For the Use of a Registered Medical Practitioner Only

1. GENERIC NAME AND BRAND NAME
Fluvoxamine Maleate extended release tablets 100 mg
UVOX® CR 100

Fluvoxamine Maleate extended release tablets 150 mg
UVOX® CR 150

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:
UVOX® CR 100
Each film coated extended release tablet contains:
Fluvoxamine Maleate I.P. ….100 mg
Excipients…..q. s.
Colors: Brilliant Blue FCF & Titanium Dioxide IP

UVOX® CR 150
Each film coated extended release tablet contains:
Fluvoxamine Maleate I.P. …..150 mg
Excipients……q. s.
Colours: Ferric oxide USP-NF Yellow & Titanium Dioxide IP

3. DOSAGE FORM AND STRENGTH
Kindly Refer section 1 & 2

4. CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS:
For the treatment of obsessive-compulsive disorder (OCD)and depression.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
The recommended starting dose is 100 mg at bedtime, with weekly increases of 50 mg as tolerated to maximum therapeutic benefit, not to exceed 300 mg per day.
Tablets should not be crushed or chewed.
Pediatric patients naïve to fluvoxamine maleate: The lowest available dose of fluvoxamine CR may not be appropriate
Hepatically impaired: Decreased clearance may require modified dose and titration
Extended treatment: Adjust dose to maintain lowest effective dose; reassess patients periodically
Discontinuation: Gradual dose reduction is recommended

4.3 CONTRAINDICATIONS
Fluvoxamine tablets are contraindicated in combination with monoamine oxidase inhibitors (MAOIs).
Treatment with fluvoxamine can be initiated:

- two weeks after discontinuation of an irreversible MAOI, or
- the following day after discontinuation of a reversible MAOI (e.g. moclobemide).

At least one week should elapse between discontinuation of fluvoxamine and initiation of therapy with

any MAOI.

- Hypersensitivity to the active substance or to any of the excipients.
- Fluvoxamine may, by inhibition of its metabolism, increase the plasma concentration of drugs such as pimozide and therefore increase the risk of QT prolongation and Torsade de Pointes caused by such drugs. Concomitant use is contraindicated. Fluvoxamine may increase the plasma concentration of tizanidine increasing its adverse effects and therefore concomitant use is contraindicated.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which fluvoxamine are prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co morbid with major depressive disorder. Therefore, when treating patients with other psychiatric disorders, they should be closely monitored.

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.

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.

Renal and hepatic impairment

Patients suffering from hepatic or renal insufficiency should start on a low dose and be carefully monitored.

Treatment with fluvoxamine has rarely been associated with an increase in hepatic enzymes, generally accompanied by clinical symptoms. In such cases treatment, should be discontinued.

Nervous system disorders

Although in animal studies fluvoxamine has no pro-convulsive properties, caution is recommended when the drug is administered to patients with a history of convulsive disorders. Fluvoxamine should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Treatment with fluvoxamine should be discontinued if seizures occur or if seizure frequency increases.

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 should be discontinued if such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, and autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated.

Metabolism and nutrition disorders
As with other SSRIs, hyponatremia has been rarely reported, and appears to be reversible when fluvoxamine is discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone secretion. The majority of reports were associated with older patients.
Glycaemic control may be disturbed (i.e., hyperglycaemia, hypoglycaemia, decreased glucose tolerance), especially in the early stages of treatment. When fluvoxamine is given to patients with a known history of diabetes mellitus, the dosage of anti-diabetic drugs may need to be adjusted.
Nausea, sometimes accompanied by vomiting, is the most frequently observed symptom associated with fluvoxamine treatment. This side effect usually diminishes within the first two weeks of treatment.

Eye Disorders
Mydriasis has been reported in association with SSRIs such as fluvoxamine. Therefore caution should be used when prescribing fluvoxamine in patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma.

Hematological disorders
There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura as well as hemorrhagic manifestations e.g. gastrointestinal bleeding with SSRIs. Caution is advised in patients taking SSRIs, particularly in elderly patients and in patients who concomitantly use drugs known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most TCAs, aspirin, NSAIDs) or drugs that increase risk of bleeding as well as in patients with a history of bleeding disorders and in those with predisposing conditions (e.g. thrombocytopenia).

