IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0047/077/005
Case No: 2039101

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

Eli Lilly and Company Limited

Lilly House, Priestley Road, **Basingstoke**, **Hampshire**, **RG24 9NL**, **United Kingdom**

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

Prozac Weekly 90mg hard gastro-resistant capsules

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 **09/08/2007**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Prozac Weekly 90 mg hard gastro-resistant capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains fluoxetine hydrochloride equivalent to 90 mg of fluoxetine base.

Excipients: Sucrose ranging from 129.8 to 164.9 mg per capsule.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard gastro-resistant capsule.
Capsules, with green cap and clear body, imprinted with “Lilly” on cap, and “334” and “90 mg” on body. The capsules contain gastro-resistant pellets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prozac Weekly is indicated for weekly dosing in the continuation treatment of depression in patients who have responded to daily therapy with 20 mg fluoxetine. Prozac Weekly is an alternative choice to daily therapy with fluoxetine in the continuation treatment of depression. As with other antidepressants, the usefulness of therapy with Prozac Weekly for extended periods should be re-evaluated periodically.

4.2 Posology and method of administration

For oral administration to adults only.

Weekly dosing with Prozac Weekly is recommended to be initiated within 7 days after the last daily dose of fluoxetine 20 mg.

Administration with food: Prozac Weekly may be taken with or without food.

Use in children: The use of Prozac Weekly in children is not recommended, as safety and effectiveness have not been established.

Use in the elderly: There are no data to suggest that alternative dosing of fluoxetine is required on the basis of age alone. If elderly patients are able to tolerate fluoxetine 20 milligram daily, it would be expected that a dose of 90 milligram weekly may be also tolerated.

Hepatic impairment: If daily fluoxetine treatment is initiated for patients with liver disease, a lower or less frequent dose should be considered. The use of Prozac Weekly in patients with hepatic impairment has not been evaluated. However, if patients with hepatic impairment are able to tolerate fluoxetine 20 milligram daily, it would be expected that a dose of 90 milligram weekly would be also tolerated.

Renal impairment: Use of a lower or less frequent daily dose of fluoxetine is not routinely necessary in renally impaired patients. If patients with renal impairment are able to tolerate fluoxetine 20 milligram daily, it would be

expected that a dose of 90 milligram weekly would be also tolerated.

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. Due to the long half-life of fluoxetine and its metabolite, there is no requirement to taper the dose on cessation of treatment.

4.3 Contraindications

Hypersensitivity to fluoxetine or to any of the excipients.

Use in patients with unstable epilepsy or convulsant disorders.

Fluoxetine should not be administered to patients with severe renal failure (GFR <10ml/min) because accumulation may occur in these patients during chronic treatment.

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

Rash and possibly allergic events: During pre-marketing clinical trials, approximately 4 per cent of patients developed a rash and/or urticaria. Almost two-thirds of those developing a rash continued to take fluoxetine without any consequence and most of the remainder improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids. All patients experiencing these events were reported to recover completely. Two patients developed a serious cutaneous systemic illness (one was possibly leucocytoclastic vasculitis and the other either a vasculitis or erythema multiforme). Serum sickness has also been reported.

Since the introduction of fluoxetine, systemic events, possibly related to vasculitis, have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events. Anaphylactoid events, including bronchospasm, angioedema, and urticaria alone and in combination, have been reported. Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events have occurred with dyspnoea as the only preceding symptom.

A specific underlying immunological basis for these events has not been identified. Upon the appearance of rash or of other possibly allergic phenomena for which an alternative aetiology cannot be identified, Prozac 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. As with all antidepressants, fluoxetine should be discontinued in any patient entering a manic phase.

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

Weight Loss: Prozac may cause weight loss which may be undesirable in underweight depressed patients. Only rarely have fluoxetine patients been discontinued for weight loss. However, in controlled clinical trials of bulimia nervosa, no patients were discontinued for weight loss.

