SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FLUOXE-FAR, Fluoxetine Hydrochloride 20 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains fluoxetine hydrochloride, equivalent to 20 mg of fluoxetine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule.
Hard gelatin capsules, size 2, green opaque cap/white opaque body, containing a white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults:
- major depressive episodes;
- Obsessive-compulsive disorder;
- bulimia nervosa: FLUOXE-FAR is indicated as a complement of psychotherapy for the reductionof binge-eating and purging activity.

Children and adolescents aged 8 years and above:
Moderate to severe major depressive episode, if depression is unresponsive to psychological therapy after 4–6 sessions. Antidepressant medication should be offered to a child or young person with moderate to severe depression only in combination with a concurrent psychological therapy.

4.2 Posology and method of administration

For oral administration.

Major depressive episodes
Adult and the elderly: The recommended dose is 20 mg/day. Dosage should be reviewed and adjusted if necessary within 3 to 4 weeks of initiation of therapy and thereafter as judged clinically appropriate. Although there may be an increased potential for undesirable effects at higher doses, in some patients, with insufficient response to 20 mg, the dose may be increased gradually up to a maximum of 60 mg (see section 5.1). Dosage adjustments should be made carefully on an individual patient basis, to maintain the patients at the lowest effective dose. Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are freefrom symptoms.

Obsessive-compulsive disorder
Adults and the elderly: The recommended dose is 20mg/day. Although there may be an increased potential for undesirable effects at higher doses in some patients, if after two weeks there is insufficient response to 20mg, the dose may be increased gradually up to a maximum of 60mg.

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, obsessive-compulsive disorder 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.

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

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.

Adults:
All indications: The recommended dose may be increased or decreased. Doses above 80 mg/dayhave 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 beborne in mind when starting or stopping treatment.

The capsule and liquid dosage forms are bioequivalent.

Children and adolescents aged 8 years and above (moderate to severe major depressiveepisode):
Treatment should be initiated and monitored under specialist supervision. The starting dose is10mg/day given as 2.5ml of oral solution.
Dose adjustments should be made carefully, on an individual basis, to maintain the patient at thelowest effective dose.
After one to two weeks, the dose may be increased to 20mg/day. Clinical trial experience with dailydoses greater than 20mg is minimal. There is only limited data on treatment beyond 9 weeks.
Lower weight children:
Due to higher plasma levels in lower weight children, the therapeutic effect may be achieved withlower doses (see Section 5.2 Pharmacokinetic properties).
For paediatric patients who respond to treatment, the need for continued treatment after 6 months should be reviewed. If no clinical benefit is achieved within 9 weeks, treatment should be reconsidered.

Elderly:
Caution is recommended when increasing the dose and the daily dose should generally notexceed 40 mg. 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 FLUOXE-FAR (see 4.5 Interaction with other medicinal products and other forms of interaction).

Since FLUOXE-FAR is not available in doses below 20 mg, its use is not recommended in indications that require lower doses.

Withdrawal symptoms seen on discontinuation of SSRIs:
Abrupt discontinuation should be avoided. When stopping treatment with FLUOXE-FAR 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. 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.

4.3 Contraindications

FLUOXE-FAR is contraindicated in patients who are hypersensitive to fluoxetine or to any of the excipients.

Monoamine Oxidase Inhibitors
Cases of serious and sometimes fatal reactions have been reported in patients receiving a 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 with fluoxetine should only be started 2 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 contraindicated in combination with a non-selective MAOI. Similarly, atleast 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 (e.g. moclobemide) is not recommended. Treatment with fluoxetine can be initiated the following day after discontinuation of a reversible MAOI.

4.4 Special warnings and precautions for use

Use in children and adolescents under 18 years of age
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 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, only limited evidence is available concerning long-term effect on safety in children and adolescents, including effects on growth, sexual maturation and cognitive, emotional and behavioural developments (see section 5.3).

In a 19-week clinical trial decreased height and weight gain was observed in children and adolescents treated with fluoxetine (see section 4.8). It has not been established whether there is an effect on achieving normal adult height. The possibility of a delay in puberty cannot be ruled out (see sections 5.3 and 4.8). Growth and pubertal development (height, weight and TANNERstaging) should therefore be monitored during and after treatment with fluoxetine. If either is slowed, referral to a paediatrician should be considered.

In paediatric trials, mania and hypomania were commonly reported (see section 4.8). Therefore, regular monitoring for the occurrence of mania/hypomania is recommended.

Fluoxetine should be discontinued in any patient entering a manic phase.

