IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0281/114/001
Case No: 2049123

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Pinewood Laboratories Ltd

Ballymacarbry, **Clonmel**, **Co. Tipperary**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Fluoxetine 20mg/5ml Oral Solution

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **11/12/2008** until **12/11/2013**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fluoxetine 20mg/5ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains 20 mg fluoxetine (as hydrochloride).
For excipients see 6.1

3 PHARMACEUTICAL FORM

Oral Solution
A clear, colourless solution with a peppermint odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

a)Major depressive episodes
b)Bulimia nervosa: Fluoxetine is indicated as a complement of psychotherapy for the reduction of binge-eating and purging activity.
c)Obsessive-compulsive disorder.

4.2 Posology and method of administration

For oral administration
Fluoxetine may be taken with or without food.

a) Major depressive episodes: Studies have shown that 20 mg/day is sufficient to achieve a satisfactory response in most patients. It is recommended that doses of more than 20 mg per day should be given in two divided daily doses. This dose may be increased gradually to 60 mg daily if necessary. A gradual dose increase should be considered only if no improvement is observed after 2-4 weeks.

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

b) Bulimia nervosa: A dose of 60 mg/day is recommended.
Long-term efficacy (more than 3 months) has not been demonstrated in bulimia nervosa. The dose can tentatively be divided in a morning and afternoon dose if troublesome adverse events appear.

c) 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 systemic 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 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.

d) All indications
The maximum daily dose should not exceed 80 mg.
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. Fluoxetine dosage tapering is usually unnecessary in most patients.

Elderly patients:
Caution is recommended when increasing the dose and the daily dose should generally not exceed 40 mg. Maximum recommended dose is 60 mg/day.

Children: Not recommended. The safety and efficacy of Fluoxetine in children and adolescents has not been established.

Hepatic dysfunction:
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 (see 4.5 Interactions).

4.3 Contraindications

Fluoxetine is contraindicated for

a) Patients with hypersensitivity to the active fluoxetine or any of the excipients stated in section 6.1.

b) Fluoxetine should not be taken concomitantly with monoamine oxidase inhibitors (MAO inhibitors), namely irreversible non-selective and B-selective MAO inhibitors and reversible A-selective MAO inhibitors.
It is recommended that at least 14 days should elapse between discontinuation of an MAOI and initiation of treatment with Fluoxetine. At least five weeks (longer if Fluoxetine has been prescribed chronically and/or at a higher dose) should elapse between discontinuation of Fluoxetine and initiation of MAOI therapy. If fluoxetine is taken for a long time and/or at a high dose, a longer period may be considered.

There have been reported cases with features resembling serotonin syndrome, which may resemble and be diagnosed as neuroleptic malignant syndrome in patients treated with fluoxetine and a MAO inhibitor in close temporal proximity. (c.f. section 4.5 Interaction with other medicaments and other forms of interaction).

4.4 Special warnings and precautions for use

a) Fluoxetine contains Benzoic acid, which is a mild irritant to the skin, eyes and mucous membrane.

b) Fluoxetine contains Glycerol, which may cause headache, upset stomach and diarrhoea.

c) Fluoxetine contains 3 g of sucrose per 5 ml. When taken according to dosage recommendations, the maximum daily dose of fluoxetine oral solution may provide up to 12 g of sucrose. Unsuitable for hereditary fructose intolerance, glucose-galactose malabsorption syndrome and sucrase-isomaltase deficiency.

d) 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 fluoxetine 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.

e) Rash: Rash and other allergic reactions have been reported to occur during treatment with Fluoxetine. Some of these reactions are: skin rashes, urticaria, anaphylactoid events as well as progressive systemic events (skin, kidney, liver and lung). Upon the appearance of rash or of other possible allergic phenomena for which an alternative aetiology cannot be identified, fluoxetine should be discontinued.