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

Suicide/suicidal thoughts: 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.
In an analysis of controlled trials in adults with major depressive disorder, the following were risk factors for suicidality with both placebo and fluoxetine:

Prior to Treatment:
- greater severity of depression
- presence of thoughts of death

During Treatment:
- worsening of depression
- development of insomnia

Development of severe psychomotor activation (e.g., agitation, akathisia, panic) was also a risk factor during treatment with fluoxetine.

The presence or emergence of these conditions prior to or during therapy suggests that consideration should be given to increased clinical monitoring or possible modification of therapy.

Patients with a history of suicide-related events, those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. In addition, there is a possibility of an increased risk of suicidal behaviour in young adults (< 25 years of age).

Patients (and caregivers of patients) should be alerted about the need to monitor for the emergence of such events and to seek medical advice immediately if these symptoms present. The risk of suicidality should be weighed against the known risks that exist from not effectively treating depression.

Use in children and adolescents under 18 years of age: Prozac Weekly should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. Prozac (20mg capsule or liquid) should only be used in children and adolescents aged 8 to 18 years for the treatment of moderate to severe major depressive episodes and it should not be used in other indications. 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 Prozac 20mg capsule or liquid SPC).

Akathisia/psychomotor restlessness: The use of fluoxetine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

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

There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking fluoxetine. While there have been reports of abnormal bleeding in several patients, it is unclear whether fluoxetine had a causative role.

Electroconvulsive Therapy (ECT) and Lithium: There is very little clinical experience of the concurrent administration of fluoxetine with ECT or lithium therapy (see section 4.5). 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.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Half-life: The long elimination half-lives of fluoxetine and norfluoxetine should be borne in mind (see sections 4.2 and 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 (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.

Although there is no clinical evidence of any unwanted effects when fluoxetine is co-administered with benzodiazepines, pharmacokinetic data suggest that the half-life of diazepam may be prolonged in some patients.

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.

Greater than 2-fold increases of previously stable plasma levels of other antidepressants have been observed when Prozac has been administered in combination.

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. There have been reports of both increased and decreased lithium levels when used concomitantly with fluoxetine. 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, vinblastine, 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 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, *Haemorrhag*e).

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: 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.

Protein binding: Fluoxetine is bound to plasma protein and concurrent administration may alter plasma concentrations of other plasma protein bound drugs, or conversely fluoxetine.

4.6 Pregnancy and lactation

*Pregnanc*y: Data on a large number of exposed pregnancies do not indicate a teratogenic effect of fluoxetine. Fluoxetine can be used during pregnancy, but caution should be exercised, especially during late pregnancy or just prior to the onset of labour since the following effects have been reported in neonates: irritability, tremor, hypotonia, persistent crying, difficulty in sucking or in sleeping. These symptoms may indicate either serotonergic effects or a withdrawal syndrome. The time to occur and the duration of these symptoms may be related to the long half-life of fluoxetine (4-6 days) and its active metabolite, norfluoxetine (4-16 days).

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

4.7 Effects on ability to drive and use machines

Although fluoxetine has been shown not to affect psychomotor performance in healthy volunteers, any psychoactive

drug may impair judgement or skills. Therefore patients should be cautioned that their ability to perform potentially hazardous tasks (e.g. driving, operating machinery) may be impaired.

4.8 Undesirable effects

The types of undesirable effects associated with the use of Prozac Weekly that have been observed during clinical trials are similar to those reported by patients taking fluoxetine every day and are also similar to those reported by patients taking other SSRIs.

In clinical trials, more patients taking Prozac Weekly reported 'nervousness' (13.8%) and 'thinking abnormal' (impairment of concentration or thought process; 7.7%) than patients taking fluoxetine 20 mg daily (6.6% and 2.9 % respectively). In the pivotal clinical trial, patients taking Prozac Weekly reported significantly less gastric discomfort than patients taking fluoxetine 20 mg daily (6.3% versus 15.3%).

Depression: The following treatment-emergent adverse events, which are listed in decreasing order of frequency under body system, were observed during placebo-controlled clinical trials at a frequency of one per cent or greater and at a significantly higher incidence than placebo (*P* value ≤0.05):

Body as a whole: Asthenia, fever.

