Faverin® 50,
50 mg film-coated tablets

Faverin® 100,
100 mg film-coated tablets

Read all of this leaflet carefully before you start taking this medicine.
Keep this leaflet. You may need to read it again. If you have further questions, please ask your doctor or pharmacist. This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

50 or 100 mg fluvoxamine maleate

Abbott

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

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

Excipients: Mannitol, maize starch, pregelatinised starch, sodium stearyl fumarate, colloidal anhydrous silica, hypromellose, polyethylene glycol 6000, talc, titaniumdioxyde (E171).

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

Dosage and administration
Depression
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.
Fluvoxamine at a fixed single daily dose 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 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.

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

Fluvoxamine tablets should be swallowed with water and without chewing.

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

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.

Warnings and special 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.

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 and 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 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 OCD. Due to lack of clinical experience the use of fluvoxamine in children for the treatment of depression cannot be recommended. 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 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 behavioural 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 (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 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.

Interactions
Fluvoxamine should not be used in combination with MAOIs (see section 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, 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 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 metabolised 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 "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 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, tramadol, SSRIs and St. John's Wort preparations). (see also "Warnings and special 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, hypoglycaemia, 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, fluvoxamine should not be used during breast-feeding.

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.

Important information about the ingredients
Mannitol may have a mild laxative effect.

Undesirable effects
Like all medicines, Faverin may have side effects. If you notice any side effects not mentioned in this leaflet, or if any of the side effects become serious, please inform your doctor or pharmacist.

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

The frequencies of study related adverse events are ranked according to the following: common (frequency 1-10%), uncommon (frequency <1%), rare (frequency <0.1%), very rare (frequency <0.01%), including isolated reports.

Metabolism and nutrition disorders
Common: Anorexia

Psychiatric disorders
Uncommon: Hallucination, confusional stage
Rare: Mania

Nervous system disorders
Common: Agitation, nervousness, anxiety, insomnia, somnolence, tremor, headache, dizziness
Uncommon: Extrapyramidal disorder, ataxia
Rare: Convulsion

Cardiac disorders
Common: Palpitations/ tachycardia

Vascular disorders
Uncommon: (Orthostatic) hypotension

Gastrointestinal disorders
Common: Abdominal pain, constipation, diarrhoea, dry mouth, dyspepsia, nausea, vomiting

Hepatobiliary disorders
Rare: Hepatic function abnormal

Skin and subcutaneous tissue disorders
Common: Hyperhydrosis
Uncommon: Cutaneous hypersensitivity reactions (incl. angioneurotic oedema, rash, pruritis)
Rare: Photosensitivity reaction

Musculoskeletal, connective tissue and bone disorders
Uncommon: Arthralgia, myalgia

Reproductive system and breast disorders
Uncommon: Abnormal (delayed) ejaculation
Rare: Galactorrhoea

General disorders and administration site reactions
Common: 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.

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 death attributed to overdose 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.

Pharmacodynamics
Pharmacotherapeutic group: Antidepressants, Selective serotonin reuptake inhibitors

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.

Pharmacokinetics
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 disproportionally 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.

Incompatibilities
Not applicable.

Shelf life and storage conditions
3 years
Do not store above 25°C.

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

Do not use the medicine after the expiry date stated on the carton.

Keep this medicine out of the reach and sight of children.

Pack sizes
10, 15, 20, 30, 50, 60, 90 or 100 film-coated tablets per pack.
The blisters are made of PVC/PVDC-aluminium, containing 10, 15, 20, 25 tablets per strip (50 mg) or 5, 10, 15, 20, 25 tablets per strip (100 mg).

Not all pack sizes may be marketed.

Further information
The information in this leaflet is limited. For further information, please contact your doctor or pharmacist.

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March 13, 2008

Manufactured by
Abbott Healthcare SAS
01400 Châtillon-sur-Chalaronne - FRANCE
for
Abbott Healthcare Products B.V.,
THE NETHERLANDS

THIS IS A MEDICAMENT

- Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The Doctor and the Pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your Doctor

Keep medicament out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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