f) Seizures: As with other antidepressants, fluoxetine should be used with caution in patients with a previous history of seizures. Treatment should be discontinued in any patient who develops seizures. Fluoxetine should be avoided in patients with unstable or uncontrolled epilepsy. Patients with controlled epilepsy should be carefully monitored.

g) Hepatic and renal function: As Fluoxetine is extensively metabolised by the liver and excreted by the kidneys, caution should be exercised in patients with impaired renal and/or hepatic function (see under 4.2 Posology).

h) Diabetes mellitus: Fluoxetine has been reported to alter blood glucose control in patients with diabetes. Hypoglycaemia has occurred during therapy with fluoxetine and hyperglycaemia has developed following discontinuation of therapy. It is therefore recommended that the dosage of insulin and/or oral antidiabetics should be monitored and where necessary adjusted when therapy with fluoxetine is initiated or discontinued.

i) Mania: As with all antidepressants, care should be used when prescribing Fluoxetine to patients who have a history of hypomania or mania. Treatment with Fluoxetine should be discontinued with the patient entering the manic phase.

j) Cardiac disease: Clinical experience with acute cardiac disease is limited, therefore caution is advisable.

k) Body weight: Overweight patients generally experience weight loss during treatment with fluoxetine. Patients with a normal body weight usually experience little or no weight loss. In patients with anorexia it is recommended that body weight should be monitored regularly during treatment with fluoxetine.
Clinical trials relating to the treatment of bulimia nervosa have shown that no patients have discontinued treatment as a result of reduction in body weight (see section 4.8 Undesirable effects).

l) Haemorrhage: Caution should be used in patients who are receiving medication which alters platelet function, as fluoxetine has been known to cause cutaneous bleeding abnormalities such as purpura while ecchymosis has been infrequently reported. There have also been rare reports of other haemorrhagic manifestations such as: gynaecological haemorrhaging, gastro-intestinal haemorrhaging and other mucous and cutaneous bleedings. 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, acetylsalicylic acid, NSAIDs) or other drugs that may increase the risk of bleeding as well as in patients with a history of bleeding disorders.

m) Hyponatraemia: Several cases of hyponatraemia (some with sodium levels lower than 110 mmol/l) have been reported. The process has been shown to be reversible. Although these cases were complex with varying aetiologies, in some there were indications of the SIADH syndrome (syndrome of inappropriate antidiuretic hormone secretion). The majority of these cases occurred in elderly patients and in patients treated with diuretics or otherwise volume-depleted.

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

o) 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.

p) Serotonin syndrome: 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

Elimination half-life: The long elimination half-lives of fluoxetine and its principal metabolite norfluoxetine are of potential consequence when medicines are prescribed which might interfere with either substance following the discontinuation of treatment with fluoxetine.

Contraindicated combinations
MAO inhibitors: There have been reports of serious, sometimes fatal reactions (including hypothermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs and mental status changes that include extreme agitation progressing to delirium and coma) in patients receiving fluoxetine in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued an SSRI and have been started on an MAOI. Some cases presented with features resembling serotonin syndrome which may resemble and be diagnosed as neuroleptic malignant syndrome (see 4.3 Contraindications). Oral cyprohepatidine or intravenous dantrolene may be of benefit to patients experiencing such reactions. At least 14 days should elapse between discontinuation of a MAOI and initiation of treatment with fluoxetine.

Since fluoxetine and its active metabolite have very long elimination half-lives at least 5 weeks (approximately 5 half-lives of norfluoxetine) should be allowed after stopping fluoxetine before starting a MAOI.

Combinations requiring precautions for use
Oral anticoagulants: Altered anticoagulant effects (laboratory values and/or clinical signs and symptoms), with no consistent pattern but with an increased tendency to bleeding, have been reported uncommonly when fluoxetine is coadministered with warfarin. As is prudent in concomitant use of warfarin with many other medicines, these patients should also be monitored with respect to their coagulation times when treatment with fluoxetine is initiated or discontinued.

