PRODUCT INFORMATION LEAFLET

MAGRILAN 20mg capsules

Fluoxetine HCl

1. NAME OF THE MEDICINAL PRODUCT

Magrilan Capsule 20mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 20mg of fluoxetine (as fluoxetine hydrochloride). For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules. The capsules are blue and white.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Depression

Magrilan is indicated for the treatment of the symptoms of depressive illness, with or without associated anxiety symptoms, especially where sedation is not required.

Obsessive-compulsive disorder

Bulimia nervosa

Magrilan is indicated for the reduction of binge-eating and purging activity.

Pre-menstrual Dysphoric Disorder (PMDD)

Magrilan is indicated for the treatment of pre-menstrual dysphoric disorder.

Diagnosis of PMDD:

The essential diagnostic features of PMDD are clear and established cyclicity (occurring during the last week of the luteal phase in most menstrual cycles) of symptoms such as depressed mood, anxiety, affective lability, accompanied by impairment in social and/or occupational function and physical symptoms (such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of bloating, weight gain) - all of which must be severe. This syndrome should be distinguished from the commoner “pre-menstrual tension (distinguished from PMDD by milder symptoms and less impact on normal activities)” and from any co-existing psychiatric disorder.

4.2 Posology and method of Administration

Depression, with or without associated anxiety symptoms

Adults and the elderly: A dose of 20 mg/day is recommended

Obsessive compulsive disorder

Adults and the elderly: 20 mg/day to 60 mg/day. A dose of 20mg/day is recommended as initial dose. Although there may be an increased potential for side effects at higher doses, a dose increase may be considered after several weeks if there is no response.

Bulimia Nervosa

Adults and the elderly: A dose of 60 mg/day is recommended.

Pre-menstrual Dysphoric Disorder (PMDD)

A dose of 20mg per day is recommended. Initial treatment should be limited to 6 months, after which patients should be reassessed regarding the benefits of continued therapy.

All indications

The recommended dose may be increased or decreased. Doses above 80 mg/day have not been systematically evaluated.

Children

The use of Magrilan in children is not recommended, as safety and efficacy have not been established.

Hepatic impairment

A lower or less frequent dose (e.g. 20mg every second day) should be considered in patients with hepatic impairment (see sections 4.4 and 5.2), or in patients where concomitant medication has the potential for interaction with Magrilan (see section 4.5).

Withdrawal symptoms seen on discontinuation of Magrilan

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

Method of administration

For oral administration, with or without food. When dosing is stopped, active drug substances will persist in the body for weeks. This should be borne in mind when starting or stopping treatment.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Monoamine Oxidase Inhibitors: Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued an SSRI and have been started on a MAOI. Treatment of fluoxetine should only be started 2 weeks after discontinuation of a MAOI.

Some cases presented with features resembling serotonin syndrome (which may resemble and be diagnosed as neuroleptic malignant syndrome). Cyproheptadine may benefit patients experiencing such reactions. Symptoms of a drug interaction with a MAOI include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma.

Therefore, fluoxetine is contraindicated in combination with a MAOI or RIMA or within 14 days of discontinuing treatment with a MAOI or RIMA. Similarly, at least 5 weeks should elapse after discontinuing fluoxetine treatment before starting a MAOI or RIMA. If fluoxetine has been prescribed chronically and/or at a high dose, a longer interval should be considered.

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 Magrilan 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, 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 antidepressants 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.

Cardiovascular Effects

Cases of QT interval prolongation and ventricular arrhythmia including torsades de pointes have been reported during the post-marketing period (see sections 4.5, 4.8 and 4.9).
Fluoxetine should be used with caution in patients with conditions such as congenital long QT syndrome, a family history of QT prolongation or other clinical conditions that predispose to arrhythmias (e.g., hypokalemia, hypomagnesemia, bradycardia, acute myocardial infarction or uncompensated heart failure) or increased exposure to fluoxetine (e.g., hepatic impairment) or concomitant use with medicinal products known to induce QT prolongation and/or torsades de pointes (see section 4.5).
If patients with stable cardiac disease are treated, an ECG review should be considered before treatment is started.
If signs of cardiac arrhythmia occur during treatment with fluoxetine, the treatment should be withdrawn and an ECG should be performed.

