Public Assessment Report

Decentralised Procedure

FLUOXETINE 20 MG HARD CAPSULES
FLUOXETINE 60 MG HARD CAPSULES
(fluoxetine hydrochloride)

Procedure No: UK/H/4687/001-2/DC

UK Licence No: PL 17907/0386-7

Bristol Laboratories Limited.
Lay summary

On 28 June 2012, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations to Bristol Laboratories Limited for the medicinal products Fluoxetine 20 mg and 60 mg Hard Capsules (PL 17907/0386-7; UK/H/4687/001-2/DC).

These are prescription-only medicines used to treat the following conditions in adults:
• major depressive episodes,
• obsessive compulsive disorder,
• bulimia nervosa: Fluoxetine is used alongside psychotherapy for the reduction of binge-eating and purging.

In children and adolescents age 8 years and above, Fluoxetine 20 mg Hard Capsules are used to treat moderate to severe major depressive disorder, if the depression does not respond to psychological therapy after 4-6 sessions. Fluoxetine should be offered to a child or young person with moderate to severe major depressive disorder only in combination with psychological therapy.

The active ingredient, fluoxetine (as fluoxetine hydrochloride), belongs to a group of medicines called ‘selective serotonin re-uptake inhibitors (SSRIs) and is an antidepressant.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Fluoxetine 20 mg and 60 mg Hard Capsules outweigh the risks and Marketing Authorisations were granted.
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# Module 1

## Information about the initial procedure

| Product Names | UK/H/4687/001/DC: Fluoxetine 20mg Hard Capsules  
               | UK/H/4687/002/DC: Fluoxetine 60mg Hard Capsules |
|---------------|-------------------------------------------------|
| Type of Applications | Generic, Article 10(1)                           |
| Active Substance | Fluoxetine                                       |
| Form | Hard capsules                                    |
| Strengths | 20 mg and 60 mg                                  |
| MA Holder | Bristol Laboratories Limited, Unit 3, Canalside, Northbridge Road, Berkhamsted, Herts HP4 1EG, United Kingdom |
| Reference Member State (RMS) | UK                                             |
| Concerned Member States (CMS) | Spain and Ireland                             |
| Procedure Numbers | UK/H/4687/001-4/DC                              |
| Timetable | Day 210 – 24 May 2012                           |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Fluoxetine 20 mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Fluoxetine 20mg capsule contains 20mg of fluoxetine as fluoxetine hydrochloride.
Excipient: Sunset Yellow (E110) 0.0014 mg per capsule
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Capsule Hard
(capsules)
Hard gelatin capsules, size ‘4’, having green coloured cap and cream coloured body filled with white to off-white powder.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Adults:
Major depressive disorders/episodes.
Obsessive-compulsive disorder.
Bulimia nervosa: Fluoxetine is indicated as a complement of psychotherapy for the reduction of 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
Fluoxetine capsules are meant for oral administration in adults only. The capsules should be swallowed whole with a glass of water.

Major depressive disorders/episodes
Adults and the elderly: A dose of 20 mg/day is recommended. 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 20mg, the dose may be increased gradually up to a maximum of 3 capsules (60mg) (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 free from symptoms.
Obsessive-compulsive disorder
Adults and the elderly: The recommended dose is 20mg daily. 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 3 capsules (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, 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.

_Bulimia nervosa; adults and the elderly:_ A dose of 3 capsules (60 mg/day) is recommended. Long-term efficacy (more than 3 months) has not been demonstrated in bulimia nervosa.

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

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

When dosing is stopped, active drug substances will persist in the body for weeks. This should be borne in mind when starting or stopping treatment.

The capsule and liquid dosage forms are bioequivalent.

_Children and adolescents aged 8 years and above (moderate to severe major depressive episode):_ Treatment should be initiated and monitored under specialist supervision. The starting dose is 10mg/day. A liquid formulation will be more suitable for this starting dose. Dose adjustments should be made carefully, on an individual basis, to maintain the patient at the lowest effective dose.

After one to two weeks, the dose may be increased to 20mg/day. Clinical trial experience with daily doses 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 with lower doses (see section 5.2).

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 not exceed 2 capsules (40mg). Maximum recommended dose is 3 capsules (60mg) per day.

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

Withdrawal symptoms seen on discontinuation of FLUOXETINE: Abrupt discontinuation should be avoided. When stopping treatment with FLUOXETINE 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 (see section 4.4 and section 4.8). 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**

Hypersensitivity to fluoxetine or any of the excipients.

_Monoamine oxidase inhibitors (MAOI):_ 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

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. FLUOXETINE 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 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 TANNER staging) 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 prescriber 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 capsules 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. Fluoxetine 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 epilepsy; patients with unstable seizure disorders/ epilepsy should be carefully monitored.

Mania: Antidepressants should be used with caution in patients with a history of mania/hypomania. As with all antidepressants, fluoxetine should be discontinued in any patient entering a manic phase.

Hepatic/Renal function: Fluoxetine is extensively metabolised by the liver and excreted by the kidneys. A lower dose, e.g., alternate day dosing, is recommended in patients with significant hepatic dysfunction When given fluoxetine 20mg/day for 2 months, patients with severe renal failure (GFR <10ml/min) requiring dialysis showed no difference in plasma levels of fluoxetine or norfluoxetine compared to controls with normal renal function.
Tamoxifen: Fluoxetine, a potent inhibitor of CYP2D6, may lead to reduced concentrations of endoxifen, one of the most important active metabolites of tamoxifen. Therefore, fluoxetine should whenever possible be avoided during tamoxifen treatment (see section 4.5).

Cardiac disease: Clinical experience in acute cardiac disease is limited, therefore caution is advisable. However, the ECG of 312 patients who received fluoxetine in doubleblind clinical trials was retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed.

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

Diabetes: Fluoxetine may alter glycaemic control in patients with diabetes. Hypoglycaemia has been reported during therapy with fluoxetine and hyperglycaemia has developed following discontinuation. In such situations, the dosage of insulin and/or oral hypoglycaemic agents 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 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.

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.

Withdrawal symptoms seen on discontinuation of SSRI treatment: Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). 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), asthenia, 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. 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 FLUOXETINE should be gradually tapered when
discontinuing treatment over a period of at least one to two weeks, according to the patient's needs (see 'Withdrawal symptoms seen on discontinuation of FLUOXETINE', section 4.2).

**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, gastro-intestinal bleedings and other cutaneous or mucous bleedings) have been reported rarely. Caution is advised in patients taking SSRIs, particularly in concomitant use with oral anticoagulants, drugs known to affect platelet function (e.g., atypical antipsychotics, such as clozapine, phenothiazines, most TCAs, aspirin, NSAIDs), or other drugs that may increase risk of bleeding, as well as in patients with a history of bleeding disorders.

**Mydriasis:** Mydriasis has been reported in association with fluoxetine; therefore, caution should be used when prescribing fluoxetine in patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma.

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

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

On rare occasions, development of a serotonin syndrome or neuroleptic malignant syndrome-like events have been reported in association with treatment of fluoxetine, particularly when given in combination with other serotonergic (among others, L-tryptophan) and/or neuroleptic drugs. As these syndromes may result in potentially life-threatening conditions, treatment with fluoxetine should be discontinued if such events (characterised by clusters of symptoms, such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes, including confusion, irritability, extreme agitation, progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated.