Lithium and tryptophan: There have been reports of serotonin syndrome when SSRIs have been given with lithium or tryptophan so care should be exercised when being administered concurrently with fluoxetine. When fluoxetine is used in combination with lithium, closer and more frequent clinical monitoring is required.

Medicines metabolised by CYP2D6: Fluoxetine can inhibit the activity of the cytochrome P450 iso-enzyme 2D6 (CYP2D6). For this reason, therapy with medications that are predominantly metabolised by CYP2D6 and that have a relatively narrow therapeutic index should be initiated at the low end of the recommended dosage range if the patient is receiving fluoxetine concurrently or has taken it in the past 5 weeks. If fluoxetine is added to the medication of a patient already receiving a drug that is metabolised by CYP2D6, then the need to decrease the dose of the original medication should be considered. This is particularly important in drugs with a narrow therapeutic index such as flecainide, encainide, vinblastine, carbamazepine and tricyclic antidepressants.

CNS active medicines: Fluoxetine, when taken concurrently with CNS active medication, may cause changes in the blood levels of carbamazepine, haloperidol, clozapine, diazepam, alprazolam, lithium, phenytoin and cyclic antidepressants (e.g. imipramine and desipramine). There have been cases where toxicity has been observed. It may be necessary to use conservative titration schedules of the concomitant medicine and to monitor 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.

Protein binding drugs: Because fluoxetine is highly bound to plasma proteins, competition in respect of protein binding may occur with other medicines that are tightly bound to protein so that plasma concentrations of either medicine may

be changed.

Electro Convulsive Treatment: There have been rare reports of prolonged seizures in patients receiving ECT treatment, while taking fluoxetine.

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 are not advisable.

St.John's Wort: Fluoxetine can pharmacodynamically interact with the herbal remedy St. John's Wort (Hypericum perforatum), causing an increase in undesirable effects.

4.6 Pregnancy and lactation

a) 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 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).

b) 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

Fluoxetine has no effect on psychomotor function in healthy volunteers. All psycho-active medicines however, may impair judgement and reaction time. Patients should be advised to avoid driving vehicles or using machines until it is certain that fluoxetine does not affect performance. (c.f. 4.8 Undesirable effects).

4.8 Undesirable effects

The most frequent undesirable effects are mostly perceived at the beginning of the treatment and as a rule they are alleviated as the treatment period proceeds.

Frequency estimates:	Very common	(≥ 10%)
	Common	(≥ 1% - < 10%)
	Uncommon	(≥ 0.1% - < 1%)
	Rare	(≥ 0.01% - < 0.1%)
	Very rare	(< 0.01%)

Body as a whole:
Common: chills, increased perspiration

Central nervous system:
Very common undesirable effects: Undesirable effects stemming from the central nervous system, such as headaches, insomnia, anxiety, exhaustion, nervousness, dizziness, tremors, impotence, mental confusion, paresthesia and nightmares. In general these undesirable effects are of a passing nature.

Common undesirable effects: The fluoxetine treatment may cause sudden hypomania and mania in patients who suffer from bipolar affective disorders.

Rare undesirable effects: Dyskinesia, movement disorders developing in patients with risk factors (including drugs associated with such events) and worsening of pre-existing movement disorders, and neuroleptic malignant syndrome-like events have been reported.

Extrapyramidal motoric symptoms may occur or they may grow stronger especially in patients that are sensitive to such symptoms (e.g. patients suffering from Parkinson's Disease).
Patients that, in addition to fluoxetine, receive electro convulsive treatment (ECT) have in sporadic cases been known to suffer from seizures and extended periods of seizures.

Digestive system:
Very common undesirable effects: Undesirable effects connected to the digestive system such as nausea, drying of the mouth, diarrhoea, constipation, loss of appetite, vomiting, stomach pains, flatulence and changes to the sense of taste. Weight loss may occur in patients taking fluoxetine but it is usually proportional to baseline body weight. However, only rarely have patients discontinued treatment with fluoxetine because of anorexia or weight loss.