Serotonin syndrome or neuroleptic malignant syndrome-like events

On rare occasions development of a serotonin syndrome or neuroleptic malignant syndrome-like events have been reported in association with treatment of fluoxetine, particularly when given in combination with other serotonergic (among others L-tryptophan) and/or neuroleptic drugs (see section 4.5). As these syndromes may result in potentially life-threatening conditions, treatment with fluoxetine 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.

Mania

Antidepressants should be used with caution in patients with a history of mania/hypomania. As with all antidepressants, fluoxetine should be discontinued in any patient entering a manic phase.

Haemorrhage

There have been reports of cutaneous bleeding abnormalities such as ecchymosis and purpura with SSRI's. Ecchymosis has been reported as an infrequent event during treatment with fluoxetine. SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see sections 4.6, 4.8). Other haemorrhagic manifestations (e.g., gynaecological haemorrhages, gastrointestinal bleedings and other cutaneous or mucous bleedings) have been reported rarely. Caution is advised in patients taking SSRI's, particularly in concomitant use with oral anticoagulants, drugs known to affect platelet function (e.g. atypical antipsychotics such as clozapine, phenothiazines, most TCA's, aspirin, NSAID's) or other drugs that may increase risk of bleeding as well as in patients with a history of bleeding disorders (see section 4.5).

Seizures

Seizures are a potential risk with antidepressant drugs. Therefore, as with other antidepressants, fluoxetine should be introduced cautiously in patients who have a history of seizures. Treatment should be discontinued in any patient who develops seizures or where there is an increase in seizure frequency. Fluoxetine should be avoided in patients with unstable seizure disorders/epilepsy and patients with controlled epilepsy should be carefully monitored (see section 4.5).

Electroconvulsive Therapy (ECT)

There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment, therefore caution is advisable.

Tamoxifen

Fluoxetine, a potent inhibitor of CYP2D6, may lead to reduced concentrations of endoxifen, one of the most important active metabolites of tamoxifen. Therefore, fluoxetine should whenever possible be avoided during tamoxifen treatment (see section 4.5).

Akathisia/psychomotor restlessness

The use of fluoxetine 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.

Diabetes

In patients with diabetes, treatment with an SSRI may alter glycaemic control. Hypoglycaemia has occurred during therapy with fluoxetine and hyperglycaemia has developed following discontinuation. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

Hepatic/Renal Function

Fluoxetine is extensively metabolized by the liver and excreted by the kidneys. A lower dose, e.g., alternate day dosing, is recommended in patients with significant hepatic dysfunction. When given fluoxetine 20 mg/day for 2 months, patients with severe renal failure (GFR <10 ml/min) requiring dialysis showed no difference in plasma levels of fluoxetine or norfluoxetine compared to controls with normal renal function.

Rash and allergic reactions

Rash, anaphylactoid events and progressive systemic events, sometimes serious (involving skin, kidney, liver or lung) have been reported. Upon the appearance of rash or of other allergic phenomena for which an alternative aetiology cannot be identified, fluoxetine should be discontinued.

Weight Loss

Weight loss may occur in patients taking fluoxetine but it is usually proportional to baseline body weight.

Withdrawal symptoms seen on discontinuation of SSRI 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 60% of patients in both the fluoxetine and placebo groups. Of these adverse events, 17% in the fluoxetine group and 12% in the placebo group were severe in nature.

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 disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), asthenia, agitation or anxiety, nausea and/or vomiting, tremor and headache 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. 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 Magrilan should be gradually tapered when discontinuing treatment over a period of at least one to two weeks, according to the patient's needs (see section 4.2).

Mydriasis

Mydriasis has been reported in association with fluoxetine; therefore, caution should be used when prescribing fluoxetine in patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma.

Pre-menstrual Dysphoric Disorder (PMDD)

The effect of Magrilan on PMDD symptoms is usually rapid, with improvement generally occurring during the first cycle of treatment, unlike the treatment of depression. Clinical trial results and observations suggest that symptoms of PMDD tend to return rapidly, usually within 1 or 2 cycles following cessation of treatment. Before initiating treatment for PMDD, clear advice should be given

and discussion take place with the patient, on the benefit/risk of taking fluoxetine (see also Section 4.6 Pregnancy and Lactation).

Sexual dysfunction

Selective serotonin reuptake inhibitors (SSRI) 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.