The colourant **sunset yellow (E 110)** in the capsule shell can cause allergic type reactions.

### 4.5 Interaction with other medicinal products and other forms of interaction

**Interaction studies have only been performed in adults.**

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

**Monoamine oxidase inhibitors:** See section 4.3.

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

**Combinations requiring precautions for use:** MAOI-B (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 medicinal products also metabolised by this enzyme system may lead to medicinal product interactions. Concomitant therapy with medicinal products predominantly metabolised by this isoenzyme, and which have a narrow therapeutic index (such as flecainide, encainide, carbamazepine and tricyclic antidepressants), should be initiated at or adjusted to the low end of their dose range. This will also apply if fluoxetine has been taken in the previous 5 weeks. Pharmacokinetic interaction between CYP2D6 inhibitors and tamoxifen, showing a 65-75% reduction in plasma levels of one of the more active forms of the tamoxifen, i.e. endoxifen, has been reported in the literature. Reduced efficacy of tamoxifen has been reported with concomitant usage of some SSRI antidepressants in some studies. As a reduced effect of tamoxifen cannot be excluded, co-administration with potent CYP2D6 inhibitors (including fluoxetine) should whenever possible be avoided (see section 4.4).

Oral anticoagulants: Altered anticoagulant effects (laboratory values and/or clinical signs and symptoms), with no consistent pattern, but including increased bleeding, have been reported uncommonly when fluoxetine is co-administered with oral anticoagulants. Patients receiving warfarin therapy should receive careful coagulation monitoring when fluoxetine is initiated or stopped (see section 4.4, ‘Haemorrhage’).

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

Alcohol: In formal testing, fluoxetine did not raise blood alcohol levels or enhance the effects of alcohol. However, the combination of SSRI treatment and alcohol is not advisable.

St. John’s wort: In common with other SSRIs, Pharmacodynamic interactions between fluoxetine and the herbal remedy St. John’s wort (Hypericum perforatum) may occur, resulting in an increase in undesirable effects.

4.6 Fertility, pregnancy and lactation

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

Pregnancy: Some epidemiological studies suggest an increased risk of cardiovascular defects associated with the use of fluoxetine during the first trimester. The mechanism is unknown. Overall the data suggest that the risk of having an infant with a cardiovascular defect following maternal fluoxetine exposure is in the region of 2/100 compared with an expected rate for such defects of approximately 1/100 in the general population.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particular in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). The observed risk was approximately 5 cases per 1000 pregnancies. In the general population 1 to 2 cases of PPHN per 1000 pregnancies occur.

Furthermore, although fluoxetine can be used during pregnancy, caution should be exercised, especially during late pregnancy or just prior to the onset of labour, since some other effects have been reported in neonates: irritability, tremor, hypotonia, persistent crying, difficulty in sucking or in sleeping. These symptoms may indicate either serotonergic effects or a withdrawal syndrome. The time to occur and the duration of these symptoms may be related to the long half-life of fluoxetine (4-6 days) and its active metabolite, norfluoxetine (4-16 days).

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

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 medicinal product may impair judgement or skills.
Patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.

4.8 Undesirable effects
The most commonly reported adverse reactions in patients treated with fluoxetine were headache, nausea, insomnia, fatigue and diarrhoea. Undesirable effects may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.

The table below gives the adverse reactions observed in clinical trials (n = 9297) and from spontaneous reporting. Some of these adverse reactions are in common with other SSRIs.

Frequency estimate: Very common (1/10), common (1/100 to <1/10), uncommon (1/1,000 to <1/100), rare (1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
<table>
<thead>
<tr>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very Rare</th>
<th>Frequency Not Known</th>
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<td>Immune system disorders</td>
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<td>Anaphylactic reaction Serum Sickness</td>
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<td>Endocrine disorders</td>
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<td>Inappropriate anti diuretic hormone secretion</td>
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<td>Metabolism and nutrition disorders</td>
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<td>Decreased appetite(^1)</td>
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<td>Hyponatraemia</td>
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<td>Psychiatric disorders</td>
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<td>Suicidal thoughts and behaviour(^1) Confusion</td>
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<td>Insomnia(^2)</td>
<td>Anxiety</td>
<td>Nervousness</td>
<td>Restlessness</td>
<td>Tension</td>
<td>Libido decreased(^4)</td>
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<td>Nervous system disorders</td>
<td>Headache</td>
<td>Disturbance in attention</td>
<td>Dizziness</td>
<td>Dysgeusia</td>
<td>Lethargy</td>
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<td>Eye disorders</td>
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<td>Vision blurred</td>
<td>Mydriasis</td>
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<td>Ear and labyrinth disorders</td>
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<td>Cardiac disorders</td>
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<td>Vascular disorders</td>
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<td>Respiratory, thoracic and mediastinal disorders</td>
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<td>Yawning</td>
<td>Dysequoia</td>
<td>Pharyngitis</td>
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<td>Pulmonary events (inflammatory processes of varying histopathology and/or fibrosis) Epistaxis</td>
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<td>Gastrointestinal disorders</td>
<td>Diarrhoea</td>
<td>Nausea</td>
<td>Vomiting</td>
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<td>Dry mouth</td>
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<td>Hepato-biliary disorders</td>
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<td>Very Common</td>
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<td><strong>Skin and subcutaneous tissue disorders</strong></td>
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<td>Rash(^1)</td>
<td>Alopecia</td>
<td>Angioedema</td>
<td>Erythema multiforme(^{13})</td>
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<td>Urticaria</td>
<td>Increased tendency to bruise</td>
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<td>Pruritus</td>
<td>Cold sweat</td>
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<td>Hyperhidrosis</td>
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<td>Purpura</td>
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<td><strong>Musculoskeletal, connective tissue and bone disorders</strong></td>
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<td>Arthralgia</td>
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<td><strong>Renal and urinary disorders</strong></td>
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<td>Frequent urination(^9)</td>
<td>Dysuria</td>
<td>Urinary retention</td>
<td>Micturition disorder</td>
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<td>Gynaecological bleeding(^{11})</td>
<td>Sexual dysfunction</td>
<td>Galactorrhoea</td>
<td>Priapism</td>
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<td>Erectile dysfunction</td>
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<td>Ejaculation disorder(^{10})</td>
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<td><strong>General disorders and administration site conditions</strong></td>
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<td>Fatigue(^{12})</td>
<td>Feeling jittery</td>
<td>Malaise</td>
<td>Mucosal haemorrhage</td>
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<td>Chills</td>
<td>Feeling abnormal</td>
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<td>Feeling cold</td>
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<td>Feeling hot</td>
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<td><strong>Investigations</strong></td>
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<td>Weight decreased</td>
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<td>Abnormal liver function tests</td>
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\(^1\)Includes anorexia  
\(^2\)Includes early morning awakening, initial insomnia, middle insomnia  
\(^3\)Includes nightmares  
\(^4\)Includes loss of libido  
\(^5\)Includes anorgasmia  
\(^6\)Includes hypersomnia, sedation  
\(^7\)Includes hot flush  
\(^8\)Includes erythema, exfoliative rash, heat rash, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash macular-papular, rash morbilliform, rash papular, rash pruritic, rash vesicular, umbilical erythema rash  
\(^9\)Includes pollakiuria  
\(^10\)Includes ejaculation failure, ejaculation dysfunction, premature ejaculation, ejaculation delayed, retrograde ejaculation  
\(^11\)Includes cervix haemorrhage, uterine dysfunction, uterine bleeding, genital haemorrhage, menometrorrhagia, menorrhagia, metrorrhagia, polymenorrhea, postmenopausal haemorrhage, uterine haemorrhage, vaginal haemorrhage  
\(^12\)Includes asthenia  
\(^13\)Could progress to Stevens-Johnson syndrome or Toxic Epidermal Necrolysis (Lyell Syndrome)  
\(^{14}\)These symptoms may be due to underlying disease.  
Cases of suicidal ideation and suicidal behaviour have been reported during fluoxetine therapy or early after treatment discontinuation (see section 4.4).  

