For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

FLUVATOR

(Fluvoxamine Tablets I.P)

1. **Generic Name**

   Fluvoxamine Tablets I.P

2. Qualitative and quantitative composition

FLUVATOR 50

Each film coated tablet contains:

Fluvoxamine Maleate I.P. ……..50 mg

Colour: Yellow Oxide of Iron & Titanium Dioxide I.P.

The excipients used are Starch, Mannitol, Hydroxypropyl Cellulose, Methanol, Pregelatinized Starch, Sodium Stearyl Fumarate, Colloidal Silicon Dioxide, Ferric Oxide Yellow.

FLUVATOR 100

Each film coated tablet contains:

Fluvoxamine Maleate I.P. ……..100 mg

Colour: Yellow Oxide of Iron & Titanium Dioxide I.P.

The excipients used are Starch, Mannitol, Hydroxypropyl Cellulose, Methanol, Pregelatinized Starch, Sodium Stearyl Fumarate, Colloidal Silicon Dioxide, Ferric Oxide Yellow.

3. Dosage form and strength

Dosage form: Film Coated Tablets

FLUVATOR 50

Strength: Fluvoxamine Maleate - 50 mg

FLUVATOR 100

Strength: Fluvoxamine Maleate – 100 mg

4. Clinical particulars

4.1 Therapeutic indication

FLUVATOR 50 mg and FLUVATOR 100 mg indicated for obsessive compulsive disorder and depression.

4.2 Posology and method of administration

Posology

Dose: As directed by the Physician.

Method of administration

FLUVATOR 50 mg and FLUVATOR 100 mg Film coated tablets should be administered orally.

4.3 Contraindications

Fluvator tablets are contraindicated in combination with tizanidine and 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, linezolid).

For precautions in the exceptional case linezolid needs to be given in combination with fluvoxamine.

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**.**

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 Fluvator is 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. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

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 greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Young adults (ages 18 to 24 years)

A meta-analysis reported study 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.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

Paediatric 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 reported 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 behavioural development are lacking.

Geriatric population

Reported 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.

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.

Withdrawal symptoms seen on discontinuation of fluvoxamine treatment

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt. In reported clinical trials, adverse events seen on treatment discontinuation occurred in approximately 12% of patients treated with fluvoxamine, which is similar to the incidence seen in patients taking placebo. The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction.

The most commonly reported symptoms in association with withdrawal of the product include: dizziness, sensory disturbances (including paraesthesia, visual disturbances and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation, irritability, confusion, emotional instability, headache, nausea and/or vomiting and diarrhoea, sweating and palpitations, tremor and anxiety (see

Generally these events are mild to moderate; however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose.

Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that fluvoxamine should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs.

Psychiatric Disorders

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.

Akathisia/psychomotor restlessness

The use of fluvoxamine has been associated with the development of akathisia, characterised 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.

Nervous system disorders

Although in reported 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 (characterised by 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) occur and supportive symptomatic treatment should be initiated.

In exceptional circumstances, linezolid (an antibiotic which is a reversible relatively weak non-selective MAOI) can be given in combination with fluvoxamine provided that there are facilities for close observation and management of symptoms of serotonin syndrome and monitoring of blood pressure. If symptoms occur, physicians should consider discontinuing one or both agents.

Metabolism and nutrition disorders

As with other SSRIs, hyponatraemia 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.

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.

Haematological disorders

There have been reports of the following haemorrhagic disorders: gastrointestinal bleeding, gynaecological haemorrhage, and other cutaneous or mucous 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, acetylsalicylic acid, NSAIDs) or drugs that increase risk of bleeding, as well as in patients with a history of bleeding and in those with predisposing conditions (e.g. thrombocytopenia or coagulation disorders).

Cardiac disorders

Fluvoxamine should not be co-administered with terfenadine, astemizole or cisapride as plasma concentrations may be increased resulting in a higher risk for QT-prolongation/Torsade de Pointes.

Due to lack of clinical experience, special attention is advised in the situation of post-acute myocardial infarction.

Electroconvulsive therapy (ECT)

There is limited clinical experience of concomitant administration of fluvoxamine and ECT therefore caution is advisable.

Sexual dysfunction

Selective serotonin reuptake inhibitors (SSRIs) may cause symptoms of sexual dysfunction. There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs.