4.5 Interaction with other medicinal products and other forms of interaction

Half-life

The long elimination half-lives of both fluoxetine and norfluoxetine should be borne in mind (see section 5.2) when considering pharmacodynamic or pharmacokinetic drug interactions (e.g. when switching from fluoxetine to other antidepressants).

Monoamine oxidase inhibitors
See section 4.3.

Metoprolol used in cardiac failure
Risk of metoprolol adverse events, including excessive bradycardia, may be increased because of an inhibition of its metabolism by fluoxetine (see section 4.3).

Not recommended combinations

Tamoxifen
Pharmacokinetic interaction between CYP2D6 inhibitors and tamoxifen, showing a 65-75% reduction in plasma levels of one of the more active forms of the tamoxifen, i.e. endoxifen, has been reported in the literature. Reduced efficacy of tamoxifen has been reported with concomitant usage of some SSRI antidepressants in some studies. As a reduced effect of tamoxifen cannot be excluded, co-administration with potent CYP2D6 inhibitors (including fluoxetine) should whenever possible be avoided (see section 4.4).

Alcohol
In formal testing, fluoxetine did not raise blood alcohol levels or enhance the effects of alcohol. However, the combination of SSRI treatment and alcohol is not advisable.

Mequitazine
Risk of mequitazine adverse events (such as QT prolongation) may be increased because of an inhibition of its metabolism by fluoxetine.

Combinations requiring caution

CNS active medication
Changes in blood levels of carbamazepine, haloperidol, clozapine, diazepam, alprazolam, lithium, phenytoin, and cyclic antidepressants (e.g. imipramine and desipramine) have been observed when combined with fluoxetine. In some cases manifestations of toxicity have occurred. Considerations should be given to using conservative titration schedules of the concomitant drug and to monitoring clinical status.

Serotoninergic drugs (lithium, tramadol, triptans, tryptophan, St. John's Wort [Hypericum perforatum])

There have been reports of mild serotonin syndrome when SSRIs were given with drugs also having a serotoninergic effect. Therefore, the concomitant use of fluoxetine with these drugs should be undertaken with caution, with closer and more frequent clinical monitoring (see section 4.4).

QT interval prolongation
Pharmacokinetic and pharmacodynamic studies between fluoxetine and other medicinal products that prolong the QT interval have not been performed. An additive effect of fluoxetine and these medicinal products cannot be excluded. Therefore, co-administration of fluoxetine with medicinal products that prolong the QT interval, such as Class IA and III antiarrhythmics, antipsychotics (e.g. phenothiazine derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial agents (e.g. sparfloxacin, moxifloxacin, erythromycin IV, pentamidine), anti-malaria treatment particularly halofantrine, certain antihistamines (astemizole, mizolastine), should be used with caution (see sections 4.4, 4.8 and 4.9).

Drugs affecting haemostasis (oral anticoagulants, whatever their mechanism, platelets antiaggregants including aspirin and NSAIDs)
Risk of increased bleeding. Clinical monitoring, and more frequent monitoring of INR with oral anticoagulants, should be made. A dose adjustment during the fluoxetine treatment and after its discontinuation may be suitable (see sections 4.4 and 4.8).

Cyproheptadine
There are individual case reports of reduced antidepressant activity of fluoxetine when used in combination with cyproheptadine.

Drugs inducing hyponatremia
Hyponatremia is an undesirable effect of fluoxetine. Use in combination with other agents associated with hyponatremia (e.g. diuretics, desmopressin, carbamazepine and oxcarbazepine) may lead to an increased risk (see section 4.8).

Drugs lowering the epileptogenic threshold
Seizures are an undesirable effect of fluoxetine. Use in combination with other agents which may lower the seizure threshold (for example, TCAs, other SSRIs, phenothiazines, butyrophenones, mefloquine, chloroquine, bupropion, tramadol) may lead to an increased risk.

Other drugs metabolised by CYP2D6
Fluoxetine is a strong inhibitor of CYP2D6 enzyme, therefore concomitant therapy with drugs also metabolised by this enzyme system may lead to drug interactions, notably those having a narrow therapeutic index (such as flecainide, encainide, propafenone and nebivolol) and those that are titrated, but also with atomoxetine, carbamazepine, tricyclic antidepressants and risperidone. They should be initiated at or adjusted to the low end of their dose range. This may also apply if fluoxetine has been taken in the previous 5 weeks.

