SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Faverin 50 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg fluvoxamine maleate.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet
Round, biconvex, scored, white to off-white film coated tablets imprinted '291' on both sides of the score.

The tablet can be divided into equal halves.

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 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 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.

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 4.4 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, linezolid).

See section 4.4 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 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.

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.

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). 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.

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 Section 4.8).

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 (see Section 4.2).

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.

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 (see section 4.3 and 4.5). 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 (see section 4.8). 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 (see section 4.5).

4.5 Interactions 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, linezolid, 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, including linezolid, 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. 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 (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).

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 SSRIs 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.
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	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 Special warnings and precautions for use).

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 and 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.

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 via the national reporting system:-

In Ireland:
Reports may be made by following the links to the online reporting option accessible from the HPRA homepage, or by completing the downloadable report form also accessible from the HPRA website, which may be completed manually and submitted to the HPRA via freepost, to the following address:
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

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 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.

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. The effects were observed at exposures > two-fold higher than exposure 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 cores:
Mannitol
Maize starch
Pregelatinised starch
Sodium stearyl fumarate
Colloidal anhydrous silica

Film-coat:
Hypromellose
Macrogol 6000
Talc
Titanium Dioxide E171

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years.

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.

Pack sizes: 5, 10, 20, 30, 50, 60, 90, 100 and 250 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special recommendation.

7. MARKETING AUTHORISATION HOLDER

Mylan IRE Healthcare Limited
Unit 35/36
Grange Parade
Baldoyle Industrial Estate
Dublin 13
Ireland

8. MARKETING AUTHORISATION NUMBER

PA 2010/31/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 21 June 2009

10 DATE OF REVISION OF THE TEXT

August 2019