Uncommon undesirable effects: Different degrees of liver disorders have been reported. An increase of the liver enzyme values is also possible, although these changes, in most instances, are normalised once the treatment is discontinued.

Rare undesirable effects: In rare cases idiosyncratic hepatitis has been observed.

Skin and Appendages:
Common undesirable effects: Pruritis, rash and urticaria, exceptionally Quincke oedema, Anaphylactic reactions including bronchospasm, angioneurotic oedema and urticaria: reactions of the skin linked with fever, leucocytosis, pain in the joints, dyspnoea might occur. These common symptoms may also be observed without simultaneous reactions of the skin. When reactions of the skin or other possible allergic reactions occur, the fluoxetine treatment should be discontinued.

Rare undesirable effects: Vasculitis, erythema polymorph, or exceptionally Lyell syndrome, and rare cases of fever and arthralgia as in serum sickness. Serotonin symptom complex have occasionally been reported. In connection with dermal reactions serious systemic lung, kidney or liver reactions have been observed in some patients. These reactions may be connected to a vascular inflammation. These systemic reactions are extremely rare, but one fatal case has been reported.

Special Senses:
Common undesirable effect: Visual disorders. In some patients, an increase of ocular pressure has been observed. Those undesirable effects are normalized once the treatment is discontinued.

Cardiovascular System:
Uncommon undesirable effects: Increased and decreased blood pressure as well as fainting have occurred. Small increase in diastolic blood pressure and tachycardia as well as bradycardia has been reported.

Endocrine System:
Uncommon undesirable effects: Hypo- or hyperthyroidism may occur. After the discontinuation of the treatment reversible hyponatraemia (<110 mmol/l) has been observed, mainly in elderly patients, and in patients who have received diuretics or patients suffering from loss of body water.

Hemic and Lymphatic System:
Uncommon undesirable effects: Ecchymosis, dermal, gastrointestinal or nasal bleeding.
There have been reports of abnormal bleeding in several patients, but casual relationship to fluoxetine and clinical importance are unclear.
Rare undesirable effects. Leucopenia is possible, although this change, in most instances, is normalised once treatment is discontinued.

Respiratory System:
Rare undesirable effects: Pharyngitis, cough and dyspnoea. Pulmonary abnormalities have been reported rarely. In sporadic cases inflammatory or fibriotic changes in the lungs have been observed, the only symptom of which has been dyspnoea.

Urogenital System:
Common undesirable effect: disorders of the sexual functions including delayed orgasm, anorgasm both in man and in woman.

Special Precautions:

Cases of suicidal ideation and suicidal behaviours have been reported during fluoxetine therapy or early after treatment discontinuation (see section 4.4)

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 stage of recovery.

Additionally, in sporadic cases the following reactions have been described. They need not however, have a casual connection to the use of fluoxetine: thrombocytopenia and changes in thrombocytic function; dermal, gastrointestinal or nasal bleedings; aplastic anaemia, haemolytic anaemia, eosinophilic, pneumonia, malignant neuroleptic symptom complex, arrhythmia, loss of hair, cytolytic or mixed pancreatitis, hyperprolactinemia, vaginal haemorrhaging after the termination of fluoxetine treatment, suicidal thoughts, aggressive behaviour.
In rare cases a prolongation of the blood coagulation time has been observed and/or haemorrhaging (such as haemotoma in the skin, gynaecological haemorrhaging, haemorrhaging of the gastrointestinal canal and other haemorrhaging of the skin or mucous membranes).

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 selflimiting. 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, seizure, 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 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: Antidepressants, selective serotonin reuptake inhibitors ATC code: N06A B03.

Fluoxetine inhibits the neuronal re-uptake of serotonin in the central nervous system, which is probably responsible for its action.

Fluoxetine is not chemically related to tri-, tetracyclic or other antidepressants. Animal studies have shown that fluoxetine is a much more potent inhibitor of serotonin (re-)uptake than of noradrenaline (re-)uptake.