**Bone fractures:** Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to the risk is unknown.
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 the most 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). It is therefore advised that when FLUOXETINE treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 and section 4.4).

Children and adolescents (see section 4.4):
Additional adverse reactions have been observed specifically in this population and are described below.

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 versus 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 from paediatric clinical use (see also section 5.3).

In paediatric clinical trials, epistaxis was commonly reported, and fluoxetine treatment was associated with a decrease in alkaline phosphatase levels.

4.9 Overdose
Cases of overdose of fluoxetine alone usually have a mild course. Symptoms of overdose have included nausea, vomiting, seizures, cardiovascular dysfunction ranging from asymptomatic arrhythmias to cardiac arrest, pulmonary dysfunction, and signs of altered CNS status ranging from excitation to coma. Fatality attributed to overdose of fluoxetine alone has been extremely rare. Cardiac and vital signs monitoring are recommended, along with general symptomatic and supportive measures. No specific antidote is known.

Forced diuresis, dialysis, haemoperfusion, and exchange transfusion are unlikely to be of benefit. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage. In managing overdosage, consider the possibility of multiple drug involvement. An extended time for close medical observation may be needed in patients who have taken excessive quantities of a tricyclic antidepressant if they are also taking, or have recently taken, fluoxetine.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic Group: selective serotonin reuptake inhibitor-ATC Code: N06AB03

Fluoxetine is a potent and highly selective serotonin (5-hydroxytryptamine, 5HT) reuptake inhibitor.

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 $\alpha_1$-, $\alpha_2$-, and $\beta$-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 of 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 some patients.

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

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

Two placebo-controlled studies were conducted in patients meeting pre-menstrual dysorphic disorder (PMDD) diagnostic criteria according to DSM-IV. Patients were included if they had symptoms of sufficient severity to impair social and occupational function and relationships with others. Patients using oral contraceptives were excluded. In the first study of continuous 20mg daily dosing for 6 cycles, improvement was observed in the primary efficacy parameter (irritability, anxiety and dysphoria). In the second study, with intermittent luteal phase dosing (20mg daily for 14 days) for 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 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 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 readily absorbed from the gastrointestinal tract after oral administration. The bioavailability is not affected by food intake.

Distribution: Fluoxetine is extensively bound to plasma proteins (about 95%) and it is widely distributed (volume of distribution: 20-40 l/kg). Steady-state plasma concentrations are achieved after dosing for several weeks. Steady-state concentrations after prolonged dosing are similar to concentrations seen at 4 to 5 weeks.

Metabolism: Fluoxetine has a non-linear pharmacokinetic profile with first pass liver effect. Maximum plasma concentration is generally achieved 6 to 8 hours after administration. Fluoxetine is extensively metabolised by the polymorphic enzyme CYP2D6. Fluoxetine is primarily metabolised by the liver to the active metabolite norfluoxetine (desmethylfluoxetine), by demethylation.

Elimination: The elimination half-life of fluoxetine is 4 to 6 days and for norfluoxetine 4 to 16 days. These long half-lives are responsible for persistence of the drug for 5-6 weeks after discontinuation. Excretion is mainly (about 60%) via the kidney. Fluoxetine is secreted into breast milk.
At-Risk Populations

Elderly: Kinetic parameters are not altered in healthy elderly when compared to younger subjects.

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). 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

There is no evidence of carcinogenicity or mutagenicity from in vitro or animal studies. In a juvenile toxicology study in CD rats, administration of 30mg/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 30mg/kg/day) and females (30mg/kg/day). The significance of these findings in humans is unknown.

In a 2-generation rat reproduction study, fluoxetine did not produce adverse effects on the mating or fertility of rats, was not teratogenic, and did not affect growth, development, or reproductive parameters of the offspring. The concentrations in the diet provided doses approximately equivalent to 1.5, 3.9 and 9.7 mg fluoxetine/kg body weight.

Male mice treated for 3 months with fluoxetine in the diet at a dose approximately equivalent to 31 mg/kg showed a decrease in testis weight and hypospermatogenesis. However, this dose level exceeded the maximum-tolerated dose (MTD) as significant signs of toxicity were seen.

Rats administered 30mg/kg also had decreased femur lengths compared with controls and skeletal muscle degeneration, necrosis and regeneration. At 10mg/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 3mg/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 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 been established.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule Contents:
Pregelatinised maize starch
Dimeticone

Capsule Shell Contents:
Gelatin
Quinoline yellow (E104)
Sunset Yellow (E110),
Titanium dioxide (E171)
Brilliant blue (E133)
Purified water
6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

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

6.5 Nature and contents of container
10, 14, 20, 28, 30, 50, 56, 60, 70, 90, 98, 100 or 500 Capsules packed in a blister pack consisting of clear PVC film with a backing aluminium foil.

Not all pack sizes may be marketed

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Bristol Laboratories Limited,
Unit 3, Canalside,
Northbridge Road
Berkhamsted
Herts HP4 1EG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 17907/0386

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
28/06/2012

10 DATE OF REVISION OF THE TEXT
28/06/2012
1 NAME OF THE MEDICINAL PRODUCT
Fluoxetine 60 mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Fluoxetine 60mg capsule contains 60mg of fluoxetine as fluoxetine hydrochloride.

Excipient: Sunset Yellow (E110) 0.0014 mg per capsule
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Capsule Hard
(capsules)

Hard gelatin capsules, size ‘1’, having cream coloured cap and cream coloured body filled with white to off-white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Adults:
Major depressive disorders/episodes.
Obsessive-compulsive disorder.
Bulimia nervosa: Fluoxetine is indicated as a complement of psychotherapy for the reduction of binge-eating and purging activity.

4.2 Posology and method of administration
Fluoxetine capsules are meant for oral administration in adults only. The capsules should be swallowed whole with a glass of water.

Major depressive disorders/episodes

Adults and the elderly: A dose of 20 mg/day is recommended. 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 20mg, the dose may be increased gradually up to a maximum of 1 capsule (60mg) (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 free from symptoms.

Obsessive-compulsive disorder
Adults and the elderly: The recommended dose is 20mg daily. 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 1 capsule (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, 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.

Bulimia nervosa; adults and the elderly: A dose of 1 capsule (60 mg/day) is recommended. Long-term efficacy (more than 3 months) has not been demonstrated in bulimia nervosa.

All indications: Adults: The recommended dose may be increased or decreased. Doses above 80mg/day have not been systematically evaluated.
Fluoxetine may be administered with or without food. 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.