Cardiac disorders
When combined with fluvoxamine plasma concentrations of terfenadine, astemizole or cisapride may be increased resulting in an increased risk for QT-prolongation/Torsade de Pointes. Therefore, fluvoxamine should not be co-administered with these drugs.
Fluvoxamine may cause an insignificant decrease in heartbeat (2-6 beats per minute).

Electroconvulsive therapy (ECT)
There is limited clinical experience of concomitant administration of fluvoxamine and ECT; therefore caution is advisable.

Withdrawal reactions
It is possible that withdrawal reactions may occur on stopping therapy with fluvoxamine although the available preclinical and clinical evidence does not suggest that this treatment causes dependence. The most commonly reported symptoms in association with withdrawal of the product include: dizziness, sensory disturbances (including paranesthesia, visual disturbances and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation, irritability, confusion, emotional instability, headache, nausea and/or vomiting, diarrhea, sweating, palpitations, tremor and anxiety (see

undesirable effects section). 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. It is therefore advised that fluvoxamine should be gradually tapered when discontinuing treatment according to the patient's needs (see dosage and administration section).
Discontinuation of fluvoxamine (particularly when abrupt) commonly leads to withdrawal symptoms. It is therefore advised that when fluvoxamine treatment is no longer required, gradual discontinuation by dose tapering should be carried out

Mania/Hypomania:
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. Proper screening for bipolar disorder is recommended.

4.5 DRUG INTERACTIONS

Monoamine oxidase inhibitors:
Fluvoxamine should not be used in combination with MAOIs (see section contraindications).
Effect of fluvoxamine on the oxidative metabolism of other drugs: Fluvoxamine can inhibit the metabolism of drugs metabolized by certain cytochrome P450 isoenzymes (CYPs). A strong inhibition of CYP1A2 and CYP2C19 is demonstrated in in vitro and in vivo studies. 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. Concomitant therapy of fluvoxamine and these drugs should be initiated at or adjusted to the low end of their dose range. Plasma concentrations, effects or adverse effects of coadministered drugs should be monitored and their dosage should be reduced if necessary. This is particularly relevant for drugs with a narrow therapeutic index.

Ramelteon: When immediate-release fluvoxamine maleate tablets 100 mg twice daily was administered for 3 days prior to single-dose co-administration of ramelteon 16 mg and immediate-release fluvoxamine maleate tablets, the AUC for ramelteon increased approximately 190-fold and the Cmax increased approximately 70-fold compared to ramelteon administered alone.

Compounds with narrow therapeutic index: Co-administration of fluvoxamine and drugs with a narrow therapeutic index (such as tacrine, theophylline, methadone, mexiletine, phenytoin, carbamazepine and cyclosporine) should be carefully monitored when these drugs are metabolized exclusively or by a combination of CYPs inhibited by fluvoxamine. If necessary, dose adjustment of these drugs is recommended

Tricyclic antidepressants and neuroleptics: 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 cytochrome P450 1A2 when given together with fluvoxamine, has been reported. A decrease in the dose of these products should be considered if treatment with fluvoxamine is initiated.

Benzodiazepines: 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.

Cases of increased plasma concentration: As plasma concentrations of ropinirol may be increased **in c**ombination with fluvoxamine thus increasing the risk of overdose, surveillance and reduction in the posology of ropinirol during fluvoxamine treatment and after its withdrawal may be required.
As plasma concentrations of propranolol are increased in combination with fluvoxamine, the propranolol dose may need to be lowered. When given with fluvoxamine, warfarin plasma concentrations were significantly increased and prothrombin times prolonged.

Cases of increased side effects: Isolated cases of cardiac toxicity have been reported when fluvoxamine was combined with thioridazine. Caffeine plasma levels are likely to be increased during co-administration with fluvoxamine. Thus, patients who consume high quantities of caffeine-containing beverages should lower their intake when fluvoxamine is administered and adverse caffeine effects (like tremor, palpitations, nausea, restlessness, insomnia) are observed.

Terfenadine, astemizole, cisapride, sildenafil: see warnings and precautions section.

Glucuronidation: Fluvoxamine does not influence plasma concentrations of digoxin.

Renal excretion: Fluvoxamine does not influence plasma concentrations of atenolol.