CYP2C19 inhibition

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of fluvoxamine that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. As a precaution concomitant use of fluvoxamine should be discouraged.

4.5 Drugs interactions

Pharmacodynamic interactions

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

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 haemorrhage 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.

<u>Monoamine oxidase inhibitors</u>

Fluvoxamine should not be used in combination with MAOIs, including linezolid, due to risk of serotonin syndrome.

<u>Effect of fluvoxamine on the oxidative metabolism of other drugs</u>

Fluvoxamine can inhibit the metabolism of drugs metabolized by certain cytochrome P450 isoenzymes (CYPs). A strong inhibition of CYP1A2 and CYP 2C19 is demonstrated in in vitro and in vivo studies. CYP2C9, CYP 2D6 and CYP3A4 are inhibited to a lesser extent. Drugs which are largely metabolised via these isoenzymes are eliminated slower and may have higher plasma concentrations when co-administered with fluvoxamine.

In case of prodrugs which are activated by CYPs mentioned above, like clopidogrel, plasma concentrations of the active substance/metabolite may be lower when co-administered with fluvoxamine. As a precaution concomitant use of clopidogrel and fluvoxamine should be

discouraged.

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 co-administered drugs should be monitored and their dosage should be reduced, if necessary. This is particularly relevant for drugs with a narrow therapeutic index.

Compounds with narrow therapeutic index

Co-administration with 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.

An increase in previously stable plasma levels of those tricyclic antidepressants (e.g. clomipramine, imipramine, amitriptyline) and neuroleptics (e.g. clozapine and olanzapine, quetiapine) which are largely metabolised 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.

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.

As plasma concentrations of ropinirole may be increased in combination with fluvoxamine thus increasing the risk of overdose, surveillance and reduction in the dosage of ropinirole 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.

Fluvoxamine does not influence plasma concentrations of digoxin.

Fluvoxamine does not influence plasma concentrations of atenolol.

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.

Fluvator 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, hypoglycaemia, 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 Fluvator impairs male and female fertility. The safety margin for this effect was not identified. The relevance of these findings to humans is unknown.

Animal data have shown that fluvoxamine may affect sperm quality. Human case reports with some SSRIs have shown that an effect on sperm quality is reversible. Impact on human fertility has not been observed so far.

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

4.7 Effects 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 Undesirable effects

Adverse events, observed in clinical studies at frequencies listed below, are often associated with the illness and are not necessarily related to treatment.

Frequency estimate: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

MedDra System Organ Class	**Frequency**	**Undesirable Effect**
Endocrine disorders	Frequency not known	Hyperprolactinemia, Inappropriate antidiuretic hormone secretion.
Metabolism and nutrition	Common	Anorexia

disorders	Frequency not known	Hyponatraemia, weight increased, weight decreased
Psychiatric disorders	Uncommon	Hallucination, confusional stage, aggression
	Rare	Mania
	Frequency not known	Suicidal ideation (see section 4.4).
Nervous system disorders	Common	Agitation, nervousness, anxiety, insomnia, somnolence, tremor, headache, dizziness
	Uncommon	Extrapyramidal disorder, ataxia
	Rare	Convulsion
	Frequency not known	Serotonin syndrome, neuroleptic malignant syndrome-like events, paresthesia, dysgeusia, and SIADH have been reported (see also section 4.4). Psychomotor restlessness/akathisia (see section 4.4).
Eye disorders	Frequency not known	Glaucoma Mydriasis.
Renal and urinary disorders	Frequency not known	micturition disorder (including urinary retention, urinary incontinence, pollakiuria, nocturia and enuresis)
Cardiac disorders	Common	Palpitations/ tachycardia
Vascular disorders	Uncommon	(Orthostatic) hypotension
	Frequency not known	Haemorrhage (e.g. gastrointestinal haemorrhage, gynaecological, haemorrhage, ecchymosis, purpura)
Gastrointestinal disorders	Common	Abdominal pain, constipation, diarrhoea, dry mouth, dyspepsia, nausea, vomiting
Hepatobiliary disorders	Rare	Hepatic function abnormal
Skin and subcutaneous tissue disorders	Common	Hyperhydrosis Sweating
	Uncommon	Cutaneous hypersensitivity reactions (incl. angioneurotic oedema, rash, pruritis)
	Rare	Photosensitivity reaction
Musculoskeletal, connective tissue and bone disorders	Uncommon	Arthralgia, myalgia
	Frequency not known	**Bone fractures
Reproductive system and breast disorders	Uncommon	Abnormal (delayed) ejaculation
	Rare	Galactorrhoea
	Frequency not known	Anorgasmia, menstrual disorders (such as amenorrhea, hypomenorrhea, metrorrhagia, menorrhagia).