**Children and adolescents**: Fluoxetine should not be used in the treatment of children and adolescents under the age of 18 years (see section 4.4 Special Warnings and Special Precautions for Use), as safety and efficacy have not been established.

**Elderly**: Caution is recommended when increasing the dose, and the daily dose should generally not exceed 40mg. Maximum recommended dose is 1 capsule (60mg/day).

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

**Withdrawal symptoms seen on discontinuation of FLUOXETINE**: Abrupt discontinuation should be avoided. When stopping treatment with FLUOXETINE 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 (see section 4.4 and section 4.8). 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

Hypersensitivity to fluoxetine or any of the excipients.

**Monoamine oxidase inhibitors (MAOI)**: 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

**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).

**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 capsules 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.
Fluoxetine 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 epilepsy; patients with unstable seizure disorders/epilepsy should be carefully monitored.

**Mania:** Antidepressants should be used with caution in patients with a history of mania/hypomania. As with all antidepressants, fluoxetine should be discontinued in any patient entering a manic phase.

**Hepatic/Renal function:** Fluoxetine is extensively metabolised by the liver and excreted by the kidneys. A lower dose, e.g., alternate day dosing, is recommended in patients with significant hepatic dysfunction. When given fluoxetine 20mg/day for 2 months, patients with severe renal failure (GFR <10ml/min) requiring dialysis showed no difference in plasma levels of fluoxetine or norfluoxetine compared to controls with normal renal function.

**Tamoxifen:** Fluoxetine, a potent inhibitor of CYP2D6, may lead to reduced concentrations of endoxifen, one of the most important active metabolites of tamoxifen. Therefore, fluoxetine should wherever possible be avoided during tamoxifen treatment (see section 4.5).

**Cardiac disease:** Clinical experience in acute cardiac disease is limited, therefore caution is advisable. However, the ECG of 312 patients who received fluoxetine in doubleblind clinical trials was retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed.

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

**Diabetes:** Fluoxetine may alter glycaemic control in patients with diabetes. Hypoglycaemia has been reported during therapy with fluoxetine and hyperglycaemia has developed following discontinuation. In such situations, the dosage of insulin and/or oral hypoglycaemic agents 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 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.

**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.

**Withdrawal symptoms seen on discontinuation of SSRI treatment:** Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). 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), asthenia, 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. 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 FLUOXETINE should be gradually tapered when discontinuing treatment over a period of at least one to two weeks, according to the patient's needs (see 'Withdrawal symptoms seen on discontinuation of FLUOXETINE', section 4.2).

**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, gastro-intestinal bleedings and other cutaneous or mucous bleedings) have been reported rarely. Caution is advised in patients taking SSRIs, particularly in concomitant use with oral anticoagulants, drugs known to affect platelet function (e.g., atypical antipsychotics, such as clozapine, phenothiazines, most TCAs, aspirin, NSAIDs), or other drugs that may increase risk of bleeding, as well as in patients with a history of bleeding disorders.

**Mydriasis:** Mydriasis has been reported in association with fluoxetine; therefore, caution should be used when prescribing fluoxetine in patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma.

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

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

On rare occasions, development of a serotonin syndrome or neuroleptic malignant syndrome-like events have been reported in association with treatment of fluoxetine, particularly when given in combination with other serotonergic (among others, L-tryptophan) and/or neuroleptic drugs. As these syndromes may result in potentially life-threatening conditions, treatment with fluoxetine should be discontinued if such events (characterised by clusters of symptoms, such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes, including confusion, irritability, extreme agitation, progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated.

The colourant **sunset yellow (E 110)** in the capsule shell can cause allergic type reactions.

### 4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

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

**Monoamine oxidase inhibitors:** See section 4.3.

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

**Combinations requiring precautions for use:** MAOI-B (selegeline): Risk of serotonin syndrome. Clinical monitoring is recommended.

**Phenotoin:** 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 medicinal products also metabolised by this enzyme system may lead to medicinal product interactions.

Concomitant therapy with medicinal products predominantly metabolised by this isoenzyme, and which have a narrow therapeutic index (such as flecainide, encainide, carbamazepine and tricyclic antidepressants), should be initiated at or adjusted to the low end of their dose range. This will also apply if fluoxetine has been taken in the previous 5 weeks.

Pharmacokinetic interaction between CYP2D6 inhibitors and tamoxifen, showing a 65-75% reduction in plasma levels of one of the more active forms of the tamoxifen, i.e. endoxifen, has been reported in the literature. Reduced efficacy of tamoxifen has been reported with concomitant usage of some SSRI antidepressants in some studies. As a reduced effect of tamoxifen cannot be excluded, co-administration with potent CYP2D6 inhibitors (including fluoxetine) should whenever possible be avoided (see section 4.4).

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

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

Alcohol: In formal testing, fluoxetine did not raise blood alcohol levels or enhance the effects of alcohol. However, the combination of SSRI treatment and alcohol is not advisable.

St. John’s wort: In common with other SSRIs, Pharmacodynamic interactions between fluoxetine and the herbal remedy St. John’s wort (Hypericum perforatum) may occur, resulting in an increase in undesirable effects.

4.6 Fertility, pregnancy and lactation

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

Pregnancy: Some epidemiological studies suggest an increased risk of cardiovascular defects associated with the use of fluoxetine during the first trimester. The mechanism is unknown. Overall the data suggest that the risk of having an infant with a cardiovascular defect following maternal fluoxetine exposure is in the region of 2/100 compared with an expected rate for such defects of approximately 1/100 in the general population.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particular in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). The observed risk was approximately 5 cases per 1000 pregnancies. In the general population 1 to 2 cases of PPHN per 1000 pregnancies occur.

Furthermore, although fluoxetine can be used during pregnancy, caution should be exercised, especially during late pregnancy or just prior to the onset of labour, since some other effects have been reported in neonates: irritability, tremor, hypotonia, persistent crying, difficulty in sucking or in sleeping. These symptoms may indicate either serotonergic effects or a withdrawal syndrome. The time
to occur and the duration of these symptoms may be related to the long half-life of fluoxetine (4-6 days) and its active metabolite, norfluoxetine (4-16 days).

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

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 medicinal product may impair judgement or skills.

Patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.

4.8 Undesirable effects
The most commonly reported adverse reactions in patients treated with fluoxetine were headache, nausea, insomnia, fatigue and diarrhoea. Undesirable effects may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.

The table below gives the adverse reactions observed in clinical trials (n = 9297) and from spontaneous reporting. Some of these adverse reactions are in common with other SSRIs.

