans is unknown.

The effects of fluvoxamine on fertility and general reproductive performance were evaluated in rats at dosages of 0, 5, 20 and 80 mg/kg/day administered orally. Male rats were treated for 9 weeks prior to mating and females were treated for 2 weeks prior to mating, during gestation, and during rearing of the young up to 21 days post-partum.

Decreased weight gain was evident among males at all dose levels but there was no apparent effect on female weight gain during the shorter pre-mating period, gestation or lactation.

Fluvoxamine did not affect mating performance, duration of gestation or pregnancy rate. However, a slight increase in pup mortality during days 4 to 12 of lactation was noted in the mid- and high-dose groups.

The effects of fluvoxamine on peri- and post-natal 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 post partum. 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 1 post partum to distinguish between direct and indirect (maternally mediated) effects on

post-natal 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 peri-natal period. However, weight gain was slightly lower in fostered and non-fostered offspring from test dams during days 8 to 21 of lactation.

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57. Product Monograph dated of January 1, 2011 **LUVOX** (fluvoxamine maleate, Film Coated and Scored Tablets), Abbott Products Inc., Control Number: 143274

PART III: CONSUMER INFORMATION

[Pr] ratio-FLUVOXAMINE
(fluvoxamine maleate)

This leaflet is part III of a three-part "Product Monograph" and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ratio-FLUVOXAMINE. Contact your doctor or pharmacist if you have any questions about the drug.

Please read this information before you start to take your medicine, even if you have taken this drug before. Keep this information with your medicine in case you need to read it again.

ABOUT THIS MEDICATION

What the medication is used for:
ratio-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 thought, feeling, idea or sensation; recurrent pattern of behaviour, or unwanted thoughts or actions)

What it does:
ratio-FLUVOXAMINE belongs to a group of medicines called selective serotonin reuptake inhibitors (SSRIs). ratio-FLUVOXAMINE is thought to work by increasing the levels of a chemical in the brain called serotonin.

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

- allergic to it or any of the components of its formulation (see What the nonmedicinal 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).
- currently taking or have recently taken thioridazine or pimozide.

What the medicinal ingredient is:
Fluvoxamine maleate.

What the nonmedicinal ingredients are:
Colloidal anhydrous silica, maize starch, mannitol, hypromellose, polyethylene glycol 6000, pregelatinized starch, sodium stearyl fumarate, talc and titanium dioxide. There is no gluten, lactose, sulfite or tartrazine in ratio-FLUVOXAMINE.

What dosage forms it comes in:
ratio-FLUVOXAMINE is available as 50 mg white tablets and 100 mg white tablets.

WARNINGS AND PRECAUTIONS

During treatment with these types of medications, it is important that you and your doctor have good ongoing communication about how you are feeling.

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

New or Worsened Emotional or Behaviour Problems
Particularly in the first few weeks or when doses are adjusted, a small number of patients taking drugs of this type may feel worse instead of better; for example, they may experience unusual feelings of agitation, hostility or anxiety, or have impulsive or disturbing thoughts such as thoughts of self-harm or harm to others. Should this happen to you, or those in your care if you are a caregiver or guardian, consult your doctor immediately. Close observation by a doctor is necessary in this situation. **Do not discontinue your medication on your own.**

BEFORE you use ratio-FLUVOXAMINE tell your doctor or pharmacist:

- if you have had any allergic reaction to medications
- all your medical conditions, including a history of seizures, liver or kidney disease, heart problems or a history of any abnormal bleeding
- any medications (prescription or non-prescription) you are taking or have recently taken, especially monoamine oxidase (MAO) inhibitors (e.g., phenelzine sulphate, moclobemide), or any other antidepressants, tizanidine, thioridazine, pimozide, mesoridazine, neuroleptics, warfarin, propranolol, phenytoin, theophylline, lithium, tryptophan, terfenadine, astemizole, cisapride, and drugs used to prevent seizures (anticonvulsants)
- if you have ever had any allergic reaction to medications, food, etc.
- any natural or herbal products you are taking (e.g., St. John's Wort)
- whether you are pregnant, or thinking about becoming pregnant, or if you are breast feeding
- 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

Post-marketing reports indicate that some newborns whose mothers took an SSRI (Selective Serotonin Reuptake Inhibitor) or other newer anti-depressants, such as ratio-FLUVOXAMINE, during pregnancy have developed complications at birth requiring prolonged hospitalization, breathing support and tube feeding. Reported symptoms included: feeding and/or breathing difficulties, seizures, tense or overly relaxed muscles, jitteriness and constant crying.

In most cases, the newer anti-depressant was taken during the third trimester of pregnancy. These symptoms are consistent with either a direct adverse effect of the anti-depressant 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.

Preliminary information suggests that use of SSRIs during the second half of pregnancy may be associated with an increased rate of a serious lung condition (PPHN) that causes breathing difficulties in newborns soon after birth. According to the study, babies born with this condition were 6 times more likely than healthy babies to have been exposed to SSRIs. In the general population, PPHN is known to occur at a rate of about 1-2 per 1000 newborns.