Antagonism of muscarinic, histaminergic and α_1 – adrenergic receptors is associated with various anticholinergic, sedative and cardiovascular effects of tricyclic antidepressants.
Fluoxetine has almost no affinity for these and other receptors in cerebral tissue.

5.2 Pharmacokinetic properties

Absorption:
Fluoxetine is readily absorbed after oral administration from the gastrointestinal tract with a peak plasma concentration of about 6 – 8 hours. The absorption rate decreases slightly under the effect of food, but the total quantity of fluoxetine absorbed is not affected; fluoxetine may therefore be taken with or without food.

Distribution:
Binding to human serum proteins, including albumin and α_1 – glycoprotein, is approximately 94.5% in vitro.

Fluoxetine is a racemic mixture (50/50) of the enantiomers R-fluoxetine and S-fluoxetine.
Animal models have shown that both enantiomers are specific and potent inhibitors of serotonin re-uptake with similar pharmacological activity.
The S-fluoxetine enantiomer is eliminated more slowly and is the main enantiomer in plasma in the steady-state situation.

Metabolism:
Fluoxetine is extensively metabolised in the liver to norfluoxetine and a number of other unidentified metabolites. The only identified active metabolite, norfluoxetine, is formed by demethylation. Animal models have shown that the potency and selectivity of S-norfluoxetine as a serotonin re-uptake inhibitor is equivalent to that of R- and S-fluoxetine.
R-norfluoxetine is a significantly less potent inhibitor of serotonin re-uptake than the parent drug, fluoxetine. The primary elimination is based on hepatic metabolism to inactive metabolites which are excreted via the kidneys.

Elimination:
The relatively slow elimination of fluoxetine (half-life 4 to 6 days) and of the active metabolite norfluoxetine (half-life 4 to 16 days) means that steady-state concentrations are reached after a few weeks if patients receive continuous administration. Patients treated with doses of 40 to 80 mg/day for a period of up to 3 years were found to have comparable plasma levels to patients treated for 4 to 5 weeks.
Plasma concentrations of fluoxetine after repeated administration were shown to be higher than expected on the basis of the plasma concentrations after a single administration, very probably because the metabolism of fluoxetine is not proportionate to the dose. Conversely, the pharmacokinetics of norfluoxetine appear to be linear.

Age:
The pharmacokinetics of single doses of fluoxetine in healthy elderly subjects (over 65 years of age) did not differ significantly from those in healthy younger subjects. However, given the long half-life and non-linear pharmacokinetics of fluoxetine, a single-dose study is not adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have concurrent diseases or are receiving multiple drugs. The effects of age on the metabolism of fluoxetine was studied in 260 depressive but otherwise healthy patients over 60 years of age, treated for 6 weeks with 20 mg fluoxetine daily. The combined fluoxetine and norfluoxetine plasma concentrations at the end of the 6 weeks were 209.3 ± 85.7 ng/ml. No unusual, age-related side-effect profile was seen in these elderly patients.

Hepatic insufficiency:
In case of hepatic insufficiency, fluoxetine and norfluoxetine half-lives are increased to 7 and 12 days, respectively. A lower or less frequent dose should be considered (c.f. 4.2 Posology).

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

Sucrose
Glycerol (E422)

Peppermint soluble
Ethanol 96%
Benzoic acid (E210)
Hydrochloric acid
Sodium hydroxide
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

24 months
In-use: 1 month

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Pharmaceutical grade, type III amber glass bottles with polypropylene child resistant closures. Pack size 70ml. Polypropylene dosing cup.

6.6 Special precautions for disposal and other handling

No special use/handling.

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Ltd., trading as Pinewood Healthcare,
Ballymacarbry,
Clonmel,
Co. Tipperary,
Ireland

8 MARKETING AUTHORISATION NUMBER

PA281/114/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 13th November 2008

10 DATE OF REVISION OF THE TEXT

December 2008