**Fluvoxamine Maleate Tablets 50 mg**
**Fluvoxamine Maleate Tablets 100 mg**

## 1. NAME OF THE MEDICINAL PRODUCT

Fluvoxamine Maleate Tablets 50 mg
Fluvoxamine Maleate Tablets 100 mg

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg or 100 mg fluvoxamine maleate.

Excipients with known effect:
Each 50 mg tablet contains 151.5 mg mannitol and each 100 mg tablet contains 303 mg mannitol.
Each tablet contains less than 1 mmol (23 mg) sodium.

For a full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM

White to off-white, round biconvex, film-coated tablets. The tablets are scored with a division mark on both sides and debossed with "FLM 50" on one side.

White to off-white, round biconvex, film-coated tablets. The tablets are scored with a division mark on both sides and debossed with "FLM 100" on one side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

- Major depressive episode.
- Obsessive Compulsive Disorder (OCD).

### 4.2 Posology and method of administration

Posology

*Depression*
*Adults*
The recommended dose is 100 mg daily. Patients should start on 50 or 100 mg, given as a single dose, in the evening. It is recommended to increase the dose gradually until an effective dose is reached. The usual effective dose is 100mg per day and should be adjusted on individual patient responses. Although there may be an increased potential for undesirable effects at higher doses, if after some weeks on the recommended dose insufficient response is seen some patients may benefit from having their dose increased gradually up to a maximum of 300mg a day (see section 5.1). Doses up to 150 mg can be given as a single dose, preferably in the evening. It is advisable that a total daily dose of more than 150 mg is given in two or three divided doses. Dosage adjustments should be made carefully on an individual patient basis, to maintain the patients at the lowest effective dose.

Patients with depression should be treated for a sufficient period of at least six months to ensure that they are free from symptoms.

*Children/adolescents*
Fluvoxamine should not be used in children and adolescents under the age of 18 years for the treatment of major depressive episode. The efficacy and safety of fluvoxamine have not been established in the treatment of paediatric major depressive episode (see section 4.4).

*Obsessive Compulsive Disorder:*
*Adults*
The recommended dose is between 100 mg and 300 mg daily. Patients should start at 50 mg per day for 3 – 4 days. Although there may be an increased potential for undesirable effects at higher doses, if after some weeks on the recommended dose insufficient response is seen some patients may benefit from having their dose increased gradually up to maximum of 300 mg a day (see section 5.1). Doses up to 150 mg can be given as a single dose, preferably in the evening. It is advisable that a total daily dose of more than 150 mg is given in two or three divided doses.

If a good therapeutic response has been obtained, treatment can be continued at a dosage adjusted on an individual basis. If no improvement is observed within 10 weeks, treatment with fluvoxamine should be reconsidered. While there are no systematic studies to answer the question of how long to continue fluvoxamine treatment, OCD is a chronic condition and it is reasonable to consider continuation beyond 10 weeks in responding patients. Dosage adjustments should be made carefully on an individual patient basis, to maintain the patient at the lowest effective dose. The need for treatment should be reassessed periodically. Some clinicians advocate concomitant behavioural psychotherapy for patients who have done well on pharmacotherapy. Long-term efficacy (more than 24 weeks) has not been demonstrated in OCD.

*Children/adolescents*
In children over eight years and adolescents there is limited data on a dose of up to 100 mg twice a day for 10 weeks. The starting dose is 25 mg per day. Increase every 4-7 days in 25 mg increments, as tolerated until an effective dose is achieved. The maximum dose in children should not exceed 200 mg/day. (For further details see sections 5.1 and 5.2). It is advisable that a total daily dose of more than 50 mg should be given in two divided doses. If the two divided doses are not equal, the larger dose should be given at bedtime.

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

*Method of administration*
Fluvoxamine tablets should be swallowed with water and without chewing.

*Withdrawal symptoms seen on discontinuation of fluvoxamine*
Abrupt discontinuation should be avoided. When stopping treatment with fluvoxamine the dose should be gradually reduced over a period of at least one or two weeks in order to reduce the risk of withdrawal reactions (see sections 4.4 and 4.8). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

## 4.3 Contraindications

Fluvoxamine tablets are contraindicated in combination with tizanidine and monoamine oxidase inhibitors (MAOIs) (see sections 4.4 and 4.5).

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 mentioned in section 6.1.

## 4.4 Special warnings and precautions for use

*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 (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.

*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).

*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.

*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.

*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.

*Young adults (ages 18 to 24 years)*
A 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.

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 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.

*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. Furthermore there is evidence that in a small group of people, antidepressants may increase the risk of suicidal thoughts and self-harm.

Other psychiatric conditions for which fluvoxamine 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 depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide-related events, 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.

*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.

*Withdrawal symptoms seen on discontinuation of fluvoxamine treatment*
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). In clinical trials adverse events seen on treatment discontinuation occurred in approximately 12% of patients treated with fluvoxamine. 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 commonly reported symptoms in associsation 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 section 4.8).

Generally these symptoms 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 (see section 4.2).

