

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Afeksin 20 mg soluble tablet.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soluble tablet contains 20 mg fluoxetine as fluoxetine hydrochloride.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soluble tablet

White round tablet, 10.5 mm in diameter; notch on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Major depressive episodes.

Obsessive-compulsive disorder.

Bulimia nervosa: Afeksin is indicated as a complement of psychotherapy for the reduction of binge-eating and purging activity.

4.2 Posology and method of administration

For oral administration to adults only.

Major depressive episodes

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

In agreement with the consensus statement of the WHO, antidepressant medication should be continued for at least 6 months.

Obsessive-compulsive disorder:

Adults and the elderly: 20 mg/day to 60 mg/day. A dose of 20 mg/day is recommended as the initial dose. Although there may be an increased potential for side-effects at higher doses, a dose increase may be considered after two weeks if there is no response. If no improvement is observed within 10 weeks, treatment with fluoxetine should be reconsidered. 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 fluoxetine treatment, OCD is a chronic condition and it is reasonable to consider continuation beyond 10 weeks in responsive

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.

Long-term efficacy (more than 24 weeks) has not been demonstrated in OCD.

Bulimia nervosa:

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

Long-term efficacy (more than 3 months) has not been demonstrated in bulimia nervosa.

General Information

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

Fluoxetine may be administered as a single or divided dose, during or between meals.

When a medication is stopped, active drug substances will persist in the body for weeks. This should be borne in mind when starting or stopping treatment. Dosage tapering is unnecessary in most patients.

Special Patient Populations:

Children:

The use of fluoxetine in children and adolescents (under the age of 18) is not recommended, as safety and efficacy have not been established.

Elderly

Caution is recommended when increasing the dose in the elderly and the daily dose should generally not exceed 40 mg. The maximum recommended dose is 60 mg/day.

A lower or less frequent dose (e.g. 20 mg every second day) should be considered in patients with hepatic impairment (see 5.2 Pharmacokinetic properties), or in patients where concomitant medication has the potential for interaction with Afeksin (see 4.5 Interaction with other medicinal products and other forms of interaction).

4.3 Contraindications

Hypersensitivity to fluoxetine or to any of its excipients.

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 an irreversible MAOI.

Some cases presented with features resembling serotonin syndrome (which may resemble and be diagnosed as neuroleptic malignant syndrome). Cyproheptadine or dantrolene 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 non-selective MAOI. Similarly, at least 5 weeks should elapse after discontinuing fluoxetine treatment before starting a MAOI. If fluoxetine has been prescribed chronically and/or at a high dose, a longer interval should be considered.

The combination of fluoxetine with a reversible MAOI is not recommended. Treatment with fluoxetine can be initiated the following day after discontinuation of a reversible MAOI (e.g. moclobemide).

4.4 Special warnings and special precautions for use

Use in children and adolescents under 18 years of age.

Afeksin should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were most 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.

Warnings

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.

Precautions

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.

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.

Hepatic/Renal Function: Fluoxetine is extensively metabolised 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.

Cardiac Disease: No conduction abnormalities that resulted in heart block were observed in the ECG of 312 patients who received fluoxetine in double-blind clinical trials. However, clinical experience in acute cardiac disease is limited, therefore caution is advisable.

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

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.

Suicide: As improvement may not occur during the first few weeks of treatment, in common with all antidepressants, patients should be closely monitored during this period. The possibility of a suicide

attempt is inherent in depression and may persist until significant remission occurs. It is general clinical experience with all therapies for depression that the risk of suicide may increase in the early stages of recovery.

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. Other hemorrhagic 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.

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

St John's Wort: An increase in serotonergic effects, such as serotonin syndrome, may occur when selective serotonin reuptake inhibitors and herbal preparations containing St John's Wort (*Hypericum perforatum*) are used together.

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. 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.

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 5.2 Pharmacokinetic properties) when considering pharmacodynamic or pharmacokinetic drug interactions (e.g. when switching from fluoxetine to other antidepressants).

Monoamine oxidase inhibitors (MAOI): (see 4.3 Contraindications).