Frequency estimate: Very common (1/10), common (1/100 to <1/10), uncommon (1/1,000 to <1/100), rare (1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
<table>
<thead>
<tr>
<th><strong>Very Common</strong></th>
<th><strong>Common</strong></th>
<th><strong>Uncommon</strong></th>
<th><strong>Rare</strong></th>
<th><strong>Very Rare</strong></th>
<th><strong>Frequency Not Known</strong></th>
</tr>
</thead>
</table>
| **Immune system disorders** | | | | | Anaphylactic reaction  
| | | | | Serum Sickness |
| **Endocrine disorders** | | | | | Inappropriate anti diuretic hormone secretion |
| **Metabolism and nutrition disorders** | | | | | |
| Decreased appetite^1 | | | | | Hyponatraemia |
| **Psychiatric disorders** | | | | | |
| Insomnia^2 | Anxiety  
| | Nervousness  
| | Restlessness  
| | Tension  
| | Libido decreased^4  
| | Sleep disorder  
| | Abnormal dreams^3  |
| | Depersonalisation  
| | Elevated mood  
| | Euphoric mood  
| | Thinking abnormal  
| | Orgasm abnormal^2  
| | Bruxism  |
| | Hypomania  
| | Mania  
| | Hallucinations  
| | Agitation  
| | Panic attacks  |
| | Suicidal thoughts and behaviour^14  
| | Confusion  |
| **Nervous system disorders** | Headache | Disturbance in attention  
| | Dizziness  
| | Dysgeusia  
| | Lethargy  
| | Somnolence^6  
| | Tremor  |
| | Psychomotor hyperactivity  
| | Dyskinesia  
| | Ataxia  
| | Balance disorder  
| | Myoclonus  |
| | Convulsion  
| | Akathisia  
| | Buccoglossal syndrome  |
| | Serotonin syndrome  |
| **Eye disorders** | Vision blurred | Mydriasis | | | |
| **Ear and labyrinth disorders** | | | | | Tinnitus |
| **Cardiac disorders** | Palpitations | | | | |
| **Vascular disorders** | Flushing^7 | Hypotension | Vasculitis  
| | | Vasodilatation |
| **Respiratory, thoracic and mediastinal disorders** | Yawning | Dyspnoea | Pharyngitis | Pulmonary events  
| | | | (inflammatory processes of varying histopathology and/or fibrosis) Epistaxis |
| **Gastrointestinal disorders** | Diarrhoea  
| | Nausea  
| | Vomiting  
| | Dyspepsia  
| | Dry mouth  
| | Dysphagia | Oesophageal pain | Gastrointestinal haemorrhage |
| **Hepato-biliary disorders** | | | Very rare idiosyncratic hepatitis | | |
### Drug Name:
Fluoxetine 20 mg and 60 mg Hard Capsules

### UK/H/4687/001-2/DC

### Table: Adverse Reactions

<table>
<thead>
<tr>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very Rare</th>
<th>Frequency Not Known</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Rash&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Alopecia</td>
<td>Angioedema</td>
<td>Erythema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urticaria</td>
<td>Increased tendency to bruise</td>
<td>Ecchymosis</td>
<td>multiforme&lt;sup&gt;13&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>Cold sweat</td>
<td>Photosensitivity</td>
<td>reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td></td>
<td>Purpura</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Musculoskeletal, connective tissue and bone disorders** | | | | | |
| Arthralgia | Muscle twitching | | | | |
| | Myalgia | | | | |

| **Renal and urinary disorders** | | | | | |
| Frequent urination<sup>9</sup> | Dysuria | Urinary retention | Micturition disorder | | |

| **Reproductive system and breast disorders** | | | | | |
| Gynaecological bleeding<sup>11</sup> | Sexual dysfunction | Galactorrhoea | Priapism | | |
| Erectile dysfunction | | | | | |
| Ejaculation disorder<sup>10</sup> | | | | | |

| **General disorders and administration site conditions** | | | | | |
| Fatigue<sup>12</sup> | Feeling jittery | Malaise | Mucosal haemorrhage | | |
| | Chills | Feeling abnormal | Feeling cold | Feeling hot | |

| **Investigations** | Weight decreased | Abnormal liver function tests | | | |

---

1Includes anorexia
2Includes early morning awakening, initial insomnia, middle insomnia
3Includes nightmares
4Includes loss of libido
5Includes anorgasmsia
6Includes hypersonnia, sedation
7Includes hot flush
8Includes erythema, exfoliative rash, heat rash, rash, rash erythematos, rash follicular, rash generalized, rash macular, rash macular-papular, rash morbilliform, rash papular, rash pruritic, rash vesicular, umbilical erythema rash
9Includes pollakiuria
10Includes ejaculation failure, ejaculation dysfunction, premature ejaculation, ejaculation delayed, retrograde ejaculation
11Includes cervix haemorrhage, uterine dysfunction, uterine bleeding, genital haemorrhage, menometrorrhagia, menorrhagia, metrorrhagia, polymenorrhea, postmenopausal haemorrhage, uterine haemorrhage, vaginal haemorrhage
12Includes asthenia
13Could progress to Stevens-Johnson syndrome or Toxic Epidermal Necrolysis (Lyell Syndrome)
14These symptoms may be due to underlying disease.

Cases of suicidal ideation and suicidal behaviour have been reported during fluoxetine therapy or early after treatment discontinuation (see section 4.4).
Bone fractures: Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to the risk is unknown.

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 the most 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). It is therefore advised that when FLUOXETINE treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 and section 4.4).

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 overdose, 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: selective serotonin reuptake inhibitor-ATC Code: N06AB03

Fluoxetine is a potent and highly selective serotonin (5-hydroxytryptamine, 5HT) reuptake inhibitor.

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 of 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 some patients.

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

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

Two placebo-controlled studies were conducted in patients meeting pre-menstrual dysphoric disorder (PMDD) diagnostic criteria according to DSM-IV. Patients were included if they had symptoms of sufficient severity to impair social and occupational function and relationships with others. Patients using oral contraceptives were excluded. In the first study of continuous 20mg daily dosing for 6
cycles, improvement was observed in the primary efficacy parameter (irritability, anxiety and dysphoria). In the second study, with intermittent luteal phase dosing (20mg daily for 14 days) for 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):** Fluoxetine 60mg capsules are not licensed for use in the treatment of children or adolescents under the age of 18 years. 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 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 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 readily absorbed from the gastrointestinal tract after oral administration. The bioavailability is not affected by food intake.

**Distribution:** Fluoxetine is extensively bound to plasma proteins (about 95%) and it is widely distributed (volume of distribution: 20-40 l/kg). Steady-state plasma concentrations are achieved after dosing for several weeks. Steady-state concentrations after prolonged dosing are similar to concentrations seen at 4 to 5 weeks.

**Metabolism:** Fluoxetine has a non-linear pharmacokinetic profile with first pass liver effect. Maximum plasma concentration is generally achieved 6 to 8 hours after administration. Fluoxetine is extensively metabolised by the polymorphic enzyme CYP2D6. Fluoxetine is primarily metabolised by the liver to the active metabolite norfluoxetine (desmethylfluoxetine), by desmethylation.

**Elimination:** The elimination half-life of fluoxetine is 4 to 6 days and for norfluoxetine 4 to 16 days. These long half-lives are responsible for persistence of the drug for 5-6 weeks after discontinuation. Excretion is mainly (about 60%) via the kidney. Fluoxetine is secreted into breast milk.

**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). 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

There is no evidence of carcinogenicity or mutagenicity from in vitro or animal studies.

In a juvenile toxicology study in CD rats, administration of 30mg/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 30mg/kg/day) and females (30mg/kg/day). The significance of these findings in humans is unknown.

In a 2-generation rat reproduction study, fluoxetine did not produce adverse effects on the mating or fertility of rats, was not teratogenic, and did not affect growth, development, or reproductive parameters of the offspring. The concentrations in the diet provided doses approximately equivalent to 1.5, 3.9 and 9.7 mg fluoxetine/kg body weight.