General disorders and administration site reactions	Common	Asthenia, malaise
	Frequency not known	drug withdrawal syndrome including drug withdrawal syndrome neonatal. (see section 4.6)

*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.

**Class effects: Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving Selective Serotonin Reuptake Inhibitors (SSRIs) and Tricyclic Antidepressants (TCAs). The mechanism leading to this risk is unknown.

Cases of suicidal ideation and suicidal behaviours have been reported during fluvoxamine therapy or early after treatment discontinuation.

Withdrawal symptoms seen on discontinuation of fluvoxamine treatment

Discontinuation of fluvoxamine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbance (including paraesthesia, visual disturbance and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation and anxiety, irritability, confusion, emotional instability, nausea and/or vomiting, diarrhoea, sweating, palpitations, headache and tremor are the most commonly reported reactions. Generally these events are mild to moderate and are self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when fluvoxamine treatment is no longer required, gradual discontinuation by dose tapering should be carried out.

Paediatric population

In one 10-week placebo-controlled trial in children and adolescents with OCD, frequently reported adverse events with a higher incidence than placebo, were: insomnia, asthenia, agitation, hyperkinesia, somnolence and dyspepsia. Serious adverse events in this study included: agitation and hypomania.

Convulsions in children and adolescents have been reported during use outside clinical trials.

Reporting of suspected adverse reactions

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:
http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting

4.9 Overdose

Symptoms

Symptoms include gastro-intestinal complaints (nausea, vomiting and diarrhoea), 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 deaths attributed to overdose of fluvoxamine alone have been extremely rare. The highest documented dose of fluvoxamine ingested by a patient is 12 grams. This patient recovered completely. Occasionally, more serious complications were observed in cases of

deliberate overdose of fluvoxamine in combination with other drugs.

Treatment

There is no specific antidote to fluvoxamine. In case of overdose 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.

5. 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 neurones. 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

Pharmacotherapeutic group: Antidepressants, Selective serotonin reuptake inhibitors, ATC code: N06AB08.

In a reported placebo controlled trial in 120 patients with OCD, aged between 8 and 17 years, a statistically significant improvement was seen in the total population in favour of fluvoxamine at 10 weeks. A further subgroup analysis showed improvement on the C-YBOCS rating scale in children whereas no effect was seen in adolescents. The mean dose was respectively 158 mg and 168 mg/day.

Dose response

No formal clinical trials were conducted investigating the dose response of fluvoxamine. However, it is clinical experience that up-titrating the dose might be beneficial for some patients.

5.3 Pharmacokinetic properties

Absorption

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

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

Distribution

In vitro plasma protein binding of fluvoxamine is 80%. Volume of distribution in humans is 25 l/kg.

Metabolism

Fluvoxamine undergoes extensive metabolism in the liver. Although CYP2D6 is in vitro the main isoenzyme involved in fluvoxamine's metabolism, plasma concentrations in poor metabolisers for CYP2D6 are not much higher than those in extensive metabolisers.

The mean plasma half-life is approximately 13-15 hours after a single dose and slightly longer (17-22 hours) during repeated dosing, when steady-state plasma levels are usually achieved within 10-14 days.

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 CYP1A2 and CYP2C19. A moderate inhibition was found for CYP2C9, CYP2D6 and CYP3A4.

Fluvoxamine displays linear single-dose pharmacokinetics. Steady-state concentrations are higher than calculated from single-dose data, and this disproportional increase is more pronounced with higher daily doses.

Special Patients groups

The pharmacokinetics of fluvoxamine is similar in healthy adults, elderly patients, and patients with renal insufficiency. The metabolism of fluvoxamine is impaired in patients with liver disease.