Pharmacodynamic interactions: The serotonergic effects of fluvoxamine may be enhanced when used in combination with other serotonergic agents (including triptans, tramadol, SSRIs and St. John's Wort preparations). (see warning and precautions section)

Fluvoxamine has been used in combination with lithium in the treatment of severely ill, drug-resistant patients. However, lithium (and possibly also tryptophan) enhances the serotonergic effects of fluvoxamine. The combination should be used with caution in patients with severe, drug-resistant depression. In patients on oral anticoagulants and fluvoxamine, the risk for hemorrhage may increase and these patients should therefore be closely monitored. As with other psychotropic drugs patients should be advised to avoid alcohol use while taking fluvoxamine.

PREGNANCY AND LACTATION

Pregnancy

Epidemiological data have suggested that the use of Selective Serotonin Reuptake Inhibitors (SSRIs) in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). The observed risk was approximately 5 cases per 1000 pregnancies. In the general population 1 to 2 cases of PPHN per 1000 pregnancies occur.
Fluvoxamine should not be used during pregnancy unless the clinical condition of the woman requires treatment with fluvoxamine.
Isolated cases of withdrawal symptoms in the newborn child have been described after the use of fluvoxamine at the end of pregnancy.
Some newborns experience feeding and/ or respiratory difficulties, seizures, temperature instability, hypoglycemia, tremor, abnormal muscle tone, jitteriness, cyanosis, irritability, lethargy, somnolence, vomiting, difficulty in sleeping and constant crying after third trimester exposure to SSRIs and may require prolonged hospitalization.

Breastfeeding

Fluvoxamine is excreted via human milk in small quantities. Therefore, the drug should not be used by

women who breast feed.

Fertility
Reproductive toxicity studies in animals have shown that fluvoxamine impairs male and female fertility. The relevance of these findings to humans is unknown (see preclinical safety data section). Fluvoxamine should not be used in patients attempting to conceive unless the clinical condition of the patient requires treatment with fluvoxamine.

4.6 USE IN SPECIAL POPULATIONS (SUCH AS PREGNANT WOMEN, LACTATING WOMEN, PAEDIATRIC PATIENTS, GERIATRIC PATIENTS ETC.)

Pregnancy
Epidemiological data have suggested that the use of Selective Serotonin Reuptake Inhibitors (SSRIs)in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). The observed risk was approximately 5 cases per 1000 pregnancies. In the general population 1 to 2 cases of PPHN per 1000 pregnancies occur.
Reproduction toxicity studies in animals revealed treatment related increases in embryotoxicity (embryofetal death, fetal eye abnormalities). The relevance to humans is unknown. The safety margin for reproductive toxicity is unknown (see section 5.3).
Fluvoxamine should not be used during pregnancy unless the clinical condition of the woman requires treatment with fluvoxamine.
Isolated cases of withdrawal symptoms in the newborn child have been described after the use of fluvoxamine at the end of pregnancy.
Some newborns experience feeding and/ or respiratory difficulties, seizures, temperature instability, hypoglycemia, tremor, abnormal muscle tone, jitteriness, cyanosis, irritability, lethargy, somnolence, vomiting, difficulty in sleeping and constant crying after third trimester exposure to SSRIs and may require prolonged hospitalization.

Breastfeeding
Fluvoxamine is excreted via human milk in small quantities. Therefore, the drug should not be used by women, who breast feed.

Pediatric population
Fluvoxamine should not be used in the treatment of children and adolescents under the age of 18 years, except for patients with Obsessive Compulsive Disorder. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioral development are lacking.

Geriatric population
Data in elderly subjects give no indication of clinically significant differences in normal daily dosages compared to younger subjects. However, upward dose titration should be done slower in the elderly, and dosing should always be done with caution.

4.7 EFFECT ON ABILITY TO DRIVE AND USE MACHINES

Fluvoxamine up to 150 mg has no or negligible influence on the ability to drive and use machines. It showed no effect on psychomotor skills associated with driving and operating machinery in healthy

volunteers. However, somnolence has been reported during treatment with fluvoxamine. Therefore, caution is recommended until the individual response to the drug has been determined.

4.8 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical Trial Data Sources

Fluvoxamine CR were studied in one 12-week controlled trial in patients with OCD (N = 124; mean exposure 66.6 days) and in two 12-week controlled trials for another condition (N = 279; mean exposure 59.2 days). Patients in these trials were initiated on 100 mg/day and were titrated in 50 mg increments over the first 6 weeks to within a range of 100 mg to 300 mg/day. The reactions listed in Table 3 show reactions from the two populations separately. Table 3 shows reactions from the three controlled studies combined.