Digestive system: Nausea, diarrhoea, mouth dryness, appetite loss, dyspepsia. Abnormal liver function tests have been reported rarely.

Nervous system: Headache, nervousness, insomnia, drowsiness, anxiety, tremor, dizziness, fatigue, decreased libido.

Respiratory system: Pharyngitis, dyspnoea.

Skin and appendages: Excessive sweating, arthralgia, myalgia (rash, see section 4.4).

Urinogenital system: Sexual dysfunction.

Bulimia nervosa: Using the same criteria for the placebo-controlled clinical trials in bulimia nervosa, the following treatment emergent adverse events were observed: insomnia, nausea, asthenia, tremor, sweating, decreased libido.

Other events that have been reported include dysphoria, psychosis and convulsions.

The more common events listed above that caused discontinuation include nausea, headache, nervousness, insomnia, anxiety, dizziness and asthenia.

During pre-marketing testing hypomania or mania occurred in approximately 1 per cent of fluoxetine treated patients.

Elevated serum transaminase values, blood urea nitrogen levels and/or depressed leucocyte counts without accompanying symptoms occurred infrequently in patients given fluoxetine, but resolved on cessation of therapy.

Hyponatraemia (including serum sodium below 110mmol/l) has been rarely reported and appeared to be reversible when Prozac 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.

Voluntary reports of adverse events temporally associated with fluoxetine, that have been received since market introduction and which may have no causal relationship with the drug, include:

Body as a whole: Infrequent reports of visual disturbance, including rare cases of photophobia, have been reported.

Nervous system: Confusion, dyskinesia (including, for example, a case of buccal-lingual-masticatory syndrome, which resolved following drug discontinuation), movement disorders developing in patients with risk factors (including drugs

associated with such events) and worsening of pre-existing movement disorders, neuroleptic malignant syndrome-like events, suicidal ideation and behaviour.

Miscellaneous: Acne, violent behaviours, ecchymosis, gastro-intestinal haemorrhage, vaginal bleeding after drug withdrawal, aplastic anaemia, hyperprolactinaemia, immune-related haemolytic anaemia, pancreatitis, pancytopenia, thrombocytopenia, thrombocytopenic purpura.

Cardiovascular System: Cerebral vascular accident. Symptoms suggestive of postural hypotension, hypotension, hypertension and tachycardia. There have also been very rare reports of supraventricular and ventricular arrhythmias. To date, causality of all these cardiovascular events has not been established.

Respiratory system: Eosinophilic pneumonia.

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

Body as a whole: Hypersensitivity (e.g. pruritis, urticaria, anaphylactoid reaction, vasculitis, serum sickness-like reaction, angioedema) (see sections 4.3 and 4.4), chills, serotonin syndrome, photosensitivity and very rarely Erythema Multiforme that could progress to Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis (Lyell syndrome).

Digestive system: Gastrointestinal disorders (e.g. vomiting, dysphagia, taste perversion). Very rare cases of idiosyncratic hepatitis.

Nervous system: Hallucinations, sleep abnormalities (e.g. abnormal dreams), anorexia, somnolence, transient abnormal movement (e.g., twitching, ataxia, myoclonus), seizures and rarely psychomotor restlessness/akathisia (see section 4.4). Impaired concentration and thought process (e.g. depersonalisation).

*Urogenital syste*m: Urinary retention, urinary frequency.

Reproductive disorders: Priapism.

Miscellaneous: Alopecia, yawn, abnormal vision (e.g., blurred vision, mydriasis), vasodilatation.

Withdrawal reactions have been reported in association with antidepressants, including the selective serotonin reuptake inhibitors (SSRIs), such as Prozac. Common symptoms include dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), asthenia, agitation or anxiety, nausea and/or vomiting, tremor and headache and may occur up to two weeks after discontinuation of treatment. The majority of symptoms on withdrawal of SSRIs are non-serious and self limiting.

Any adverse reactions or events should be reported to the Irish Medicines Board.