Male mice treated daily for 3 months with fluoxetine in the diet at a dose approximately equivalent to 31 mg/kg showed a decrease in testis weight and hypospermatogenesis. However, this dose level exceeded the maximum-tolerated dose (MTD) as significant signs of toxicity were seen.

Rats administered 30mg/kg also had decreased femur lengths compared with controls and skeletal muscle degeneration, necrosis and regeneration. At 10mg/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 3mg/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 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 been established.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Capsule Contents:
- Pregelatinised maize starch
- Dimeticone

Capsule Shell Contents:
- Gelatin
- Quinoline yellow (E104)
- Sunset Yellow (E110),
- Titanium dioxide (E171)
- Sodium lauril sulfate
- Purified water

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions

6.5 Nature and contents of container
10, 14, 20,28,30,50,56,60,70, 90, 98, 100 or 500 Capsules packed in a blister pack consisting of clear PVC film with a backing aluminium foil.

Not all pack sizes may be marketed
6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Bristol Laboratories Limited,
Unit 3, Canalside,
Northbridge Road
Berkhamsted
Herts HP4 1EG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 17907/0387

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
28/06/2012

10 DATE OF REVISION OF THE TEXT
28/06/2012
Fluoxetine 20 mg and 60 mg Hard Capsules

Fluoxetine may possibly change the blood level of these medicines, your doctor may have to increase or decrease the dose of Fluoxetine.

1. What Fluoxetine capsules are and what they are used for

Fluoxetine capsules are used in adults to treat depression, anxiety, panic disorder, obsessive-compulsive disorder, and eating disorders. Fluoxetine is also used to treat depression in children and adolescents aged 12 years and older who have been previously treated with an antidepressant.

2. What you need to know before you take Fluoxetine capsules

- Do not take Fluoxetine if you are:
  - allergic to the active substance, fluoxetine (see section 5.2), or any of the other ingredients of Fluoxetine.
  - pregnant or breastfeeding.

- Do not take Fluoxetine if you are taking any other medicines that may interact with Fluoxetine.

- Do not take Fluoxetine if you have any of the following medical conditions:
  - heart disease
  - diabetes
  - kidney or liver problems

- Do not take Fluoxetine if you are on any other medicine that may interact with Fluoxetine.

- Do not take Fluoxetine if you have had a stroke or are at risk of having one.

- Do not take Fluoxetine if you have had recent surgery or are at risk of having surgery.

- Do not take Fluoxetine if you have had a recent myocardial infarction or are at risk of having one.

- Do not take Fluoxetine if you have had a recent cerebrovascular accident or are at risk of having one.

- Do not take Fluoxetine if you have had a recent severe respiratory condition or are at risk of having one.

- Do not take Fluoxetine if you have had a recent severe psychiatric condition or are at risk of having one.

- Do not take Fluoxetine if you have had a recent severe gastrointestinal condition or are at risk of having one.

- Do not take Fluoxetine if you have had a recent severe neurological condition or are at risk of having one.

- Do not take Fluoxetine if you have had a recent severe endocrine condition or are at risk of having one.

- Do not take Fluoxetine if you have had a recent severe cardiovascular condition or are at risk of having one.

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Fluoxetine 20 mg and 60 mg Hard Capsules

Fluoxetine is a serotonin reuptake inhibitor used to treat depression and other mental health conditions. It works by increasing the amount of serotonin in the brain.

3. How to take Fluoxetine Capsules

Always take Fluoxetine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The capsules should be swallowed whole with a glass of water. Do not break or chew the capsules.

If you forget to take a dose:

Do not take a double dose or extra dose. If you are taking more than 1 capsule a day, you should take it at the times prescribed by your doctor. If you remember later, take it as soon as you can. If this is less than 2 hours before your next dose, you should skip the missed dose.

If you take too much Fluoxetine:

See your doctor or go to A&E immediately. Take the capsule to the hospital. The doctor may want to wash your stomach if it is more than 2 hours since you took the drug. If you have taken more than 2 capsules, you should also have an antidote hour later.

If you or anyone else take Fluoxetine and has an overdose:

See your doctor or go to A&E immediately. Take the capsule to the hospital. The doctor may want to wash your stomach if it is more than 2 hours since you took the drug. If you have taken more than 2 capsules, you should also have an antidote hour later.

If you think you have taken Fluoxetine too much:

See your doctor or go to A&E immediately. Take the capsule to the hospital. The doctor may want to wash your stomach if it is more than 2 hours since you took the drug. If you have taken more than 2 capsules, you should also have an antidote hour later.

4. Possible side effects

Like all medicines, Fluoxetine can cause side effects, although not everyone gets them. If you have any side effects, contact your doctor or pharmacist, even if you are not sure they are side effects of Fluoxetine. The most common side effects are:

- Feeling anxious or depressed
- Feeling nervous
- Shaking of the hands, neck, or feet
- Difficulty concentrating
- Headache
- Temporary sexual problems
- Skin rash
- Vomiting
- Sweating
- Stomach pain
- Constipation
- Diarrhoea
- Changes in appetite
- Changes in weight
- Muscle pain
- Numbness or tingling
- Dizziness
- Fast or slow heartbeat
- Swelling of the legs or ankles
- Swelling of the face, hands, or feet
- Difficulty sleeping
- Insomnia
- Headache
- Nausea
- Vomiting

If you get any unusual side effects while taking Fluoxetine, contact your doctor or pharmacist immediately. If any of the side effects are serious or persistent, see your doctor at once.

5. How to store Fluoxetine Capsules

Store the capsules in a cool, dry place. Keep them out of reach of children. Do not mix with other drugs or foods. Do not freeze the capsules. Do not clean the capsules with water or alcohol.

6. Contents of the pack and other information

What Fluoxetine Capsules contain

Each Fluoxetine 20 mg capsule contains 20 mg Fluoxetine hydrochloride. Each Fluoxetine 60 mg capsule contains 60 mg Fluoxetine hydrochloride.

Fluoxetine 20 mg and 60 mg tablets are round and green. They are coated with a film to make them easier to swallow. They are also coated with a yellow film to make them easier to distinguish from other tablets.

Fluoxetine is a prescription-only medicine. It is available from your pharmacist or doctor.

If you have any questions about Fluoxetine, please contact your doctor or pharmacist.

This is a summary of the manufacturer's leaflet. For full information, please read the leaflet provided with your capsules.

UK/H/4687/001-2/DC
Module 4
Labelling
Fluoxetine 20 mg and 60 mg Hard Capsules

UK/H/4687/001-2/DC

Batch details

Artwork Same Size
Size: 82 x 60 x 64 mm
Layout No.: BFQOS-60799
Keyooe Design
24 05 12

Pl. 17907/0387
POM

Bristol Laboratories Ltd.,
Brislington, Har, NP4 1EG, UK.
Module 5
Scientific discussion during initial procedure

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Fluoxetine 20 mg and 60 mg Hard Capsules (PL 17907/0386-7; UK/H/4687/001-2/DC) could be approved. These are prescription-only medicines (POM) used to treat the following conditions in adults:

- major depressive episodes,
- obsessive compulsive disorder,
- bulimia nervosa: Fluoxetine is used alongside psychotherapy for the education of binge-eating and purging.