Adverse Reactions Observed in Controlled Trials

Adverse Reactions Associated with Discontinuation of Treatment: Of the 124 patients with OCD and 279 patients in other studies treated with Fluvoxamine CR in controlled clinical trials, 19% and 26% discontinued treatment due to an adverse reaction. The most common reactions (≥1%) associated with discontinuation and considered to be drug related (i.e., those reactions associated with dropout at a rate at least twice that of placebo) were anorexia (including, but not limited to, loss of appetite and decreased appetite) (1%), anxiety (3%), asthenia (3%), diarrhea (2%), dizziness (4%), headache (2%), insomnia (5%), nausea (7%), nervousness (1%), somnolence (5%), and thinking abnormal (1%).

Commonly Observed Adverse Reactions: Fluvoxamine CR have been studied in one controlled trial in patients with OCD (N = 124) and two controlled trials for another condition (N = 279). In general, adverse reaction rates were similar in the two data sets as well as in a study of pediatric patients with OCD treated with immediate-release fluvoxamine maleate tablets. The most commonly observed treatment-emergent adverse reactions associated with the use of Fluvoxamine CR and likely to be drug-related (incidence of 5% or greater and at least twice that for placebo) and derived from Table 2 were: abnormal ejaculation, anorexia, anorgasmia, asthenia, diarrhea, nausea, somnolence, sweating, and tremor. In the one controlled trial in patients with OCD, the following additional reactions occurred at an incidence of 5% or greater and at least twice that for placebo: anxiety, decreased libido, myalgia, pharyngitis, and vomiting. The following additional reactions occurred in another studied population: dyspepsia, dizziness, insomnia, and yawning. In a study evaluating immediate-release fluvoxamine maleate tablets in pediatric patients with OCD, the following additional reactions were identified using the above rule: agitation, depression, dysmenorrhea, flatulence, hyperkinesia, and rash.

Adverse Reactions Occurring at an Incidence of ≥2%: Table 2 enumerates adverse reactions that occurred in adults at a frequency of 2% or more, and were more frequent than in the placebo group, among patients treated with Fluvoxamine CR in two short-term, placebo-controlled trials (12 weeks) in another population and one short-term placebo-controlled OCD trial (12 weeks) and in which patients were dosed once-a-day in a range of 100 to 300 mg/day. This table shows the percentage of patients in each group who had at least one occurrence of a reaction at some time during their treatment. Reported adverse reactions were classified using a COSTART-based Dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors may differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The

cited figures, however, do provide the prescribing health care provider with some basis for estimating the relative contribution of drug and non-drug factors to the side-effect incidence rate in the population studied.

TABLE 3 TREATMENT-EMERGENT ADVERSE REACTION INCIDENCE RATES BY BODY SYSTEM IN ADULT OCD PATIENTS AND ANOTHER STUDIED POPULATION[1] PERCENTAGE OF PATIENTS REPORTING REACTION				
OBSESSIVE COMPULSIVE DISORDER			**OTHER STUDIED POPULATION**	
BODY SYSTEM/ ADVERSE REACTION	Fluvoxamine **CR N = 124**	**PLACEBO N = 124**	Fluvoxamine **CR N = 279**	**PLACEBO N = 276**
BODY AS A WHOLE				
Headache	32	31	35	30
Asthenia	26	8	24	10
Pain2	10	8	–	–
Abdominal Pain	–	–	5	4
Accidental Injury	5	3	–	–
Chest Pain	–	–	3	1
Viral Infection	2	<1	–	–
CARDIOVASCULAR				
Palpitation	–	–	3	1
Vasodilatation	–	–	2	<1
Hypertension	2	<1	–	–
DIGESTIVE SYSTEM				
Nausea	34	13	39	11
Diarrhea	18	8	14	5
Anorexia3	13	5	14	1
Dyspepsia	8	5	10	4
Constipation	4	<1	6	5
Vomiting	6	2	–	–
Tooth Disorder	2	<1	–	–
Liver Function Test Abnormal	–	–	2	<1
Gingivitis	2	0	–	–
HEMIC AND LYMPHATIC				
Ecchymosis	4	2	–	–
METABOLIC AND NUTRITIONAL DISORDERS				
Weight Loss	2	<1	–	–
MUSCULOSKELETAL				
Myalgia	5	2	–	–
NERVOUS SYSTEM				
Insomnia	35	20	32	13
Somnolence	27	11	26	9
Dizziness	12	10	15	7
Dry Mouth	10	9	11	8
Nervousness	–	–	10	9