Long term safety data in children and adolescents, especially related to growth, sexual function, cognitive and behavioural development, are lacking. Careful monitoring is therefore recommended in this patient population.

*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 (see section 4.5).

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

## 4.5 Interaction with other medicinal products and other forms of interaction

*Pharmacodynamic interactions*
The serotonergic effects of fluvoxamine may be enhanced when used in combination with other serotonergic agents (including tramadol, triptans, SSRIs and St. John´s Wort preparations). (See also section 4.4).
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.

*Monoamine-oxidase inhibitors*
Fluvoxamine should not be used in combination with MAOIs, due to risk of serotonin syndrome (see also section 4.3 and 4.4).

*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 CYP 2C19 is demonstrated in in vitro and in vivo studies. CYP2C9, CYP 2D6 and CYP3A4 are inhibited to a lesser extent. 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 (see also section 4.4).

Fluvoxamine does not influence plasma concentrations of digoxin.

Fluvoxamine does not influence plasma concentrations of atenolol.

## 4.6 Fertility, 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.

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, 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 Fluvoxamine impairs male and female fertility. The safety margin for this effect was not identified. The relevance of these findings to humans is unknown (see section 5.3).
Animal data have shown that fluvoxamine may affect sperm quality (see section 5.3). 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.

Fluvoxamine 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).

| System organ class | Common | Uncommon | Rare | Very rare | Frequency not known |
|---|---|---|---|---|---|
| **Endocrine disorders** | | | | | Hyperprolactinemia, Inappropriate antidiuretic hormone secretion |
| **Metabolism and nutrition disorders** | Anorexia | | | | Hyponatraemia, weight increased, weight decreased |

| | | | | | |
|---|---|---|---|---|---|
| **Psychiatric disorders** | | Hallucination, confusional stage, aggression | Mania | | Suicidal ideation (see section 4.4) |
| **Nervous system disorders** | Agitation, nervousness, anxiety, insomnia, somnolence, tremor, headache, dizziness | Extrapyramidal disorder, ataxia | Convulsion | | 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** | | | | | Glaucoma, mydriasis |
| **Renal and urinary disorders** | | | | | micturition disorder (including urinary retention, urinary incontinence, pollakiuria, nocturia and enuresis) |
| **Cardiac disorders** | Palpitations/ tachycardia | | | | |
| **Vascular disorders** | | (Orthostatic) hypotension | | | Haemorrhage (e.g. gastrointestinal haemorrhage, gynaecological, haemorrhage, ecchymosis, purpura) |
| **Gastrointestinal disorders** | Abdominal pain, constipation, diarrhoea, dry mouth, dyspepsia, nausea, vomiting | | | | |
| **Hepatobiliary disorders** | | | Hepatic function abnormal | | |
| **Skin and subcutaneous tissue disorders** | Hyperhydrosis Sweating | Cutaneous hypersensitivity reactions (incl. angioneurotic oedema, rash, pruritis) | Photosensitivity reaction | | |
| **Musculoskeletal, connective tissue and bone disorders** | | Arthralgia, myalgia | | | **Bone fractures |

| | | | | | |
|---|---|---|---|---|---|
| **Reproductive system and breast disorders** | | Abnormal (delayed) ejaculation | Galactorrhoea | | Anorgasmia, menstrual disorders (such as amenorrhea, hypomenorrhea, metrorrhagia, menorrhagia). |
| **General disorders and administration site reactions** | Asthenia, malaise | | | | 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 (see section 4.4).

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.

*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(see sections 4.2 and 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the Health Sciences Authority.

## 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 Pharmacodynamic properties

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

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.

In a 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.

### 5.2 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 1/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, CYP2D6and 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.

### 5.3 Preclinical safety data

*Carcinogenis 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.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients
Tablet core
Maize starch
silica colloidal anhydrous
pregelatinised starch
sodium stearyl fumarate

mannitol

Tablet coating
Polyethylene glycol 6,000
talc
titanium dioxide (E171)
methyl hydroxypropyl cellulose.

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

The shelf life of Fluvoxamine Maleate Tablets 50 mg and Fluvoxamine Maleate Tablets 100 mg is 36 months. The expiry date ("exp") can be found on the packaging. Do not use these tablets after this date. The first 2 digits indicate the month and the last 4 digits indicate the year.

### 6.4 Special precautions for storage

Fluvoxamine Maleate Tablets 50 mg and Fluvoxamine Maleate Tablets 100 mg should be stored in the original undamaged package at room temperature (at or below 25 °C).

**Keep all medicines out of the reach of children.**

### 6.5 Nature and content of the container

The Fluvoxamine Maleate Tablets are packaged in PVC/PVDC/Al strips.
The strips are packaged in lithographed carton boxes with a patient information leaflet. Packs of 30 tablets are available.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and handling

No special requirements.

## 7. PRODUCT OWNER

Genthon BV
Microweg 22, 6545 CM Nijmegen
The Netherlands

## 8. PRODUCT LICENSE NUMBER

SIN 11823 P - Fluvoxamine Maleate Tablets 50 mg
SIN 11824 P - Fluvoxamine Maleate Tablets 100 mg