Steady-state plasma concentrations of fluvoxamine were twice as high in children (aged 6-11) as in adolescents (aged 12- 17). Plasma concentrations in adolescents are similar to those in adults**.**

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Carcinogenesis and mutagenesis

There is no evidence of carcinogenicity or mutagenicity with fluvoxamine.

Fertility and reproductive toxicity

Reported 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 >twofold 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.

Reported 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.

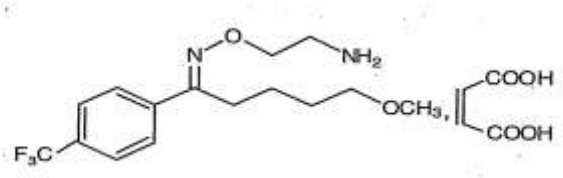
The safety margin for reproductive toxicity is unknown.

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. Description

Fluvoxamine Maleate has a molecular weight of 434.4 and its empirical formula is $C_{19}H25F3N2O6$ and chemical name is E-5-methoxy-1-[4-(trifluoromethyl)phenyl)phenyl]-1-pentanone O-(2-Aminoethyl) oxime maleate. The structural formula is:



Fluvoxamine Maleate is a white to off white crystalline powder.

Product Description

FLUVATOR -50 Yellow colored, round, biconvex, film coated tablets plain break on both side.

FLUVATOR -100 Yellow colored, round, biconvex, film coated tablets with break line on one side and plain on other side.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

FLUVATOR 50 and FLUVATOR 100 is packed in blister strip of 10 tablets.

8.4 Storage and handing instructions

9 Store protected from light and moisture, at a temperature not exceeding 25°C.

10 Patient counselling information

FLUVATOR

(Fluvoxamine I.P)

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.6.Contents of the pack and other information

9.1 What FLUVATOR is and what it is used for

Fluvator belongs to a group of medicines called selective serotonin re-uptake inhibitors (SSRI). Fluvator contains a substance called fluvoxamine.

It is used in treatment for obsessive compulsive disorder and depression.

9.2 What you need to know before you take FLUVATOR

Do not take Fluvator if any of the following applies to you:

- You are allergic (hypersensitive) to fluvoxamine.
- You are taking medicines called monoamine oxidase inhibitors (MAOI) sometimes prescribed to treat depression or anxiety, including linezolid (an antibiotic which is also an MAOI). Treatment with fluvoxamine should only be started at least 2 weeks after discontinuation of an irreversible MAOI. However treatment with fluvoxamine after discontinuation of certain reversible MAOIs can be started the following day. In exceptional cases linezolid (an antibiotic MAOI) may be used with fluvoxamine provided the doctor can monitor you closely. Your doctor will advise you how you should begin taking Fluvator once you have stopped taking the MAOI.
- You are taking tizanidine, a medicine often used as a muscle relaxant
- You are breast-feeding

If any of the above apply to you, do not take Fluvator and talk to your doctor.

Take special care

Talk to your doctor or a pharmacist before taking your medicine if:

- you recently had a heart attack
- you are pregnant, or could be pregnant
- you have epilepsy
- you have a history of bleeding problems or if you regularly use medicines which increase the risk of bleeding, such as common pain killers
- you have diabetes
- you are having treatment with electro convulsive therapy (ECT)
- you ever had mania (a feeling of elation or over-excitement)
- you have liver or kidney problems
- you have high pressure in your eyes (glaucoma)
- you are less than 18 years old (See also section 9.3 ‘How to take Fluvator’)

If any of the above applies to you, your doctor will tell you whether it is safe for you to start taking Fluvator. Occasionally, thoughts of restlessness, for example, you cannot sit or stand still (akathisia) may occur or may increase during the first few weeks of treatment with Fluvator, until the anti depressant effect has worked.

Tell your doctor immediately if you experience these symptoms. Then a dosage adjustment may be helpful.

Medicines like Fluvator (so called SSRIs) may cause symptoms of sexual dysfunction (see section 9.4). In some cases, these symptoms have continued after stopping treatment.

Thoughts of suicide and worsening of your depression or anxiety disorder

If you are depressed and/or have anxiety disorders you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer.

You may be more likely to think like this:

- If you have previously had thoughts about killing or harming yourself.
- If you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in adults aged less than 25years with psychiatric conditions who were treated with an antidepressant.