4.6 Fertility, pregnancy and lactation

Pregnancy

Some epidemiological studies suggest an increased risk of cardiovascular defects associated with the use of fluoxetine during the first trimester. The mechanism is unknown. Overall the data suggest that the risk of having an infant with a cardiovascular defect following maternal fluoxetine exposure is in the region of 2/100 compared with an expected rate for such defects of approximately 1/100 in the general population.

Epidemiological data have suggested that the use of 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.

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see sections 4.4, 4.8).

Fluoxetine should not be used during pregnancy unless the clinical condition of the woman requires treatment with fluoxetine and justifies the potential risk to the foetus. Abrupt discontinuation of therapy should be avoided during pregnancy (see section 4.2). If fluoxetine is used during pregnancy, caution should be exercised, especially during late pregnancy or just prior to the onset of labour since some other effects have been reported in neonates: irritability, tremor, hypotonia, persistent crying, difficulty in sucking or in sleeping. These symptoms may indicate either serotonergic effects or a withdrawal syndrome. The time to occur and the duration of these symptoms may be related to the long half-life of fluoxetine (4-6 days) and its active metabolite, norfluoxetine (4-16 days).

Breast-feeding

Fluoxetine and its metabolite norfluoxetine, are known to be excreted in human breast milk. Adverse events have been reported in breastfeeding infants. If treatment with fluoxetine is considered necessary, discontinuation of breastfeeding should be considered; however, if breastfeeding is continued, the lowest effective dose of fluoxetine should be prescribed.

Fertility

Animal data have shown that fluoxetine 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.

4.7 Effects on ability to drive and use machines

Magrilan has no or negligible influence on the ability to drive and use machines. Although fluoxetine has been shown not to affect psychomotor performance in healthy volunteers, any psychoactive drug may impair judgement or skills. Patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.

4.8 Undesirable effects

The most commonly reported adverse reactions in patients treated with fluoxetine were headache, nausea, insomnia, fatigue and diarrhoea. Undesirable effects may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.

The list below gives the adverse reactions observed with fluoxetine treatment in adult and paediatric populations. Some of these adverse reactions are in common with other SSRIs.

The following frequencies have been calculated from clinical trials in adults (n = 9297) and from spontaneous reporting.

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), not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Rare:

- Thrombocytopenia
- Neutropenia
- Leucopenia

Immune system disorders

Rare:

- Anaphylactic reaction
- Serum sickness

Endocrine disorders

Rare:

- Inappropriate antidiuretic hormone secretion

Metabolism and nutrition disorders

Common:

- Decreased appetite

Rare:

- Hyponatraemia

Psychiatric disorders

Very common:

- Insomnia

Common:

- Anxiety
- Nervousness
- Restlessness
- Tension
- Libido decreased
- Sleep disorder
- Abnormal dreams

Uncommon:

- Depersonalisation
- Elevated mood
- Euphoric mood
- Thinking abnormal
- Orgasm abnormal5
- Bruxism
- Suicidal thoughts and behaviour

Rare:

- Hypomania
- Mania
- Hallucinations
- Agitation
- Panic attacks
- Confusion
- Dysphemia
- Aggression

Nervous system disorders

Very common:

- Headache

Common:

- Disturbance in attention
- Dizziness
- Dysgeusia
- Lethargy
- Somnolence
- Tremor

Uncommon:

- Psychomotor hyperactivity
- Dyskinesia
- Ataxia
- Balance disorder
- Myoclonus
- Memory impairment

Rare:

- Convulsion
- Akathisia
- Buccoglossal syndrome
- Serotonin syndrome

Eye disorders

Common:

- Vision blurred

Uncommon:

- Mydriasis

Ear and labyrinth disorders

Uncommon:

- Tinnitus

Cardiac disorders

Common:

- Palpitations
- Electrocardiogram QT prolonged (QTcF ≥ 450 msec)

Rare:

- Ventricular arrhythmia including torsades de pointes

Vascular disorders

Common:

- Flushing

Uncommon:

- Hypotension

Rare:

- Vasculitis
- Vasodilatation

Respiratory, thoracic and mediastinal disorders

Common:

- Yawning

Uncommon:

- Dyspnoea
- Epistaxis

Rare:

