

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Affex 20 mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Fluoxetine 20 mg (as Fluoxetine Hydrochloride).

Excipients: Contains Soya Lecithin

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard

A hard, gelatin capsule with a light-green opaque cap and a yellow opaque body. The capsule is marked 'F20'.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Major depressive episodes.

Obsessive-compulsive disorder.

Bulimia nervosa: Affex 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: 20mg/day to 60mg/day. A dose of 20mg/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 six months.

Obsessive-compulsive disorder (OCD):

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 ten 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 ten 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.

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 three months) has not been demonstrated in bulimia nervosa.

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

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

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. Dosage tapering is unnecessary in most patients.

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, and the daily dose should generally not exceed 40mg. Maximum recommended dose is 60mg/day.

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

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 selective serotonin reuptake inhibitor (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 two weeks after discontinuation of an irreversible MAOI and the following day after discontinuation of a reversible MAOI-A.

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 contra-indicated in combination with a non-selective MAOI. Similarly, at least five 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 (e.g., moclobemide) is not recommended. Treatment with fluoxetine can be initiated the following day after discontinuation of a reversible MAOI.

Affex 20mg Hard Capsules contain soya lecithin. If you are allergic to soya or peanut oil, do not use this medicinal product.

4.4 Special warnings and precautions for use

Warnings

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 Affex 20mg Hard Capsules is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients, (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

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, eg, alternate day dosing, is recommended in patients with significant hepatic dysfunction. When given fluoxetine 20mg/day for two months, patients with severe renal failure (GFR <10ml/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.

Haemorrhage: There have been reports of cutaneous bleeding abnormalities, such as ecchymosis and purpura, with SSRIs. Ecchymosis has been reported as an infrequent event during treatment with fluoxetine. Other haemorrhagic manifestations (eg, gynaecological haemorrhages, gastro-intestinal bleedings, and other cutaneous or mucous bleedings) have been reported rarely. Caution is advised in patients taking SSRIs, particularly in concomitant use with oral anticoagulants, drugs known to affect platelet function (eg, atypical antipsychotics, such as clozapine, phenothiazines, most tricyclic antidepressants - TCAs, aspirin, non steroidal anti inflammatory drugs - NSAIDs), 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.

Use in children and adolescents under 18 years of age

Affex 20 mg Hard Capsules should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicidal attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

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.

Not recommended combinations: MAOI-A (see section 4.3).

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: 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 anticoagulant 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 section 4.4).

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 Fertility, 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 breast-feeding infants. If treatment with fluoxetine is considered necessary, discontinuation of breast-feeding should be considered; however, if breast-feeding is continued, the lowest effective dose of fluoxetine should be prescribed.

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.

Animal data have shown that fluoxetine may affect sperm quality (see section 5.3). Human case reports with some SSRIs have shown that an effect on sperm quality is reversible. Impact on human fertility has not observed so far.

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., pruritus, rash, urticaria, anaphylactoid reaction, vasculitis, serum sickness-like reaction, angioedema) (see section 4.3 and section 4.4), chills, serotonin syndrome, photosensitivity, and, very rarely, toxic epidermal necrolysis (Lyell syndrome).

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

Suicidal ideation and behaviour: Cases of suicidal ideation and suicidal behaviours have been reported during Affex 20mg Hard Capsules therapy or early after treatment discontinuation (see section 4.4).

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), and, 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, gastro-intestinal bleedings, and other cutaneous or mucous bleedings) have been reported rarely (see section 4.4).

Hyponatraemia: Hyponatraemia (including serum sodium below 110mmol/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.

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

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 at the conclusion 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. 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

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; histaminergic $_1$; 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: In short-term trials (under 24 weeks), fluoxetine was shown to be significantly more effective than placebo. There was a therapeutic effect at 20mg/day, but higher doses (40 or 60mg/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 60mg/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 20mg daily dosing for six cycles, improvement was observed in the primary efficacy parameter (irritability, anxiety, and dysphoria). In the second study, with intermittent luteal phase dosing (20mg daily for 14 days) for three 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 gastro-intestinal 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 four to five weeks.

Metabolism: Fluoxetine has a non-linear pharmacokinetic profile with first pass liver effect. Maximum plasma concentration is generally achieved six to eight 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.

At-Risk Populations

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.

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 does approximately equivalents to 1.5, 3.9 and 9.7 mg 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule Contents

Pregelatinised maize starch

Colloidal anhydrous silica

Magnesium stearate

Talc

Capsule Shell

Quinoline yellow (E104)

Indigo carmine (E132)

Titanium dioxide (E171)

Gelatin

Erythrosine (E127)

Printing Ink

Shellac

Black iron oxide (E172)

Soya lecithin

Antifoam DC1510 (includes dimethylsiloxane)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Al/PVC blisters;
7, 14, 28, 30, 56, 60, 100, 120 capsules per pack.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Astellas Pharma Co. Ltd
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Naas Road
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8 MARKETING AUTHORISATION NUMBER

PA 1241/11/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 26 November 2009

10 DATE OF REVISION OF THE TEXT

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