If you are pregnant and taking an SSRI, or other newer anti-depressants, 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 ratio-FLUVOXAMINE if you are taking or have recently taken monoamine oxidase (MAO) inhibitors, thioridazine or pimozide.

ratio-FLUVOXAMINE should not be used with tizanidine, terfenadine, astemizole and cisapride.

You should tell your doctor if you are taking or have recently taken any medications (prescription, non-prescription or natural/herbal), especially:

- other antidepressants, such as SSRIs and certain tricyclics
- other drugs that affect serotonin such as lithium, linezolid, 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., warfarin), acetylsalicylic acid (e.g., Aspirin) and other non-steroidal anti-inflammatory drugs (e.g. ibuprofen)
- propanolol 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)
- sedatives such as benzodiazapines

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

PROPER USE OF THIS MEDICATION

Usual dose:

- It is very important that you take ratio-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.
- ratio-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.
- Never increase or decrease the amount of ratio-FLUVOXAMINE you are taking unless your doctor tells you to change your dosage.
- Do not stop taking this medication without consulting your doctor.
- As with all antidepressants, improvement with ratio-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.
- Talk to your doctor before you stop taking your medication on your own.

- You should avoid taking St. John's Wort if you are taking ratio-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.

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.

Overdose:

In case of an overdose contact your doctor, the regional Poison Control Centre, or the nearest hospital emergency department, even if you do not feel sick.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medications, ratio-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 ratio-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.

ratio-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.

New or Worsened Emotional or Behavioural Problems

Particularly in the first few weeks or when doses are adjusted, a small number of patients taking a drug of this type may feel worse instead of better; for example, they may experience new or worsened feelings of agitation, hostility, anxiety, or thoughts about suicide or harming others. Your doctor should be informed of such changes immediately. Close observation by a doctor is necessary in this situation. Do not discontinue your medication on your own. See also the WARNINGS AND PRECAUTIONS section.

Depression and other serious mental illness are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions. A recent U.S. Food and Drug Administration review showed that antidepressants may increase suicidal thoughts or actions in young adults (18 to 24 years of age). Suicidal thoughts and actions do not necessarily decrease above 24 years of age. Inform your doctor, caregiver, guardian or a family member if you are having any suicidal thoughts. Your doctor should evaluate you for signs of your suicidal behaviour, including looking for emotional and behavioural changes. Your doctor may recommend increased supervision, irrespective of your age.

Discontinuation Symptoms

Contact your doctor before stopping or reducing your dosage of ratio-FLUVOXAMINE. Symptoms such as dizziness, abnormal dreams, unusual skin sensations (burning, prickling, tingling), confusion, fatigue, agitation, anxiety, difficulty concentrating, headache, tremor, nausea, vomiting, sweating or other symptoms may occur after stopping or reducing the dosage of ratio-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 ratio-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.

Effects on Newborns

Some newborns whose mothers took an SSRI (Selective Serotonin Reuptake Inhibitor) or other

newer antidepressants during pregnancy have shown such symptoms as breathing and feeding difficulties, jitteriness and constant crying. If your baby experiences any of these symptoms, contact your doctor as soon as you can. See WARNINGS AND PRECAUTIONS section for more information.

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

Symptom / effect		Talk with your doctor or pharmacist		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)			√
Uncommon	Akathisia (feeling restless and unable to sit or stand still)		√	
Uncommon	Hallucinations (strange visions or sounds)		√	
Rare	Bruising or unusual bleeding from the skin or other areas		√	
Rare	Low sodium level in the blood (symptoms of tiredness, weakness, confusion, combined with achy, stiff or uncoordinated muscles)		√	

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

Symptom / effect		Talk with your doctor or pharmacist		Seek immediate emergency medical assistance
		Only if severe	In all cases	
Rare	Gastrointestinal bleeding (vomiting blood or passing blood in stools)			√
Rare	Seizures (loss of consciousness with uncontrollable shaking)			√
Rare	Liver disorder (symptoms include nausea, vomiting, loss of appetite combined with itching, yellowing of the skin or eyes, dark urine)			√
Rare	Serotonin syndrome (a combination of most or all of the following: confusion, restlessness, sweating, shaking, shivering, hallucinations, sudden jerking of the muscles, fast heartbeat)			√
See Warnings & Precautions	New or Worsened Emotional or Behavioural Problems			√

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

HOW TO STORE IT

Store ratio-FLUVOXAMINE at room temperature (15 – 25ºC), in a dry place. Protect from light. Keep ratio-FLUVOXAMINE out of reach of children. Keep container tightly closed. If your doctor tells you to stop taking ratio-FLUVOXAMINE please return any leftover medicine to your pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 866-234-2345
By toll-free fax: 866-678-6789
Online: www.healthcanada.gc.ca/medeffect
By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effects, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.hc-sc.gc.ca (Drug Product Database) or by contacting the sponsor, Teva Canada Limited., at:
1-800-268-4127 ext. 1255005 (English)
1-877-777-9117 (French)
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