- Pharyngitis
- Pulmonary events (inflammatory processes of varying histopathology and/or fibrosis)

Gastrointestinal disorders

Very common:

- Diarrhoea
- Nausea

Common:

- Vomiting
- Dyspepsia
- Dry mouth

Uncommon:

- Dysphagia
- Gastrointestinal haemorrhage

Rare:

- Oesophageal pain

Hepato-biliary disorders

Rare:

- Idiosyncratic hepatitis

Skin and subcutaneous tissue disorders

Common:

- Rash12
- Urticaria
- Pruritus
- Hyperhidrosis

Uncommon:

- Alopecia
- Increased tendency to bruise
- Cold sweat

Rare:

- Angioedema
- Ecchymosis
- Photosensitivity reaction
- Purpura Erythemamultiforme
- Stevens-Johnson syndrome
- Toxic Epidermal Necrolysis (Lyell Syndrome)

Musculoskeletal and connective tissue disorders

Common:

- Arthralgia

Uncommon:

- Muscle twitching

Rare:

- Myalgia

Renal and urinary disorders

Common:

- Frequent urination

Uncommon:

- Dysuria

Rare:

- Urinary retention
- Micturition disorder

Reproductive system and breast disorders

Common:

- Gynaecological bleeding
- Erectile dysfunction
- Ejaculation disorder

Uncommon:

- Sexual dysfunction

Rare:

- Galactorrhoea
- Hyperprolactinemia
- Priapism

Not known:

Postpartum haemorrhage

General disorders and administration site conditions

Very common:

- Fatigue

Common:

- Feeling jittery
- Chills

Uncommon:

- Malaise
- Feeling abnormal
- Feeling cold
- Feeling hot

Rare:

- Mucosal haemorrhage

Investigations

Common:

- Weight decreased

Uncommon:

- Transaminases increased
- Gamma-glutamyltransferase increased

Injury, Poisoning and Procedural Complications: Contusion

Suicide/suicidal thoughts or clinical worsening: Cases of suicidal ideation and suicidal behaviour have been reported during fluoxetine therapy or early after treatment discontinuation (see section 4.4).

Bone fractures: Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to the risk is unknown.

Withdrawal symptoms seen on discontinuation of fluoxetine treatments: Discontinuation of fluoxetine commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), asthenia, agitation or anxiety, nausea and/or vomiting, tremor and headache 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 (see section 4.4). It is therefore advised that when Magrilan treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

4.9 Overdose

Symptoms

Cases of overdose of fluoxetine alone usually have a mild course. Symptoms of overdose have included nausea, vomiting, seizures, cardiovascular dysfunction ranging from asymptomatic arrhythmias (including nodal rhythm and ventricular arrhythmias) or ECG changes indicative of QTc prolongation to cardiac arrest (including very rare cases of Torsades de Pointes), pulmonary dysfunction, and signs of altered CNS status ranging from excitation to coma. Fatality attributed to overdose of fluoxetine alone has been extremely rare.

Management

Cardiac and vital signs monitoring are recommended, along with general symptomatic and supportive measures. No specific antidote is known.

Forced diuresis, dialysis, haemoperfusion, and exchange transfusion are unlikely to be of benefit. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage. In managing overdosage, consider the possibility of multiple drug involvement. An extended time for close medical observation may be needed in patients who have taken excessive quantities of a tricyclic antidepressant if they are also taking, or have recently taken, fluoxetine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective serotonin reuptake inhibitors, ATC code: N06A B03.

Mechanism of action

Fluoxetine is a selective inhibitor of serotonin reuptake, and this probably accounts for the mechanism of action. Fluoxetine has practically no affinity to other receptors such as α1-, α2-, and β-adrenergic serotonergic; dopaminergic; histaminergic1; muscarinic; and GABA receptors.

Clinical Efficacy and Safety

Pre-menstrual Dysphoric Disorder (PMDD): In clinical trials fluoxetine was shown to be effective in relieving both the cyclical mood changes and the physical symptoms (such as tension, irritability and dysphoria, bloating and breast tenderness) associated with PMDD. The aetiology of Pre-menstrual Dysphoric Disorder is unknown, but endogenous steroids (neuro and/or ovarian) involved in the menstrual cycle may interrelate with neuronal serotonergic activity.