Libido Decreased	6	2	6	4
Male	10	5	8	6
Female	4	1	4	3
Anxiety	6	2	8	5
Tremor	6	0	8	<1
Abnormal Thinking	3	<1	3	2
Abnormal Dreams	–	–	3	2
Agitation	2	<1	3	<1
Hypertonia	–	–	2	1
Apathy	3	0	–	–
Paresthesia	–	–	3	2

PERCENTAGE OF PATIENTS REPORTING REACTION				
OBSESSIVE COMPULSIVE DISORDER			**OTHER STUDIED POPULATION**	
BODY SYSTEM/ ADVERSE REACTION	**fluvoxamine CR N = 124**	**PLACEBO N = 124**	**fluvoxamine CR N = 279**	**PLACEBO N = 276**
Neurosis	2	<1	–	–
Twitching	2	0	–	–
RESPIRATORY SYSTEM				
Pharyngitis	6	<1	–	–
Yawn	2	0	5	<1
Laryngitis	3	0	–	–
Bronchitis	–	–	2	1
Epistaxis	2	0	–	–
SKIN				
Sweating	7	<1	6	2
Acne	2	0	–	–
SPECIAL SENSES				
Taste Perversion	2	<1	2	<1
Amblyopia	2	<1	–	–
UROGENITAL				
Abnormal Ejaculation	10	0	11	2
Anorgasmia	5	0	5	1
Male	4	0	4	2
Female	5	0	5	0
Menorrhagia	3	0	–	–
Sexual Function Abnormal	2	<1	3	<1
Male	4	3	2	1
Female	0	0	3	0
Urinary Tract Infection	–	–	2	<1
Polyuria	2	<1	–	–

Male and Female Sexual Dysfunction with SSRIs

Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder and with aging, they may also be a consequence of pharmacologic treatment. In particular, evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward sexual experiences.
Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and health care providers may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence.

Weight and Vital Sign Changes
No statistically significant differences in weight gain or loss were found between patients treated with fluvoxamine CR or placebo. Comparisons of immediate-release fluvoxamine maleate tablets or fluvoxamine CR versus placebo groups in separate short-term trials on (1) median change from baseline on various vital signs variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various measures of vital signs variables revealed no important differences between fluvoxamine maleate and placebo.

Laboratory Changes
Comparisons of immediate-release fluvoxamine maleate tablets or fluvoxamine CR versus placebo groups in separate short-term trials on (1) median change from baseline on various serum chemistry, hematology, and urinalysis variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various serum chemistry, hematology, and urinalysis variables revealed no important differences between fluvoxamine maleate and placebo.

ECG Changes
Comparisons of immediate-release fluvoxamine maleate tablets or fluvoxamine CR and placebo groups in separate pools of short-term OCD and depression trials on (1) mean change from baseline on various ECG variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various ECG variables revealed no important differences between fluvoxamine maleate and placebo.
For fluvoxamine CR, all reported events are included in the list below, with the following exclusions: 1) those events already listed in Table 2 or previous sections of this prescribing information; 2) those events for which there is no basis to suspect a causal relationship; and 3) events that were reported in only one patient and judged not to be potentially serious.

Body as a Whole: Infrequent: chills, malaise, photosensitivity reaction, suicide attempt.
Cardiovascular System: Infrequent: syncope.
Digestive System: Infrequent: eructation, increased salivation.
Metabolic and Nutritional Disorders: Frequent: weight gain.
Nervous System: Infrequent: confusion, incoordination, sleep disorder, suicidal tendency.
Skin and Appendages: Infrequent: eczema, urticaria.
Special Senses: Infrequent: dry eyes, photophobia, taste loss.
Urogenital System: Infrequent: vaginal haemorrhage, Persistent Sexual dysfunction after drug withdrawal
For immediate-release fluvoxamine tablets, all reported events are included in the list below, with the following exclusions: 1) those events already listed in Table 3, in previous sections of this prescribing information 2) those events for which there is no basis to suspect a causal relationship; and 3) events