It is important that the prescribers discusses carefully the risks and benefits of treatment with the

child/young person and/or their parents.

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.

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. Aswith 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 bodyweight.

Diabetes:

In patients with diabetes, treatment with a 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/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 FLUOXE-FAR 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 disorders. 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 should be alerted about the need to monitor for the emergence of such events and to seek medical advice immediately if these symptoms present.

Akathisia/psychomotor restlessness:
The use of FLUOXE-FAR 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.

Withdrawal symptoms seen on discontinuation of SSRI treatment:
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuationis abrupt (see section 4.8 Undesirable effects). 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), 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; however, they have also been very rarely reported in patients who inadvertently fail to take the medicine. 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 FLUOXE-FAR should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see "Withdrawal Symptoms Seen on Discontinuation of SSRIs", Section 4.2 Posology and Method of Administration).

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 (e.g., gynaecological haemorrhages,gastrointestinal 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 (e.g. atypical antipsychotics such as clozapine, phenothiazines, most tricyclic antidepressants, acetylsalicylic acid, NSAIDs) or other drugs that may increase the 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 selectiveserotonin 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 with 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

Interaction studies have been performed only in adults.

Half-life:
The long elimination half-lives of both fluoxetine and its main metabolite, norfluoxetine, should be borne in mind (see section 5.2. 'Pharmacokinetic properties') when considering pharmacodynamic or pharmacokinetic drug interactions (e.g. when switching from fluoxetine to other antidepressants).

Monoamine oxidase inhibitors:
(see section 4.3. 'Contraindications').
Not recommended combinations: MAOI-A (see section 4.3)

Combinations requiring precautions for use: MAOI-B (selegeline): 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 alsoapply if fluoxetine has been taken in the previous 5 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 section 4.4. 'Special warnings and 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:
Like other SSRIs, pharmacodynamic interactions between fluoxetine and the herbal product St. John's Wort (Hypericum perforatum) may occur, which may result in an increase of undesirable effects.

4.6 Fertility, pregnancy and lactation

Pregnancy:
Fluoxetine can be used during pregnancy, but caution should be exercised when prescribing to pregnant women, 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).

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.

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 2/100 compared with an expected rate for such defects of approximately 1/100 in the general population.

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 judgment 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.

Like other SSRIs the following undesirable effects have been seen:

Body as a whole:
Hypersensitivity (pruritis, rash, urticaria, anaphylactoid reaction, vasculitis, serum sickness-like reaction, angioedema) (see section 4.3. 'Contraindications' and 'Warnings'), chills, serotonin syndrome, photosensitivity and, very rarely, Toxic Epidermal Necrolysis (Lyell syndrome).

Digestive system:
Gastrointestinal disorders (diarrhoea, nausea, vomiting, dyspepsia, dysphagia, taste disturbances),dry mouth. Abnormal liver function tests have been reported rarely. Idiosyncratic hepatitis has been reported very rare.

Nervous system:
Headache, sleep abnormalities (abnormal dreams, insomnia), dizziness, anorexia, fatigue (somnolence, drowsiness), euphoria, transient abnormal movement (twitching, ataxia, tremor, myoclonus), seizures and rarely psychomotor restlessness/akathisia (see section 4.4 Special warning and precautions for use). Hallucinations, manic reaction, confusion, agitation, anxiety and associated symptoms (nervousness), impaired concentration and thought process(depersonalisation), panic attacks, suicidal thoughts and behaviour (these symptoms may be dueto the underlying disease), very rarely serotonin syndrome.
Rare: psychomotor restlessness/akathisia (see section 4.4 Special warnings and precautions for use).

Cases of suicidal thoughts/suicide-related behaviour have been reported during treatment with fluoxetine or immediately after its discontinuation (see section 4.4 "Special warnings and precautions for use").

Urogenital system:
Urinary retention, increase in urinary frequency

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

Miscellaneous:
Alopecia, yawn, abnormal vision (blurred vision, mydriasis), sweating, vasodilatation, arthralgia, myalgia, postural hypotension, ecchymosis. Other haemorrhagic manifestations (gynaecological haemorrhages, gastrointestinal bleedings and other cutaneous or mucous bleedings) have been reported rarely (see section 4.4. "Special warnings and 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 thesyndrome 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.

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 themost 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 Special warnings and precautions for use). It is therefore advised that when the treatment with FLUOXE-FAR is no longer required, it should be gradually discontinued by dose tapering (see section 4.2 “Posology and Method of Administration” and section 4.4 “Special warnings and precautions for use”).