If you have thoughts of harming or killing yourself at any time, ***contact your doctor or go to a hospital straight away***.

You may find it helpful to tell a relative or close friend that you are depressed or have an anxiety disorder, and ask them to read this leaflet.

You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.

Tell your doctor immediately if you have any distressing thoughts or experiences.

Use in children and adolescents under 18 years of age

Children and adolescents under 18 years should not take this medicine, unless they are being treated for obsessive compulsive disorder (OCD).

When taking this type of medicine, people under 18 have an increased risk of side effects such as attempting suicide, thoughts about suicide and hostility, such as aggression, oppositional behaviour and anger.

If your doctor has prescribed Faverin for someone under 18 years and you want to discuss this, please go back to your doctor. You should tell your doctor if any of the symptoms listed above develop or worsen when patients under 18 are taking Faverin.

Also, it is not known whether taking Faverin under the age of 18 years can affect growth, maturation or development of intelligence or behaviour in the long term.

Are you taking any other medicines?

You should not start to take the herbal remedy St John's Wort while you are being treated with Fluvator since this may result in an increase of undesirable effects. If you are already taking St John's Wort when you start on Fluvator, stop taking the St John's Wort and tell your doctor at your next visit.

If you have been taking a medicine to treat depression or anxiety within the last two weeks, or you suffer from schizophrenia, check with your doctor or a pharmacist.

Your doctor or pharmacist will check if you are taking other medicines to treat your depression or related conditions, these may include:

- benzodiazepines
- tricyclic antidepressants

- neuroleptic or anti-psychotics
- lithium
- tryptophan
- monoamine oxidase inhibitors (MAOI) such as moclobemide.
- Selective serotonin reuptake inhibitors (SSRI) such as citalopram

Your doctor will tell you if it is safe for you to start taking Fluvator.

You should also tell your doctor or pharmacist if you have been taking any of the medicines listed below:

- aspirin (acetylsalicylic acid) or aspirin-like medicines, used to treat pain and inflammation (arthritis)
- ciclosporin, used to reduce the activity of the immune system
- methadone, used to treat pain and withdrawal symptoms
- mexiletine, used to treat abnormal heart rhythms
- phenytoin or carbamazepine, used to treat epilepsy
- propranolol, used to treat high blood pressure and heart conditions
- ropinirole, for Parkinson's disease.
- a 'triptan', used to treat migraines, such as sumatriptan
- terfenadine, used to treat allergies. Fluvator should not be taken together with terfenadine.
- sildenafil, used to treat erectile dysfunction
- theophylline, used to treat asthma and bronchitis
- tramadol, a pain-killer
- clopidogrel, warfarin, nicoumalone or any other drug used to prevent blood clots

If you are taking or have recently taken any of the medicines in the above list and you have not already discussed these with your doctor, go backto your doctor and ask what you should do. Your dose may need to be changed or you may need to be given a different medicine.

Please tell your doctor or pharmacist if you are taking or have taken any other medicines, including medicines obtained without a prescription. This includes herbal medicines.

Taking Fluvator with food and drink

- Do not drink alcohol if you are taking this medicine. This is because alcohol works together with Fluvator and will make you sleepy and unsteady.
- If you normally drink a lot of tea, coffee and soft drinks with caffeine in them, you may have symptoms such as your hands shaking, feeling sick, fast heart rate (palpitations), restlessness and difficulty sleeping (insomnia). If you lower how much caffeine you drink, these symptoms might disappear.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Pregnancy

There is only limited experience concerning the use of fluvoxamine during pregnancy. Do not take fluvoxamine if you are pregnant unless your doctor considers it absolutely necessary. If you are currently taking fluvoxamine and are planning to become pregnant or to father a child, please consult with your physician to decide if an alternative medication is necessary or appropriate. Fluvoxamine has been shown to reduce the quality of sperm in animal studies. Theoretically, this could affect fertility, but impact on human fertility has not been observed as yet.

Make sure your midwife and/or doctor know you are on fluvoxamine. When taken during pregnancy, particularly in the last 3 months of pregnancy, medicines like fluvoxamine may increase the risk of a serious condition in babies, called persistent pulmonary hypertension of the newborn (PPHN), making the baby breathe faster and appear bluish. These symptoms usually begin during the first 24 hours after the baby is born. If this happens to your baby you should contact your midwife and/or doctor immediately.