In children and adolescents age 8 years and above, Fluoxetine 20 mg Hard Capsules are used to treat moderate to severe major depressive disorder, if the depression does not respond to psychological therapy after 4-6 sessions. Antidepressant medication should be offered to a child or young person with moderate to severe major depressive disorder only in combination with psychological therapy.

Fluoxetine 60mg Hard capsules should not be used in the treatment of children and adolescents under the age of 18 years as safety and efficacy have not been established.

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Spain and Ireland as Concerned Member States (CMS). The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications referring to the innovator medicinal products Prozac 20 mg and 60 mg Capsules (Eli Lilly and Company Limited, UK) first licensed in the UK on 25 November 1998.

The active ingredient, fluoxetine (as fluoxetine hydrochloride) is a selective inhibitor of serotonin reuptake, and this 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.

No new non-clinical data were submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

Two single-dose, bioequivalence studies were submitted to support these applications, comparing the applicant’s test product Fluoxetine 60 mg Capsules (manufactured by Ipca Laboratories Limited, India) with the reference products 3 x 20 mg Prozac 20 mg Hard Capsules (Eli Lilly and Company Limited, UK) and Fluoxetine 60 mg Capsules (Generic UK Limited, UK). The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence studies, no new clinical data were submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of these products. For manufacturing sites within the Community, the RMS has accepted copies of
current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates, satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the applications could be approved at the end of procedure (Day 210) on 23 May 2012. After a subsequent national phase, licences were granted in the UK on 28 June 2012.
### II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | UK/H/4687/001/DC: Fluoxetine 20 mg Hard Capsules  
| UK/H/4687/002/DC: Fluoxetine 60 mg Hard Capsules |
| Name(s) of the active substance (INN) | Fluoxetine hydrochloride |
| Pharmacotherapeutic classification (ATC code) | Selective serotonin reuptake inhibitor (ATC code: N06AB03) |
| Pharmaceutical form and strength(s) | Hard capsule; 20 mg and 60 mg |
| Reference numbers for the Decentralised Procedure | UK/H/4687/001-2/DC |
| Reference Member State (RMS) | United Kingdom |
| Concerned Member States (CMS) | Spain and Ireland |
| Marketing Authorisation Number(s) | PL 17907/0386-7 |
| Name and address of the authorisation holder | Bristol Laboratories Limited, Unit 3, Canalside, Northbridge Road, Berkhamsted, Herts HP4 1EG, United Kingdom |
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

INN:  Fluoxetine hydrochloride
Chemical Name:  (3RS)-N-methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]-propan-1-amine hydrochloride
Molecular formula:  C_{17}H_{18}F_{3}NO. HCl
Structure:

Molecular mass:  345.8
Appearance:  A white or almost white crystalline powder
Solubility:  Freely soluble in methanol, sparingly soluble in water and methylene chloride.

Fluoxetine hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance fluoxetine hydrochloride are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients in the capsule fill and the capsule shell, namely pregelatinised maize starch, dimeticone, gelatin, sodium lauril sulphate (60 mg strength capsule only), quinoline yellow (E104), sunset yellow (E110), titanium dioxide (E171), brilliant blue (E133, 20 mg strength capsule only) and purified water. Appropriate justifications for the inclusion of each excipient have been provided.

With the exception of brilliant blue (E133), quinoline yellow (E104) and sunset yellow (E110), all excipients comply with their respective European Pharmacopoeia monographs. Brilliant blue (E133), quinoline yellow (E104) and sunset yellow (E110) are controlled to suitable in-house specifications and are also in compliance with current EU Directives concerning the use of colouring agents. Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

With the exception of gelatin, none of the excipients contain materials of animal or human origin. A Certificate of Suitability from the European Directorate for the Quality of Medicines (EDQM) has been provided for the supplier of gelatin, showing compliance with current guidelines concerning the minimising of TSE/BSE transmission.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, stable products that could be considered generic medicinal products of the reference products Prozac 20 mg and 60 mg Hard Capsules (Eli Lilly).

Suitable pharmaceutical development data have been provided for these applications.
Comparative *in-vitro* dissolution and impurity profiles have been provided for these products and their respective reference products.

**Manufacturing Process**
Satisfactory batch formulae have been provided for the manufacture of all strengths of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with pilot-scale batches and has shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation studies on the first 3 full-scale production batches.

**Control of Finished Product**
The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

**Container Closure System**
The tablets are packaged in blisters consisting of clear polyvinylchloride (PVC) film with a backing of aluminium foil. These are packed into cardboard cartons with Patient Information Leaflets in pack sizes of 10, 14, 20, 28, 30, 50, 56, 60, 70, 90, 98, 100 and 500 hard capsules.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with current European regulations concerning materials in contact with foodstuff.

**Stability**
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years has been proposed, with no special storage conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

**Bioequivalence/Bioavailability**
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence studies. The bioequivalence studies are discussed in Section III.3, Clinical Aspects.

**Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling**
The SmPCs, PIL and labelling are satisfactory from a pharmaceutical perspective.

A user consultation with target patient groups (‘user test’) on the package information leaflet has been performed on the basis of a bridging report making reference to the successful user-testing of the ‘parent’ PIL for Venlafaxine 37.5 mg and 75 mg Tablets (PL 17907/0250-0251, Bristol Pharmaceuticals Limited), which belongs to the same pharmacotherapeutic group (selective serotonin reuptake inhibitors) as Fluoxetine 20 mg and 60 mg Hard Capsules. The bridging is accepted, without the need for further testing.
MAA (Marketing Authorisation Application) Forms
All aspects of the MAA forms are satisfactory from a pharmaceutical perspective.

Expert Report (Quality Overall Summary)
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of Marketing Authorisations is recommended.
III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of fluoxetine hydrochloride are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT (NON-CLINICAL OVERVIEW)
The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

ENVIRONMENTAL RISK ASSESSMENT
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As these products are intended for generic substitution with products that are already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION
The grant of Marketing Authorisations is recommended.
**III.3 CLINICAL ASPECTS**

The clinical pharmacology of fluoxetine hydrochloride is well-known. With the exception of data from the bioequivalence studies detailed below, no new pharmacodynamic or pharmacokinetic data are provided or required for these applications.

In support of the applications, the Marketing Authorisation Holder submitted the following bioequivalence studies:

**Study 1**

An open label, single-dose, randomised, two-period, two-treatment, two-sequence, crossover study comparing the pharmacokinetics of the test product Fluoxetine 60 mg capsules (manufactured by Ipca Laboratories Limited, India) and the reference product 3 x 20 mg Prozac 20 mg Hard Capsules (Eli Lilly and Company Limited, UK) in healthy adult subjects under fasting conditions.