Children and adolescents (see section 4.4 Special warnings and precautions for use):
In paediatric clinical trials suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility were more frequently observed among children and adolescents treated with antidepressants compared to those treated with placebo.

The safety of fluoxetine has not been systematically assessed for chronic treatment longer than 19 weeks.

In paediatric clinical trials, manic reactions, including mania and hypomania, were reported (2.6% of fluoxetine-treated patients vs. 0% in placebo-controls), leading to discontinuation in the majority of cases. These patients had no prior episodes of hypomania/mania.

After 19 weeks of treatment, paediatric subjects treated with fluoxetine in a clinical trial gained an average of 1.1 cm less in height (p=0.004) and 1.1 kg less in weight (p=0.008) than subjects treated with placebo. Isolated cases of growth retardation have also been reported from clinical use.

Isolated cases of adverse events potentially indicating delayed sexual maturation or sexual dysfunction have been reported with paediatric clinical use. (see also section 5.3)
In paediatric clinical trials, fluoxetine treatment was associated with a decrease in alkaline phosphatase levels.

Class effects
Epidemiological studies, mainly conducted in patients with 50 years of age or older, show an increased risk of bone fractures in patients receiving SSRIs and tricyclic antidepressants. The underlying mechanism is unknown.

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 for fluoxetine 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 overdosage, the possibility of multiple drug involvement should be considered. An extended timefor 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: 2.9.3 - Central Nervous System. Psychiatric Medication. Antidepressants.

ATC code: N06A B03

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; histaminergic; 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.

Dose response: In the fixed dose studies on patients with major depression there is a flat dose response curve, providing no suggestion of advantage in terms of efficacy for using higher than the recommended doses.

However, it is clinical experience that uptitrating might be beneficial for somepatients.

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 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 at 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

Major depressive episodes (children and adolescents):
Clinical trials in children and adolescents aged 8 years and above have been conducted versus placebo. Fluoxetine, at a dose of 20mg, has been shown to be significantly more effective than placebo in two short-term pivotal studies, as measured by the reduction of Childhood Depression Rating Scale-Revised (CDRS-R) total scores and Clinical Global Impression of Improvement (CGI- I) scores. In both studies, patients met the criteria for moderate to severe MDD (DSM-III or DSM- IV) at three different evaluations by practising child psychiatrists. Efficacy in the fluoxetine trials may depend on the inclusion of a selective patient population (one that has not spontaneously recovered within a period of 3-5 weeks and whose depression persisted in the face of considerable attention). There is only limited data on the safety and efficacy beyond 9 weeks. In general,efficacy of fluoxetine was modest.

Response rates (the primary endpoint, defined as a 30% decrease in the CDRS-R score) demonstrated a statistically significant difference in one of the two pivotal studies (58% for fluoxetine versus 32% for placebo, p=0.013 and 65% for fluoxetine versus 54% for placebo, p=0.093). In these two studies the mean absolute changes in CDRS-R from baseline to endpoint were 20 for fluoxetine versus 11 for placebo, p=0.002 and 22 for fluoxetine versus 15 for placebo, p<0.001.

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 metabolized

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 to16 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.

Children and adolescents: The mean fluoxetine concentration in children is approximately 2-fold higher than that observed in adolescents and the mean norfluoxetine concentration 1.5-fold higher. Steady state plasma concentrations are dependent on body weight and are higher in lower weight children (see section 4.2 Posology and method of administration). As in adults, fluoxetine and norfluoxetine accumulated extensively following multiple oral dosing; steady-state concentrations were achieved within 3 to 4 weeks of daily dosing.

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

In vitro studies carried out in animals provided no evidence of carcinogenicity, mutagenicity or reduced fertility associated with fluoxetine

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. -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 beenestablished.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Corn starch
Anhydrous colloidal silica.

The capsule shell contains
Gelatine
Indigotin (E132)
Quinoline Yellow (E104)
Purified Water
Titanium Dioxide (E171).

6.2. Incompatibilities

None have been described.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25ºC.

Keep in the original package in order to protect from moisture.

6.5 Nature and contents of the container

Packs of 56 capsules in PVC-Alu blisters.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

GP – Genéricos Portugueses, Lda.
Rua Henrique de Paiva Couceiro, n.º 29
Venda Nova
2700-451 Amadora
Portugal

8. MARKETING AUTHORISATION NUMBER(S)

04435/06935/REN/2019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF MARKETING AUTHORISATION

Date of first authorization: 16/01/2015
Date of latest renewal: 25/04/2019

10. DATE OF REVISION OF THE TEXT

November 2023