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Prescribing Information

FAVOXIL

Tablets

NAME OF THE MEDICINAL PRODUCT

Favoxil 50, 50 mg film-coated tablets
Favoxil 100, 100 mg film-coated tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: fluvoxamine maleate
Each tablet contains 50 mg or 100 mg of fluvoxamine maleate.

For a full list of excipients see section 6.1

PHARMACEUTICAL FORM

50 mg: Round, biconvex, scored, white to off-white film coated tablets for oral administration.

100 mg: Oval, biconvex, scored, white to off-white film coated tablets for oral administration

CLINICAL PARTICULARS

Indications

- ♣ For the treatment of depression.
- ♣ For the treatment of Obsessive Compulsive Disorder (OCD).

Contraindications

Favoxil tablets are contraindicated in combination with tizanidine and monoamine oxidase inhibitors (MAOIs).

Treatment with fluvoxamine can be initiated:

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

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.

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). The 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 again in the early stages of recovery.

Obsessive compulsive disorders 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 obsessive compulsive 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 a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes.

Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behavior 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 OCD. Due to lack of clinical experience the use of fluvoxamine in children for the treatment of depression cannot be recommended. Suicide-related behaviors (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behavior and anger) were more frequently observed in clinical trials among children and adolescents treated with an antidepressant compared to those treated with placebo. If based on clinical need, a decision to treat is 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 behavioral development are lacking.

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.

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.

Akathisia/psychomotor restlessness

The use of fluvoxamine has been associated with the development of akathisia, characterized by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Renal and hepatic impairment

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

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

Nervous system disorders

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

On rare occasions development of a serotonin syndrome or neuroleptic malignant syndrome-like events have been reported in association with treatment of fluvoxamine, particularly when given in combination with other serotonergic and/or neuroleptic drugs. As these syndromes may result in potentially life-threatening conditions, treatment with fluvoxamine should be discontinued if such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated.

Metabolism and nutrition disorders

As with other SSRIs, hyponatremia has been rarely reported, and appears to be reversible when fluvoxamine is discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone secretion. The majority of reports were associated with older patients.

Glycaemic control may be disturbed, especially in the early stages of treatment. 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.

Haematological disorders

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

Cardiac disorders

When combined with fluvoxamine plasma concentrations of terfenadine, astemizole or cisapride may be increased resulting in an increased risk for QT-prolongation/Torsade de Pointes. Therefore, fluvoxamine should not be co-administered with these drugs.

Fluvoxamine may cause an insignificant decrease in heartbeat (2-6 beats per minute).

Withdrawal reactions

It is possible that withdrawal reactions may occur on stopping therapy with fluvoxamine although the available preclinical and clinical evidence does not suggest that this treatment causes dependence. The following symptoms have been reported in association with withdrawal of the product: dizziness, paresthesia, headache, nausea and anxiety. The majority of the withdrawal reactions are mild and self-limiting. When stopping, a gradual dose reduction may be considered.

Interaction with other medicinal products and other forms of interaction

Fluvoxamine should not be used in combination with MAOIs (see also contraindications).

Fluvoxamine is a potent inhibitor of CYP1A2, and to a lesser extent of CYP2C and CYP3A4. Drugs which are largely metabolized 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, olanzapine) which are largely metabolized through cytochrome P450 1A2 when given together with fluvoxamine, has been reported. A decrease in the dose of these products should be considered if treatment with fluvoxamine is initiated.

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 ropinirol may be increased in combination with fluvoxamine thus increasing the risk of overdose, surveillance and reduction in the posology of ropinirol during fluvoxamine treatment and after its withdrawal may be required.

CYP2C

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

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

CYP3A4

Terfenadine, astemizole, cisapride: see also special warnings and special precautions for use.

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

The plasma levels of oxidatively metabolized 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

Serotonin syndrome

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

Pregnancy and lactation

Pregnancy

Data on a limited number of exposed pregnancies indicate no adverse effects of fluvoxamine on pregnancy. To date, no other relevant epidemiological data are available.

Reproduction studies in animals revealed impaired fertility (Note: at doses exceeding about 4 times the maximum recommended human dosage), increased embryo foetal death, decreased foetal body weight and increased incidences of foetal eye abnormalities (folded retina) in fluvoxamine doses which markedly exceed maximum recommended human dose. The potential risk for humans is unknown. Caution should be exercised when prescribing to pregnant women.