that were reported in only one patient and judged not to be potentially serious.
Body as a Whole: Infrequent: allergic reaction, neck pain, neck rigidity, overdose;
Rare: sudden death.
Cardiovascular System:
Frequent: hypotension;
Infrequent: angina pectoris, bradycardia, cardiomyopathy, cardiovascular disease, cold extremities, conduction delay, myocardial infarction, pallor, pulse irregular, ST segment changes; **Rare:** AV block, cerebrovascular accident, embolus, pericarditis, phlebitis, pulmonary infarction, supraventricular extrasystoles.
Digestive System:
Frequent: elevated liver transaminases;
Infrequent: colitis, esophagitis, gastritis, gastroenteritis, gastrointestinal haemorrhage, gastrointestinal ulcer, glossitis, haemorrhoids, melena, rectal haemorrhage, stomatitis;
Rare: biliary pain, cholecystitis, cholelithiasis, fecal incontinence, hematemesis, intestinal obstruction, jaundice.
Endocrine System:
Infrequent: hypothyroidism;
Rare: goitre.
Hemic and Lymphatic Systems:
Infrequent: leucocytosis, lymphadenopathy, thrombocytopenia;
Rare: leukopenia, purpura.
Metabolic and Nutritional Systems:
Frequent: oedema
Infrequent: dehydration, hypercholesterolemia;
Rare: diabetes mellitus, hyperglycaemia, hyperlipidaemia, hypoglycaemia, hypokalaemia, lactate dehydrogenase increased.
Musculoskeletal System:
Infrequent: arthralgia, arthritis, bursitis, generalized muscle spasm, myasthenia;
Rare: myopathy.

4.9 OVERDOSAGE

Symptoms

Symptoms include gastro-intestinal complaints (nausea, vomiting and diarrhea), somnolence and dizziness. Cardiac events (tachycardia, bradycardia, hypotension), liver function disturbances, convulsions and coma have also been reported.
Fluvoxamine has a wide margin of safety in overdose. Since market introduction, reports of death attributed to overdose of fluvoxamine alone have been extremely rare. The highest documented dose of fluvoxamine ingested by a patient is 12 gram. This patient recovered completely. Occasionally, more serious complications were observed in cases of deliberate overdose of fluvoxamine in combination with other drugs.
In the controlled clinical trials with 403 patients treated with fluvoxamine CR, there was one nonfatal intentional overdose.
Commonly (≥5%) observed adverse reactions associated with fluvoxamine maleate overdose include gastrointestinal complaints (nausea, vomiting, and diarrhea), coma, hypokalemia, hypotension, respiratory difficulties, somnolence, and tachycardia. Other notable signs and symptoms seen with immediate-release fluvoxamine maleate overdose (single or multiple drugs) include bradycardia, ECG abnormalities (such as heart arrest, QT interval prolongation, first degree atrioventricular block, bundle

branch block, and junctional rhythm), convulsions, dizziness, liver function disturbances, tremor, and increased reflexes.

Treatment
There is no specific antidote to fluvoxamine. In case of overdosage the stomach should be emptied as soon as possible after tablet ingestion and symptomatic treatment should be given. The repeated use of medicinal charcoal, if necessary accompanied by an osmotic laxative, is also recommended. Forced diuresis or dialysis is unlikely to be of benefit.
Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.
Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for fluvoxamine are known.
A specific caution involves patients taking, or recently having taken, fluvoxamine maleate who might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation

5.0 PHARMACOLOGICAL PROPERTIES
5.1 MECHANISM OF ACTION
The mechanism of action of fluvoxamine is thought to be related to selective serotonin re-uptake inhibition in brain neurons. There is minimum interference with noradrenergic processes. Receptor binding studies have demonstrated that fluvoxamine has negligible binding capacity to alpha adrenergic, beta adrenergic, histaminergic, muscarine cholinergic, dopaminergic or serotonergic receptors.

5.2 PHARMACODYNAMIC PROPERTIES
Receptor binding studies have demonstrated that fluvoxamine is a potent serotonin reuptake inhibitor in vitro as well as in vivo and has a minimal affinity for serotonin receptors subtypes. Its capacity of binding to alpha adrenergic, beta adrenergic, histaminergic, muscarinic, cholinergic or dopaminergic receptors is negligible.
Fluvoxamine has a high affinity for sigma-1 receptors, where it acts as an agonist at therapeutic doses.