5.2 Pharmacokinetic properties

Absorption

Fluoxetine is well absorbed from the gastrointestinal tract after oral administration. The bioavailability is not affected by food intake.

Distribution

Fluoxetine is extensively bound to plasma proteins (about 95%) and it is widely distributed (Volume of Distribution: 20 - 40 L/kg). Steady-state plasma concentrations are achieved after dosing for several weeks. Steady-state concentrations after prolonged dosing are similar to concentrations seen at 4 to 5 weeks.

Biotransformation

Fluoxetine has a non-linear pharmacokinetic profile with first pass liver effect. Maximum plasma concentration is generally achieved 6 to 8 hours after administration. Fluoxetine is extensively metabolised by the polymorphic enzyme CYP2D6. Fluoxetine is primarily metabolised by the liver to the active metabolite norfluoxetine (desmethylfluoxetine), by desmethylation.

Elimination

The elimination half-life of fluoxetine is 4 to 6 days and for norfluoxetine 4 to 16 days. These long half-lives are responsible for persistence of the drug for 5-6 weeks after discontinuation. Excretion is mainly (about 60%) via the kidney. Fluoxetine is secreted into breast milk.

Elderly: Kinetic parameters are not altered in healthy elderly when compared to younger subjects

Hepatic insufficiency: In case of hepatic insufficiency (alcoholic cirrhosis), fluoxetine and norfluoxetine half-lives are increased to 7 and 12 days, respectively. A lower or less frequent dose should be considered.

Renal insufficiency: After single-dose administration of fluoxetine in patients with mild, moderate or complete (anuria) renal insufficiency, kinetic parameters have not been altered when compared to healthy volunteers. However, after repeated administration, an increase in steady-state plateau of plasma concentrations may be observed.

5.3 Preclinical safety data

There is no evidence of carcinogenicity or mutagenicity from in vitro or animal studies.

Adult animal studies

In a 2-generation rat reproduction study, fluoxetine did not produce adverse effects on the mating or fertility of rats, was not teratogenic, and did not affect growth, development, or reproductive parameters of the offspring.

The concentrations in the diet provided doses approximately equivalent to 1.5, 3.9, and 9.7mg fluoxetine/kg body weight.

Male mice treated daily for 3 months with fluoxetine in the diet at a dose approximately equivalent to 31 mg/kg showed a decrease in testis weight and hypospermatogenesis. However, this dose level exceeded the maximum-tolerated dose (MTD) as significant signs of toxicity were seen.

Juvenile animal studies

In a juvenile toxicology study in CD rats, administration of 30 mg/kg/day of fluoxetine hydrochloride on postnatal days 21 to 90 resulted in irreversible testicular degeneration and necrosis, epididymal epithelial vacuolation, immaturity and inactivity of the female reproductive tract and decreased fertility. Delays in sexual maturation occurred in males (10 and 30 mg/kg/day) and females (30 mg/kg/day). The significance of these findings in humans is unknown. Rats administered 30 mg/kg also had decreased femur lengths compared with controls and skeletal muscle degeneration, necrosis and regeneration. At 10 mg/kg/day, plasma levels achieved in animals were approximately 0.8 to 8.8 fold (fluoxetine) and 3.6 to 23.2 fold (norfluoxetine) those usually observed in paediatric patients. At 3 mg/kg/day, plasma levels achieved in animals were approximately 0.04 to 0.5 fold (fluoxetine) and 0.3 to 2.1 fold (norfluoxetine) those usually achieved in paediatric patients.

A study in juvenile mice has indicated that inhibition of the serotonin transporter prevents the accrual of bone formation. This finding would appear to be supported by clinical findings. The reversibility of this effect has not been established.

Another study in juvenile mice (treated on postnatal days 4 to 21) has demonstrated that inhibition of the serotonin transporter had long lasting effects on the behaviour of the mice. There is no information on whether the effect was reversible. The clinical relevance of this finding has not been established.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, microcrystalline cellulose, magnesium stearate

Capsule components: Gelatin, Patent Blue V, titanium dioxide

6.2 Special precautions for storage

Store below 30°C

6.3 Nature and contents of container

Alu/PVC blister packs of 10, 30, 100 or 1000 capsules per unit carton

7. PRODUCT OWNER

MEDOCHEMIE LTD, 1-10 Constantinoupoleos street, 3011 Limassol, Cyprus

This leaflet was last revised in October 2022