You should not discontinue treatment with fluvoxamine abruptly. If you are taking fluvoxamine in the last 3 months of pregnancy, your baby might have some other symptoms when it is born in addition to having trouble breathing or bluish skin, such as not being able to sleep or feed properly, being too hot or cold, being sick, crying a lot, stiff or floppy muscles, lethargy, drowsiness, tremors, jitters or fits. If your baby has any of these symptoms when it is born contact your doctor immediately.

Breast-feeding

Fluvoxamine passes into breast milk. There is a risk of an effect on the baby. Therefore, you should discuss the matter with your doctor, and he/she will decide whether you should stop breast-feeding or stop the therapy with fluvoxamine.

Driving and using machines

You can drive and use machines while you are taking this treatment, so long as this medicine does not make you sleepy.

9.3 How to take FLUVATOR

How much Fluvator to take

Always take Fluvator as your doctor has told you to. You should check with your doctor or pharmacist if you are not sure.

Usual starting dose for adults (18 years and older):

The treatment for depression:

• Start with 50 or 100 mg daily, taken in the evening.

The treatment for obsessive compulsive disorder:

• Start with 50 mg daily, preferably in the evening.

If you don’t start to feel better after a couple of weeks, talk to your doctor, who will advise you. He or she may decide to increase the dose gradually.

The highest daily dose that is recommended is 300 mg.

If your doctor advises you to take more than 150 mg per day, do not take them all at once; ask your doctor when you should take them.

The usual dose for children and adolescents with obsessive compulsive disorder – OCD (8 years and older is):

Start with 25 mg (half a tablet) per day, preferably at bedtime Your doctor may increase the dose every 4 – 7 days in 25 mg increments as tolerated until an effective dose is achieved.

The highest daily dose is 200 mg.

If your doctor advises you to take more than 50 mg per day, do not take them all at once; ask your doctor when you should take them. If the dose is not divided equally, the larger dose should be taken at night. Children and adolescents under the age of 18 should not take this medicine to treat depression. This medicine should be prescribed for children or adolescents for Obsessive Compulsive Disorder (OCD) only.

How to take Fluvator

Swallow the tablets with water. Do not chew them.

You can break the tablets in half if your doctor has advised you to

How long does it take to work?

Fluvator may take a little time to start working. Some patients do not feel better in the first 2 or 3weeks of treatment.

Keep taking your tablets until your doctor tells you to stop. Even when you start feeling better, your doctor may want you to carry on taking the tablets for some time, for at least six months to make sure that the medication has worked completely.

Do not stop taking Fluvator too quickly.

You may suffer from withdrawal symptoms such as:

- agitation
- anxiety
- confusion
- diarrhoea
- difficulty sleeping / intense dreams
- dizziness
- emotional instability
- headaches
- irritability
- nausea and/or vomiting
- palpitations (faster heartbeat)
- sensory disturbance (such as electric shock sensations or visual disturbances)
- sweating
- tremors

When stopping Fluvator your doctor will help you to reduce your dose slowly over a number of weeks or months, this should help reduce the chance of withdrawal effects. Most

people find that any symptoms on stopping Fluvator are mild and go away on their own within two weeks. For some people, these symptoms may be more severe, or go on for longer.

If you get withdrawal effects when you are coming off your tablets your doctor may decide that you should come off them more slowly. If you get severe withdrawal effects when you stop taking Fluvator, please see your doctor. He or she may ask you to start taking your tablets again and come off them more slowly (see section 4 'Possible Side Effects').

If you experience any symptoms on stopping the treatment, contact your doctor.

If you take more Fluvator than you should

If you or someone else takes too much Fluvator (an overdose), talk to a doctor or go to a hospital straight away. Take the medicine pack with you.

Symptoms of overdose include, but are not limited to, nausea, vomiting, diarrhoea and feeling drowsy or dizzy. Cardiac events (slow or fast heartbeat, low blood pressure), liver problems, convulsions (fits) and coma have also been reported.

If you forget to take Fluvator

If you miss a tablet, wait until the next dose is due. Do not try to make up for the dose you have missed. If you have any further questions on the use of this product, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines Fluvator can cause side effects (unwanted effects or reactions), but not everyone gets them.