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. Accumulation of the parent tricyclic or an active metabolite may increase the possibility of clinically relevant sequelae.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Fluoxetine is a selective inhibitor of serotonin reuptake, and this probably accounts for the mechanism of action. The ATC code for fluoxetine is N06A B03. Fluoxetine has practically no affinity to other receptors such as alpha$_1$, alpha $_2$ and beta- adrenergic; serotonergic; dopaminergic; histaminergic$_1$, muscarinic; and GABA receptors.

5.2 Pharmacokinetic properties

Prozac Weekly capsules contain enteric-coated pellets which resist dissolution until the dosage form is in a segment of the gastrointestinal tract where the pH exceeds 5.5, and thereby delay the onset of absorption 1 to 2 hours relative to the immediate release formulation.

Administration of Prozac Weekly once-weekly provides plasma concentrations of fluoxetine and norfluoxetine that have a greater difference between peak and trough concentrations compared to once-daily dosing. Plasma concentrations may not necessarily be predictive of clinical response. Peak concentrations from once weekly doses of Prozac Weekly are in the range of the average concentration for 20 mg once-daily dosing. Trough concentrations are lower than the minimum concentrations maintained by 20 mg once-daily dosing. Average steady-state concentrations of either once-daily or once-weekly dosing are in relative proportion to the total dose administered.

Fluoxetine is well absorbed after oral administration. Peak plasma concentration (immediate-release formulation) is reached in 6 to 8 hours. Fluoxetine is extensively bound to plasma proteins. Fluoxetine is widely distributed. Steady-state plasma concentrations are achieved after daily dosing for several weeks. Steady-state concentrations after prolonged dosing are similar to concentrations seen at 4 to 5 weeks.

Fluoxetine is extensively metabolised in the liver to norfluoxetine and a number of other, unidentified metabolites, which are excreted in urine. The elimination half-life of fluoxetine is 4 to 6 days and that of its active metabolite is 4 to 16 days.

5.3 Preclinical safety data

There is no evidence of carcinogenicity ot mutagenicity from in vitro or animal studies. Impairment of fertility in adult animals at doses up to 12.5 mg/kg/day (approximately 1.5 times the MRHD on a mg/m^2 basis) was not observed.

In a juvenile toxicity 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 occured in males (10 and 30 mg/kg/day) and females (30 mg/kg/day). The significance of these findings in humans is unknown. Rats administered 30 mg/kg also had decreased femur lengths compared with controls and skeletal muscle degeneration, necrosis and regeneration. At 10 mg/kg/day, plasma levels achieved in animals were approximately 0.8 to 8.8 fold (fluoxetine) and 3.6 to 23.2 fold (norfluoxetine) those usually observed in paediatric patients. At 3 mg/kg/day, plasma levels achieved in animals were approximately 0.04 to 0.5 fold (fluoxetine) and 0.3 to 2.1 fold (norfluoxetine) those usually achieved in paediatric patients.

A study in juvenile mice has indicated that the 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 mice. There is no information on whether the effect was reversible. The clinical relevance of this finding has not been established.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pellets:

Sucrose
Hypromellose
Sugar spheres containing sucrose and maize starch
Talc
Hypromellose acetate succinate (enteric-coating agent)
Triethyl citrate
Titanium dioxide (E171)

Capsule shell:

Indigo carmine (E132)
Titanium dioxide (E171)
Quinoline yellow (E104)
Gelatin
Sodium laurilsulfate

Black ink, containing:

Shellac
Propylene glycol
Concentrated ammonia solution
Black iron oxide-synthetic (E172)
Potassium hydroxide or dimeticone

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Polyvinylchloride (PVC), polyethylene (PE) and polychlorotrifluoroethylenen (PCTFE or Aclar®) blisters with aluminium foil lid.
Available in packs of 4 and 12 capsules.

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

Eli Lilly and Company Limited
Lilly House
Priestley Road
Basingstoke
Hampshire
RG24 9NL
UK

8 MARKETING AUTHORISATION NUMBER

PA 47/77/5

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 December 2001

Date of last renewal: 14 December 2006

10 DATE OF REVISION OF THE TEXT

August 2007