The subjects were administered 60 mg of either the test (1 x 60 mg capsule) or the reference product (3 x 20 mg capsules) with 240 ml of water, after at least a 10-hour overnight fast. As Prozac 60mg Hard Capsules (Eli Lilly and Company Limited, UK) was not available in the EU market at the time of this bioequivalence study, the choice of 3 x 20 mg Prozac 20mg Hard Capsules as reference product for the bioequivalence study is considered acceptable. Blood samples were collected before and up to and including 672 hours after each administration. The washout period between the treatment phases was 63 days. The pharmacokinetic results are presented below:

### Pharmacokinetic parameters (geometric means, ratios and confidence intervals [CI]) of fluoxetine

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Fluoxetine 60 mg (Test)</th>
<th>Prozac 20 mg (3x20 mg) (Reference)</th>
<th>Test/Ref Ratio</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>51.000</td>
<td>52.764</td>
<td>0.97</td>
<td>0.93–1.00</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng.hr/mL)</td>
<td>3118.027</td>
<td>3143.495</td>
<td>0.99</td>
<td>0.96–1.03</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (ng.hr/mL)</td>
<td>3191.633</td>
<td>3226.067</td>
<td>0.99</td>
<td>0.95–1.03</td>
</tr>
</tbody>
</table>

*<i>C<sub>max</sub></i>* maximum plasma concentration  
*AUC<sub>0-t</sub>* area under the plasma concentration-time curve from time zero to t hours  
*AUC<sub>0-inf</sub>* area under the plasma concentration-time curve from time zero to infinity  
Ratios and 90% CI calculated from log-transformed data

### Pharmacokinetic parameters (geometric means, ratios and confidence intervals [CI]) of norfluoxetine

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Fluoxetine 60 mg (Test)</th>
<th>Prozac 20 mg (3x20 mg) (Reference)</th>
<th>Test/Ref Ratio</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>34.377</td>
<td>34.430</td>
<td>1.00</td>
<td>0.96–1.04</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng.hr/mL)</td>
<td>10433.977</td>
<td>10729.215</td>
<td>0.97</td>
<td>0.94–1.01</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (ng.hr/mL)</td>
<td>11441.197</td>
<td>11699.230</td>
<td>0.98</td>
<td>0.95–1.01</td>
</tr>
</tbody>
</table>

*<i>C<sub>max</sub></i>* maximum plasma concentration  
*AUC<sub>0-t</sub>* area under the plasma concentration-time curve from time zero to t hours  
*AUC<sub>0-inf</sub>* area under the plasma concentration-time curve from time zero to infinity  
Ratios and 90% CI calculated from log-transformed data

The 90% confidence intervals of the test/reference ratio for AUC<sub>0-t</sub>, AUC<sub>0-inf</sub> and C<sub>max</sub> lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**). Thus, the data support the claim that the test product, Fluoxetine 60 mg capsules (manufactured by Ipca Laboratories Limited, India), is bioequivalent to the reference product, 3 x 20 mg Prozac 20 mg Hard Capsules (Eli Lilly and Company Limited, UK), under fasting conditions.
As the 20 mg and 60 mg strengths of the product meet all the criteria specified in the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), the results and conclusions from the bioequivalence study with the 60 mg capsule can be extrapolated to the 20 capsule strength.

**Study 2**

An open label, single-dose, randomised, two-period, two-treatment, two-sequence, crossover study comparing the pharmacokinetics of the test product Fluoxetine 60 mg Capsules (manufactured by Ipca Laboratories Limited, India) and the reference generic product Fluoxetine hydrochloride 60 mg Capsules (Generics (UK) Limited, UK) in healthy adult subjects under fasting conditions.

The subjects were administered one 60 mg capsule of either the test or the reference product with 240 ml of water, after at least a 10-hour overnight fast. Blood samples were collected before and up to and including 672 hours after each administration. The washout period between the treatment phases was 63 days. The pharmacokinetic results are presented below:

### Pharmacokinetic parameters (geometric means, ratios and confidence intervals [CI]) of fluoxetine

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Fluoxetine 60 mg (Test)</th>
<th>Fluoxetine 60 mg (Reference)</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>42.675</td>
<td>42.203</td>
<td>101.12</td>
<td>97.12-105.28</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-4&lt;/sub&gt; (ng.hr/mL)</td>
<td>3319.554</td>
<td>3246.360</td>
<td>102.25</td>
<td>97.25-107.52</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (ng.hr/mL)</td>
<td>3436.434</td>
<td>3362.036</td>
<td>102.21</td>
<td>97.26-107.42</td>
</tr>
</tbody>
</table>

*C<sub>max</sub>* maximum plasma concentration  
*AUC<sub>0-inf</sub>* area under the plasma concentration-time curve from time zero to infinity  
*AUC<sub>0-4</sub>* area under the plasma concentration-time curve from time zero to t hours  
Ratios and 90% CI calculated from log-transformed data

### Pharmacokinetic parameters (geometric means, ratios and confidence intervals [CI]) of norfluoxetine

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Fluoxetine 60 mg (Test)</th>
<th>Fluoxetine 60 mg (Reference)</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>19.497</td>
<td>19.984</td>
<td>97.56</td>
<td>92.24-103.19</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-4&lt;/sub&gt; (ng.hr/mL)</td>
<td>6884.612</td>
<td>6928.306</td>
<td>99.37</td>
<td>96.37-102.46</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (ng.hr/mL)</td>
<td>7706.950</td>
<td>7789.605</td>
<td>98.94</td>
<td>95.29-102.73</td>
</tr>
</tbody>
</table>

*C<sub>max</sub>* maximum plasma concentration  
*AUC<sub>0-inf</sub>* area under the plasma concentration-time curve from time zero to infinity  
*AUC<sub>0-4</sub>* area under the plasma concentration-time curve from time zero to t hours  
Ratios and 90% CI calculated from log-transformed data

Bioequivalence was also demonstrated in this study. However, the use of a generic product as reference product is not appropriate for an abridged application and thus the data was considered as supportive only and not pivotal to the overall conclusion.

**Efficacy**

The efficacy of fluoxetine hydrochloride is well-known. No new efficacy data have been submitted and none are required for applications of this type.
SAFETY
With the exception of the safety data generated during the bioequivalence studies, no new safety data were submitted and none are required for applications of this type. No new or unexpected safety issues arose during the bioequivalence studies.

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN
The RMS considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a Risk Management Plan for these products.

SUMMARIES OF PRODUCT CHARACTERISTICS (SmPCs), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
The SmPCs, PIL and labelling are acceptable from a clinical perspective. The SmPCs are consistent with those for the reference products (Prozac 20 mg and 60 mg Hard Capsules, Eli Lilly and Company Limited, UK). The PIL is consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with the current guidelines.

CLINICAL EXPERT REPORT (CLINICAL OVERVIEW)
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

CONCLUSION
The grant of Marketing Authorisations is recommended.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The quality characteristics of Fluoxetine 20 mg and 60 mg Capsules (PL 17907/0386-7; UK/H/4687/001-2/DC) are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of fluoxetine hydrochloride are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence studies, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s 60 mg strength capsule and the originator reference product 3 x 20 mg Prozac 20 mg Hard Capsules. As the 20 mg and 60 mg capsule strengths of the product meet the biowaiver criteria specified in the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), the results and conclusions from the bioequivalence studies with the 60 mg strength can be extrapolated to the 20 mg capsule strength.

SAFETY
With the exception of the safety data from the bioequivalence studies, no new data were submitted and none are required for applications of this type. As the safety profile of fluoxetine hydrochloride is well known, no additional data were required. No new or unexpected safety concerns arose from the bioequivalence studies.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory, and consistent with those for the reference products, where appropriate, along with current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with fluoxetine hydrochloride is considered to have demonstrated the therapeutic value of the products. The benefit/risk balance is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
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