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

5.3 PHARMACOKINETIC PROPERTIES
Fluvoxamine is completely absorbed following oral administration.
Fluvoxamine undergoes extensive metabolism in the liver. Although CYP2D6 is in vitro the main isoenzyme involved in fluvoxamine's metabolism, plasma concentrations in poor metabolizers for CYP2D6 are not much higher than those in extensive metabolizers.
Fluvoxamine undergoes extensive hepatic transformation, mainly via oxidative demethylation, into at

least nine metabolites, which are excreted by the kidneys. The two major metabolites showed negligible pharmacological activity. The other metabolites are not expected to be pharmacologically active. Fluvoxamine is a potent inhibitor of CYP 1 A2 and a moderate inhibitor of CYP2C and CYP3A4, with only marginal inhibitory effects on CYP2D6.

Bioavailability: A single-dose crossover study in 28 healthy subjects was conducted to compare the pharmacokinetics of fluvoxamine after administration of Fluvoxamine CR and immediate-release fluvoxamine maleate tablets. In the single-dose crossover study, mean Cmax was 38% lower and relative bioavailability was 84% for Fluvoxamine CR versus immediate-release fluvoxamine maleate tablets.
In a multiple-dose proportionality study, Fluvoxamine CR were administered over a dose range of 100 mg/day to 300 mg/day to 20 healthy volunteers. Steady-state plasma concentrations were achieved within a week of dosing. Mean maximum plasma concentrations were 47 ng/mL, 161 ng/mL, and 319 ng/mL, respectively, at the 100 mg, 200 mg, and 300 mg administered dose levels. Fluvoxamine exhibited nonlinear pharmacokinetics producing disproportionately higher concentrations over the dose range. The AUC and Cmax values increased 5.7-fold following the 3-fold increase in dose from 100 mg to 300 mg. Food caused the mean AUC and Cmax of fluvoxamine to increase only slightly; therefore, administration of Fluvoxamine CR with food does not significantly affect the absorption of fluvoxamine.

Distribution/Protein Binding: The mean apparent volume of distribution for fluvoxamine is approximately 25 L/kg, suggesting extensive tissue distribution. Approximately 80% of fluvoxamine is bound to plasma protein, mostly albumin, over a concentration range of 20 to 2000 ng/mL.

Metabolism: Fluvoxamine maleate is extensively metabolized by the liver; the main metabolic routes are oxidative demethylation and deamination. Nine metabolites were identified following a 5 mg radiolabeled dose of fluvoxamine maleate, constituting approximately 85% of the urinary excretion products of fluvoxamine. The main human metabolite was fluvoxamine acid which, together with its N-acetylated analog, accounted for about 60% of the urinary excretion products. A third metabolite, fluvoxethanol, formed by oxidative deamination, accounted for about 10%. Fluvoxamine acid and fluvoxethanol were tested in an in vitro assay of serotonin and norepinephrine reuptake inhibition in rats; they were inactive except for a weak effect of the former metabolite on inhibition of serotonin uptake (1-2 orders of magnitude less potent than the parent compound). Approximately 2% of fluvoxamine was excreted in urine unchanged.

Elimination: Following a 14C-labelled oral dose of fluvoxamine maleate (5 mg), an average of 94% of drug-related products was recovered in the urine within 71 hours. After administration of a 100 mg, single oral dose of Fluvoxamine CR, the mean plasma half-life of fluvoxamine in healthy male and female volunteers was 16.3 hours.

Gender: In a study with 15 male and 13 female healthy volunteers who were administered Fluvoxamine CR 100 mg, AUC and Cmax of fluvoxamine were increased by approximately 60% in females compared to males. There were no differences in the elimination half-life between males and females.

Elderly Subjects: In a study using immediate-release fluvoxamine maleate tablets at 50 mg and 100 mg and comparing elderly (ages 66-73 years) and young subjects (ages 19-35 years), mean maximum plasma concentrations in the elderly were 40% higher. The multiple-dose elimination half-life of fluvoxamine was 17.4 hours and 25.9 hours in the elderly compared to 13.6 hours and 15.6 hours in the young subjects at steady state for 50 mg and 100 mg doses, respectively. In elderly patients administered immediate-

release fluvoxamine maleate tablets, the clearance of fluvoxamine was reduced by about 50%; therefore, fluvoxamine CR should be slowly titrated during initiation of therapy.