Combinations not recommended: MAOI-A (see section 4.3 Contraindications).

Combinations requiring precautions for use: MAOI-B (selegiline): risk of serotonin syndrome. Clinical monitoring is recommended.

Phenytoin: Changes in blood levels have been observed when combined with fluoxetine. In some cases manifestations of toxicity have occurred. Consideration should be given to using conservative titration schedules of the concomitant drug and to monitoring clinical status.

Serotonergic drugs: Co-administration with serotonergic drugs (e.g. tramadol, triptans) may increase the risk of serotonin syndrome. Use with triptans carries the additional risk of coronary vasoconstriction and hypertension.

Lithium and tryptophan: There have been reports of serotonin syndrome when SSRIs have been given with lithium or tryptophan and, therefore, the concomitant use of fluoxetine with these drugs should be undertaken with caution. When fluoxetine is used in combination with lithium, closer and more frequent clinical monitoring is required.

CYP2D6 isoenzyme (Cytochrome P450IID6): Because fluoxetine's metabolism (like tricyclic antidepressants and other selective serotonin antidepressants) involves the hepatic cytochrome CYP2D6 isoenzyme system, concomitant therapy with drugs also metabolised by this enzyme system may lead to drug interactions. Concomitant therapy with drugs predominantly metabolised by this isoenzyme, and which have a narrow therapeutic index (such as flecainide, encainide, carbamazepine and tricyclic antidepressants), should be initiated at or adjusted to the low end of their dose range. This will also apply if fluoxetine has been taken in the previous five weeks.

Oral anticoagulants: Altered anti-coagulant effects (laboratory values and/or clinical signs and symptoms), with no consistent pattern, but including increased bleeding, have been reported uncommonly when fluoxetine is co-administered with oral anticoagulants. Patients receiving warfarin therapy should receive careful coagulation monitoring when fluoxetine is initiated or stopped. (see 4.4 Special warnings and special precautions for use, *Haemorrhage*).

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

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.

St. John 's Wort: In common with other SSRIs, pharmacodynamic interactions between fluoxetine and the herbal remedy St. John's Wort (*Hypericum perforatum*) may occur, which may result in an increase of undesirable effects.

4.6 Pregnancy and lactation

Pregnancy:

Data on a large number of exposed pregnancies do not indicate a teratogenic effect of fluoxetine. Fluoxetine can be used during pregnancy, but caution should be exercised, especially during late pregnancy or just prior to the onset of labour since the following 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).

Lactation:

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.

4.7 Effects on 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

Undesirable effects may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.

In common with other SSRIs the following undesirable effects have been seen:

Body as a whole: Hypersensitivity (e.g. pruritis, rash, urticaria, anaphylactoid reaction, vasculitis, serum sickness-like reaction, angioedema) (see 4.4 Special warnings and special precautions for use), chills, serotonin syndrome, photosensitivity, very rarely Toxic Epidermal Necrolysis (Lyell syndrome).

Digestive system: Gastrointestinal disorders (e.g. diarrhoea, nausea, vomiting, dyspepsia, dysphagia, taste perversion), dry mouth. Abnormal liver function tests have been reported rarely. Very rare cases of idiosyncratic hepatitis.

Nervous system: Headache, sleep abnormalities (e.g. abnormal dreams, insomnia), dizziness, anorexia, fatigue (e.g. somnolence, drowsiness), euphoria, transient abnormal movement (e.g., twitching, ataxia, tremor, myoclonus), seizures and psychomotor restlessness. Hallucinations, manic reaction, confusion, agitation, anxiety and associated symptoms (e.g. nervousness), impaired concentration and thought process (e.g. depersonalisation), panic attacks (these symptoms may be due to the underlying disease), very rarely serotonin syndrome.

Urogenital system: Urinary retention, urinary frequency.

Reproductive disorders: Sexual dysfunction (delayed or absent ejaculation, anorgasmia), priapism, galactorrhoea.

