

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Faverin 100mg film-coated tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100mg fluvoxamine maleate.

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Film-coated tablet

*Product imported from The Netherlands:*

Oval, biconvex, scored, white to off-white film-coated tablets imprinted “313” on both sides of the score. The tablet can be divided into equal doses.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

- Major depressive episode
- Obsessive Compulsive Disorder (OCD)

### 4.2 Posology and method of administration

#### 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. Dosage should be reviewed and adjusted if necessary within 3 to 4 weeks of initiation of therapy and thereafter as judged clinically appropriate. 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 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 2 or 3 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 6 months to ensure that they are free from symptoms.

##### *Children/adolescents*

Faverin 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 Faverin 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 100-300 mg daily. Patients should start at 50 mg per day. 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 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 2 or 3 divided doses.

If a good therapeutic response has been obtained, treatment can be continued at a dosage adjusted on an individual basis.

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 patients 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 8 years and adolescents there is limited data on a dose of up to 100 mg b.i.d 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 section 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.

#### *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 section 4.4 Special warnings and special precautions for use and section 4.8 Undesirable effects). 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.

#### *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.

### **4.3 Contraindications**

Faverin tablets are contraindicated in combination with tizanidine and monoamine oxidase inhibitors (MAOIs) (see section 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.

### **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 Faverin 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. 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.

#### *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.

#### *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 (see section 4.8 Undesirable effects). In 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.

Dizziness, sensory disturbance (including paraesthesia, visual disturbances and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation and anxiety, irritability, confusion, emotional instability, nausea and/or vomiting and diarrhoea, sweating and palpitations, headache and tremor are the most commonly reported reactions. 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 "Withdrawal Symptoms Seen on Discontinuation of Fluvoxamine", Section 4.2 Posology and method of administration).

#### *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 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 disorder*

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.

*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.

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

Fluvoxamine should not be used in combination with MAOIs (see also section 4.3 Contraindications).

Fluvoxamine is a potent inhibitor of CYP1A2, and to a lesser extent of CYP2C and CYP3A4. Drugs which are largely metabolised via these isoenzymes are eliminated slower and may have higher plasma concentrations when co-administered with fluvoxamine. This is particularly relevant for drugs with a narrow therapeutic index. Patients should be carefully monitored and, if necessary, dose adjustment of these drugs is recommended.

Fluvoxamine has marginal inhibitory effects on CYP2D6 and seems not to affect non-oxidative metabolism or renal excretion.

### **CYP1A2**

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

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

Isolated cases of cardiac toxicity have been reported when fluvoxamine was combined with thioridazine.

As plasma concentrations of propranolol are increased in combination with fluvoxamine, the propranolol dose may need to be lowered.

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.

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.

### **CYP2C**

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

### **Warfarin:**

When given with fluvoxamine, warfarin plasma concentrations were significantly increased and prothrombin times prolonged.

The cytochrome P-450 isozymes involved in the metabolism of warfarin include 2C9, 2C19, 2C8, 2C18, 1A2, and 3A4. 2C9 is likely to be the principal form of human liver P-450 which modulates the *in vivo* anticoagulant activity of warfarin.

### **CYP3A4**

Terfenadine, astemizole, cisapride (see also section 4.4 Special Warnings and Precautions for Use).

Patients co-administered fluvoxamine and CYP3A4 metabolised drugs with a narrow therapeutic index (such as carbamazepine and ciclosporin) should be carefully monitored and, if necessary, dose adjustment of these drugs is recommended.

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

***Glucuronidation***

Fluvoxamine 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, SSRIs and St. John's Wort preparations). (See also section 4.4 Special Warnings and Precautions for Use).

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.

**4.6 Fertility, pregnancy and lactation****Pregnancy**

Epidemiological data have suggested that the use of Selective Serotonin Reuptake Inhibitors (SSRIs) in pregnancy, particular 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).

Faverin 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 Faverin 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 SSRI's have shown that an effect on sperm quality is reversible. Impact on human fertility has not been observed so far.

Faverin 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.

MedDra system organ class	Common ≥1/100, <1/10	Uncommon ≥1/1,000, <1/100	Rare ≥1/10,000, <1/1,000	Very rare <1/10,000 incl. isolated reports
Metabolism and nutrition disorders	Anorexia			
Psychiatric disorders		Hallucination, confusional stage	Mania	
Nervous system disorders	Agitation, nervousness, anxiety, insomnia, somnolence, tremor, headache, dizziness	Extrapyramidal disorder, ataxia	Convulsion	
Cardiac disorders	Palpitations/ tachycardia			
Vascular disorders		(Orthostatic) hypotension		
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		
Reproductive system and breast disorders		Abnormal (delayed) ejaculation	Galactorrhoea	
General disorders and administration site reactions	Asthenia, malaise			

In addition to those adverse events reported during clinical trials, the following side effects have been reported spontaneously during postmarketing use of fluvoxamine. A precise frequency cannot be provided and is therefore classified as ‘not known’.

Blood and lymphatic system disorders: Haemorrhage (e.g. gastrointestinal haemorrhage, ecchymosis, purpura)

Endocrine disorders: Hyperprolactinemia, Inappropriate antidiuretic hormone secretion

Metabolism and nutrition disorders: Hyponatraemia, weight increased, weight decreased

Nervous system disorders: Serotonin syndrome, neuroleptic malignant syndrome-like events, paresthesia, dysgeusia, and SIADH have been reported (see also section 4.4 Special warnings and special precautions for use).

Eye Disorders: Mydriasis

Renal and urinary disorders: micturition disorder (including urinary retention, urinary incontinence, pollakiuria, nocturia and enuresis)

Reproductive system and breast disorders: Anorgasmia, menstrual disorders (such as amenorrhea, hypomenorrhea, metrorrhagia, menorrhagia)

General disorders and administration site conditions: drug withdrawal syndrome including drug withdrawal syndrome neonatal (see section 4.6 Fertility, Pregnancy and Lactation)

Psychomotor restlessness/akathisia (see section 4.4 Special warnings and precautions for use)

Cases of suicidal ideation and suicidal behaviours have been reported during Fluvoxamine therapy or early after treatment discontinuation (see section 4.4 Special warnings and precautions for use).

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 section 4.2 Posology and method of administration and section 4.4 Special warnings and precautions for use).

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.

## **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.

### *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.

### **5.2 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 Faverin 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 a moderate inhibitor of CYP2C and CYP3A4, with only marginal inhibitory effects on CYP2D6.

Fluvoxamine displays linear single-dose pharmacokinetics. Steady-state concentrations are higher than calculated from single-dose data, and are disproportionately higher at 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

### 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.

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 cores:*

Mannitol  
Maize starch  
Pregelatinised starch  
Sodium stearyl fumarate  
Colloidal anhydrousilica

#### *Film-coat:*

Hypromellose  
Macrogol 6000  
Talc  
Titanium Dioxide E171

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

### 6.4 Special precautions for storage

Do not store above 25°C.

### 6.5 Nature and contents of container

PVC/PVdC/Aluminium press-through blister in a cardboard carton.  
Pack contains: 30 tablets.

## **6.6 Special precautions for disposal**

No special recommendation.

## **7 PARALLEL PRODUCT AUTHORISATION HOLDER**

PCO Manufacturing  
Unit 10, Ashbourne Business Park  
Rath  
Ashbourne  
Co. Meath  
Ireland

## **8 PARALLEL PRODUCT AUTHORISATION NUMBER**

PPA0465/319/002

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 16<sup>th</sup> August 2013

## **10 DATE OF REVISION OF THE TEXT**