Isolated cases of withdrawal symptoms in the newborn child have been described after the use of fluvoxamine at the end of pregnancy. Some newborns experience feeding and/ or respiratory difficulties, seizures, temperature instability, hypoglycemia, tremor, abnormal muscle tone, jitteriness, and constant crying after third trimester exposure to SSRIs and may require prolonged hospitalization.

Lactation

Fluvoxamine is excreted in breast milk. Therefore, Favoxil should not be used during breast-feeding.

Effects on ability to drive and use of machines

Favoxil 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.

Undesirable effects

Adverse reactions, 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	Extra-pyramidal 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	Hyper-hydrosis	Cutaneous hyper-sensitivity reactions (incl. angioneurotic oedema, rash, pruritis.)	Photo-sensitivity 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 post marketing 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: Inappropriate antidiuretic hormone secretion

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

Nervous system disorders: Serotonin syndrome, neuroleptic malignant syndrome-like events, akathisia/psychomotor restlessness, paresthesia, dysgeusia

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

Renal and urinary disorders: Micturition disorder (including urinary retention, urinary incontinence, frequency, nocturia and enuresis)

Reproductive system and breast disorders: Anorgasmia

General disorders and administration site conditions: drug withdrawal syndrome including drug withdrawal syndrome neonatal.

Dosage and Administration

Favoxil tablets should be swallowed with water and without chewing.

Depressive Illness

The recommended starting dose is 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 100 mg per day and should be adjusted on individual patient response. Doses of up to 300 mg per day have been given. Dosages above 150 mg should be given in divided doses.

In agreement with the consensus statement of the WHO, antidepressant medication should be continued for at least 6 months after recovery from a depressive episode. Favoxil at a fixed single daily dosage of 100 mg is the recommended dose for the prevention of recurrence of depression.

Obsessive compulsive disorder

The recommended starting dose is 50 mg per day for 3-4 days. The effective dosage usually lies between 100 mg and 300 mg per day. The dosage should be increased gradually until the effective dosage is achieved, with a maximum of **300 mg per day for adults and 200 mg per day for children from 8 years on/adolescents**. 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. 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 adjustment 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 behavioral psychotherapy for patients who have done well on pharmacotherapy.

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

Overdosage

Symptoms

Symptoms include gastro-intestinal complaints (nausea, vomiting and diarrhea), somnolence and dizziness. Cardiac events (tachycardia, bradycardia, hypotension), liver function disturbances, convulsions and coma have also been reported.

Fluvoxamine has a wide margin of safety in overdose. Since market introduction, reports of death attributed to overdosage of fluvoxamine alone have been extremely rare. The highest documented dose of fluvoxamine ingested by a patient is 12 gram. This patient recovered completely. Occasionally, more serious complications were observed in cases of deliberate overdose of fluvoxamine in combination with other drugs.

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 are unlikely to be of benefit.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

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

Receptor binding studies have demonstrated that fluvoxamine is a potent serotonin reuptake inhibitor *in vitro* as well as *in vivo* and has a minimal affinity for serotonin receptors subtypes. Its capacity of binding to alpha adrenergic, beta adrenergic, histaminergic, muscarinic, cholinergic or dopaminergic receptors is negligible.

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 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.

Preclinical safety data

Carcinogenesis and mutagenesis

There is no evidence of carcinogenicity or mutagenicity with fluvoxamine.

Fertility and reproductive toxicity

Reproduction studies in animals revealed impaired fertility

(Note: at doses exceeding about 4 times the maximum recommended human dosage), increased embryofetal death, decreased foetal body weight and increased incidences of foetal eye abnormalities (folded retina) in fluvoxamine doses which markedly exceed maximum recommended human dose.

Physical and psychological dependence

The potential for abuse, tolerance and physical dependence has been studied in a nonhuman primate model. No evidence of dependency phenomena was found.

PHARMACEUTICAL PARTICULARS

List of excipients

Favoxil tablets contain the following excipients: Mannitol, maize starch, pregelatinised starch, sodium stearyl fumarate, colloidal anhydrous silica, hypromellose, polyethylene glycol 6000, talc, titaniumdioxide (E171).

Shelf life

4 years

Special precautions for storage

Do not store above 25°C.

Store in the original package in order to protect from light.

Special precautions for disposal

Not applicable.

Any unused product or waste material should be disposed of in accordance with local requirements.

Presentation

Favoxil 50 mg: 20 tablets, 60 tablets.

Favoxil 100 mg: 10 tablets, 30 tablets.

Perrigo Israel Pharmaceuticals, Yeruham

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