Miscellaneous: Alopecia, yawn, abnormal vision (e.g., blurred vision, mydriasis), sweating, vasodilatation, arthralgia, myalgia, postural hypotension, ecchymosis. Other haemorrhagic manifestations (e.g., gynaecological haemorrhages, gastrointestinal bleedings and other cutaneous or mucous bleedings) have been reported rarely (see 4.4 Special warnings and special precautions for use, *Haemorrhage*).

Hyponatraemia: Hyponatraemia (including serum sodium below 110 mmol/l) has been rarely reported and appeared to be reversible when fluoxetine was discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone secretion. The majority of reports were associated with older patients, and patients taking diuretics or otherwise volume depleted.

Respiratory system: Pharyngitis, dyspnoea. Pulmonary events (including inflammatory processes of varying histopathology and/or fibrosis) have been reported rarely. Dyspnoea may be the only preceding symptom.

When stopping treatment, withdrawal symptoms have been reported in association with SSRIs, although the available evidence does not suggest this is due to dependence. Common symptoms include dizziness, paraesthesia, headache, anxiety and nausea, the majority of which are mild and self limiting. Fluoxetine has been only rarely associated with such symptoms. Plasma fluoxetine and norfluoxetine concentrations decrease gradually upon termination of therapy, which makes dosage tapering unnecessary in most patients.

4.9 Overdose

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 to cardiac arrest, pulmonary dysfunction, and signs of altered CNS status ranging from excitation to coma. Fatality attributed to overdose of fluoxetine alone has been extremely rare. 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. When managing overdose, the possibility of multiple drug involvement should be considered. 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: N 06 AB 03.

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 α_1 -, α_2 -, and β -adrenergic serotonergic; dopaminergic; histaminergic₁; muscarinic; and GABA receptors.

Major depressive episodes: Clinical trials in patients with major depressive episodes have been conducted versus placebo and active controls. Fluoxetine has been shown to be significantly more effective than placebo as measured by the Hamilton Depression Rating Scale (HAM-D). In these studies, fluoxetine produced a significantly higher rate of response (defined by a 50% decrease in the HAM-D score) and remission, compared to placebo.

Obsessive-compulsive disorder (OCD): In short-term trials (under 24 weeks), fluoxetine was shown to be significantly more effective than placebo. There was a therapeutic effect at 20 mg/day, but higher doses (40 or 60 mg/day) showed a higher response rate. In long term studies (three short term studies extension phase and a relapse prevention study) efficacy has not been shown.

Bulimia nervosa: In short term trials (under 16 weeks), in out-patients fulfilling DSM-III-R-criteria for bulimia nervosa, fluoxetine 60 mg/day was shown to be significantly more effective than placebo for the reduction of bingeing and purging activities. However, for long-term efficacy no conclusion can be drawn.

Two placebo-controlled studies were conducted in patients meeting Pre-Menstrual Dysphoric Disorder (PMDD) diagnostic criteria according to DSM-IV. Patients were included if they had symptoms of sufficient severity to impair social and occupational function and relationships with others. Patients using oral contraceptives were excluded. In the first study of continuous 20 mg daily dosing for 6 cycles, improvement was observed in the primary efficacy parameter (irritability, anxiety and dysphoria). In the second study, with intermittent luteal phase dosing (20 mg daily for 14 days) for 3 cycles, improvement was observed in the primary efficacy parameter (Daily Record of Severity of Problems score). However, definitive conclusions on efficacy and duration of treatment cannot be drawn from these studies.

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.

Metabolism: 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.

Populations at risk

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, mutagenicity, or impairment of fertility from *in vitro* or animal studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Croscarmellose sodium
Colloidal anhydrous silica
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special precautions for storage.

6.5 Nature and contents of container

Blisters consisting of PVC/PE/PVDC and aluminium foil

Pack Sizes: 10, 10x1, 12, 14, 20, 28, 30, 30x1, 50, 100 or 250 soluble tablets.
Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

Actavis Ltd.
B16 Bulebel Industrial Estate,
Zejtun ZTN 08
Malta

8. MARKETING AUTHORISATION NUMBER(S)

MA245/00701

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12th July, 2006

10. DATE OF REVISION OF THE TEXT