Frequencies of the observed side effects are defined as:

very common	affects more than 1 user in 10
common	affects 1 to 10 users in 100
uncommon	affects 1 to 10 users in 1,000
rare	affects 1 to 10 users in 10,000
very rare	affects less than 1 user in 10,000
not known	frequency cannot be estimated from the available data

Side effects related to this type of medicine

Occasionally, thoughts of suicide or self harm may occur or may increase in the first few weeks of treatment with Fluvator, until the antidepressant effect has worked.

Tell your doctor immediately if you have any distressing thoughts or experiences.

If you have several symptoms at the same time you might have one of the following rare conditions:

- Serotonin syndrome: if you have sweating, muscle stiffness or spasms, instability, confusion, irritability or extreme agitation.

- Neuroleptic malignant syndrome: if you have stiff muscles, high temperature, confusion and other related symptoms.
- SIADH: if you feel tired, weak or confused and have achy, stiff or uncontrolled muscles.

Stop taking Fluvator and contact your doctor immediately.

If unusual bruising or purple patches appear on your skin or you vomit blood or pass blood in your stool, contact your doctor for advice. Stopping of fluvoxamine (particularly when abrupt) commonly leads to withdrawal symptoms (see section 3 withdrawal symptoms).

Sometimes patients feel slightly sick as Fluvator begins to work. Although the feeling of sickness is unpleasant, it should soon pass if you keep taking your tablets as prescribed. This may take a few weeks.

Side effects specifically related to Fluvator

Common side effects:

- agitation
- anxiety
- constipation
- diarrhoea
- difficulty sleeping
- dizziness
- dry mouth
- faster heart beat
- feeling drowsy (lethargy)
- feeling unwell (malaise)
- headache
- indigestion
- loss of appetite
- nervousness
- stomach pain
- sweating
- tremor
- muscle weakness (asthenia)
- vomiting

Uncommon side effects:

- allergic skin reactions (including swelling of face, lip or tongue, rash or itching)
- confusion
- delayed ejaculation

- dizziness when standing up too quickly
- hallucinations
- lack of co-ordination
- muscle or joint pain
- aggression

Rare side effects:

- convulsions
- liver complaints
- mania (a feeling of elation or over-excite ment)
- sensitivity to sunlight
- unexpected milk flow

Other side effects reported:

- akathisia (restlessness)
- abnormal taste
- anorgasmy (failure to achieve orgasm)
- for female patients: disorders with menstruation (monthly bleeding)
- micturition disorders (such as the need to urinate frequently during the day and/or the night, the sudden lack of control over urination during the day and/or the night, or the lack of ability to urinate)
- paraesthesia (tingling or numbness)
- glaucoma (increased pressure in eye)
- dilated pupils
- increase in the hormone prolactin (a hormone that supports milk production in a nursing mother)
- weight changes

An increased risk of bone fractures has been observed in patients taking this type of medicine.

Side effects related to the treatment for OCD, in children and adolescents, no frequencies are given:

- Hypomania (a feeling of elation and over excitement)
- Agitation
- Convulsions
- Difficulty sleeping (insomnia)
- Lack of energy (asthenia)
- Hyperactivity (hyperkinesia)

- Feeling drowsy (somnolence)
- Indigestion

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:
http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

9.5 How to store Fluvator

Store protected from light and moisture, at a temperature not exceeding 25°C.

9.6 Contents of the pack and other information

What Fluvator contains

The active substance Fluvator contains Fluvoxamine Maleate.

FLUVATOR 50

Fluvoxamine Maleate - 50 mg

FLUVATOR 100

Fluvoxamine Maleate – 100 mg

The excipients used are Starch, Mannitol, Hydroxypropyl Cellulose, Methanol, Pregelatinized Starch, Sodium Stearyl Fumarate, Colloidal Silicon Dioxide, Ferric Oxide Yellow.

10. Details of manufacturer

Torrent Pharmaceuticals Ltd

Indrad – 382721, Dist. Mehsana, INDIA.

At: Vill.Sainimajra, Nalagarh-Ropar Road, Nalagarh, Distt. Solan[H.P.]

11. Details of permission or licence number with date

L/13/1225/MNB issued on 11.05.2018

12. Date of revision

Jun/2020

MARKETED BY

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