Pediatric Subjects: The pharmacokinetics of fluvoxamine CR have not been evaluated in pediatric patients. However, the multiple-dose pharmacokinetics of fluvoxamine were determined in male and female children (ages 6-11) and adolescents (ages 12-17). Steady-state plasma fluvoxamine concentrations were 2- to 3-fold higher in children than in adolescents. AUC and Cmax in children were 1.5- to 2.7-fold higher than that in adolescents (see Table 1). As in adults, both children and adolescents exhibited nonlinear multiple-dose pharmacokinetics. Female children showed significantly higher AUC (0-12) and Cmax compared to male children and, therefore, lower doses of immediate-release fluvoxamine maleate tablets may produce therapeutic benefit (table 5). No gender differences were observed in adolescents. Steady-state plasma fluvoxamine concentrations were similar in adults and adolescents at a dose of 300 mg/day, indicating that fluvoxamine exposure was similar in these two populations. Dose adjustment in adolescents (up to the adult maximum dose of 300 mg) may be indicated to achieve therapeutic benefit.

6. NONCLINICAL PROPERTIES

6.1 ANIMAL TOXICOLOGY OR PHARMACOLOGY

Preclinical safety data

Carcinogenesis and mutagenesis

There is no evidence of carcinogenicity or mutagenicity with fluvoxamine.

Fertility and reproductive toxicity

Animal studies on male and female fertility revealed reduction of mating performance, decreased sperm count, and fertility index and increased ovary weights at levels higher than human exposure. The effects were observed at exposures >two-fold higher than exposures at the maximum therapeutic dose. As there is no safety margin between exposure at the NOAEL in the reproductive studies and the exposure at the maximum therapeutic dose a risk to patients cannot be ruled out.

Reproductive toxicity studies in rats have shown that fluvoxamine is embryotoxic (increased embryofetal death [resorptions], increased fetal eye abnormalities [folded retina], reduced fetal weights and delayed ossification). The effects on fetal weights and ossification are likely to be secondary to maternal toxicity (reduced maternal bodyweight and bodyweight gain).

In addition, an increased incidence of perinatal pup mortality in pre-and postnatal studies was seen.

The safety margin for reproductive toxicity is unknown.

Physical and psychological dependence the potential for abuse, tolerance and physical dependence has been studied in a non-human primate model. No evidence of dependency phenomena was found.

7.0 DESCRIPTION

Uvox CR 100:

UVOX CR 100 is supplied for oral administration, as an extended release tablet of Fluvoxamine Maleate. Each film coated tablet of UVOX contains Fluvoxamine Maleate 100 mg.

Uvox CR 150:

UVOX CR 150 is supplied for oral administration, as a extended release tablet of Fluvoxamine Maleate. Each film coated tablet of UVOX contains Fluvoxamine Maleate 150 mg.

8.0 PHARMACEUTICAL PARTICULARS

8.1 INCOMPATIBILITIES
Not Applicable

8.2 SHELF-LIFE
Refer pack

8.3 PACKAGING INFORMATION
Refer pack

8.4 STORAGE CONDITION AND HANDING INSTRUCTIONS
Refer pack

9. PATIENT COUNSELLING INFORMATION
Fluvoxamine tablets are contraindicated in combination with monoamine oxidase inhibitors (MAOIs). Treatment with fluvoxamine can be initiated:

- two weeks after discontinuation of an irreversible MAOI, or
- the following day after discontinuation of a reversible MAOI (e.g. moclobemide).

At least one week should lapse between discontinuation of fluvoxamine and initiation of therapy with any MAOI.

- Hypersensitivity to the active substance or to any of the excipients.
- Fluvoxamine may, by inhibition of its metabolism, increase the plasma concentration of drugs such as pimozide and therefore increase the risk of QT prolongation and Torsade de Pointes caused by such drugs. Concomitant use is contraindicated. Fluvoxamine may increase the plasma concentration of tizanidine increasing its adverse effects and therefore concomitant use is contraindicated.
- In combination with tizanidine and monoamine oxidase inhibitors (MAOIs) (for more details refer section 4.4)

10. DETAILS OF MANUFACTURER
Refer Pack for manufacturer details.

Marketed By:
Abbott India Limited
Angel Space, Lifestyle Bldg. No. D-4,
Gala No. 4 to 10 & 14 to 20 Ground Floor,
107 to 110 & 117 to 120 First Floor, 207 to 210
& 217 to 220 2nd Floor, Pimplas Village, Dist. Thane,
Bhiwandi - 421 302, Maharashtra, India.

11. DETAILS OF PERMISSION OR LICENCE NUMBER
Refer Pack for Permission/License details.

12. DATE OF REVISION
Version 6.0, dated 25-Mar-26

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