The European Agency for the Evaluation of Medicinal Products
Pre-authorisation Evaluation of Medicines for Human Use

London, 18 June 2003
EMEA/CPMP/3263/03

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

SUMMARY INFORMATION ON REFERRAL OPINION FOLLOWING ARBITRATION

PURSUANT TO ARTICLE 30 OF COUNCIL DIRECTIVE 2001/83/EC FOR

Prozac and associated names

International NonProprietary Name (INN): fluoxetine

BACKGROUND INFORMATION

Fluoxetine is a Selective Serotonin Re-uptake Inhibitor (SSRI). This compound is granted a licence in many countries for Major Depressive Disorder and/or the following indications: Obsessive Compulsive Disorder (OCD), Bulimia Nervosa (BN) and Pre-Menstrual Dysphoric Disorder (PMDD).

From the registrations in Member States, different Summaries of Product Characteristics have been issued, based on national, divergent decisions. On 4 July 2000, France presented to the EMEA a referral under Article 30 of Directive 2001/83/EC[1].

The referral procedure started on 1 March 2001 in order to harmonise the Summaries of Product Characteristics (SPC) within the Member States and Norway and Iceland. The CPMP having considered the Rapporteur and the Co-Rapporteur assessment reports, scientific discussion within the Committee and comments from the Marketing Authorisation Holders, was of the opinion that the benefit/risk ratio of fluoxetine is considered to be favourable for the agreed indications. The CPMP issued a positive opinion, on 19 September 2002, recommending the harmonisation of the SPC for Prozac and associated names. The grounds for referral are appended to this report.

An overall summary of the scientific evaluation is provided together with the amended summary of product characteristics.

A Decision was issued by the European Commission on 23 May 2003.

[1] Corresponding to Article 11 of Directive 75/319/EEC, for referrals presented before 18 December 2001

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.eu.int http://www.emea.eu.int

SCIENTIFIC CONCLUSIONS

Overall Summary of the Scientific Evaluation of Prozac and Associated names

- Quality issues

No significant issues relating to Quality were identified.

The pharmaceutical particulars of the SPC were harmonised, except the sections, which need to be introduced nationally by the Member States when implementing the harmonised SPC (sections 6).

- Efficacy issues

The divergences that previously existed across the SPCs of EU Member States included:

Section 4.1. Therapeutic indications

For the majority of the EU Member States, the approved indications for Prozac (and associated names) is the treatment of Major Depressive Disorder, however there was a disharmony in the labelling relating to;

- The indication Obsessive-Compulsive Disorder (OCD), an indication currently authorised in 13 EU countries, not submitted in Belgium and Luxembourg and rejected in Netherlands and Denmark.
- The indication Bulimia Nervosa (BN), an indication currently authorised in 14 EU countries, not submitted in Belgium and Luxembourg and rejected in France.
- The indication Pre-Menstrual Dysphoric Disorder (PMDD), an indication currently authorised in 4 EU countries; not submitted in France; withdrawn in 3 EU countries (Finland, Netherlands and Norway); rejected in 3 EU countries (Germany, Spain and Denmark) and still pending in 6 EU countries.

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Prozac (and associated names), the CPMP was of the view that Major depressive episodes, Obsessive-compulsive disorder and Bulimia nervosa could be included in the 4.1 Therapeutic indications section of the harmonised SPC. However, the view of the CPMP was that the indication Pre-Menstrual Dysphoric Disorder (PMDD) could not be included in the Therapeutic indications section of the harmonised SPC for the following reasons:

CPMP noted that, PMDD is not a well-established disease entity across Europe. It is not listed in the International Classification of Diseases (ICD) and remains only a research diagnosis in DSM-IV. There was considerable concern that women with less severe pre-menstrual symptoms might erroneously receive a diagnosis of PMDD resulting in widespread inappropriate short and long-term use of fluoxetine.

Several deficiencies were identified with the following two pivotal, multicentre, placebo controlled, double blind, randomised trials that the MAH provided the CPMP in support of the PMDD indication:

1. Study C019: A *six-cycle continuous dosing trial* in women with LLPDD (earlier definition of PMDD). This was a three-arm trial with placebo, fluoxetine 20 mg/day and fluoxetine 60 mg/day arms. A total of 320 patients were randomised and 172 completed the study. The primary efficacy criterion was “Changes in luteal phase of Visual Analogue Scale (VAS) Mood -3 Average (for dysphoria, irritability and tension).”

2. Study HCJN: A *three-cycle intermittent dosing trial* (treatment administered daily only during luteal phase) in women with PMDD. This was a three-arm trial with placebo, fluoxetine 10 mg/day and fluoxetine 20 mg/day arms. A total of 260 patients were randomised and 216 completed the study.

The primary efficacy criterion was "change in the luteal phase average of Daily Record of Severity of Problems (DRSP) score".

In both studies, improvement was observed in the primary efficacy criterion in the group treated with fluoxetine 20 mg/day. These studies specifically excluded women using oral contraception. CPMP noted that oral contraception does not seem to abolish symptoms of PMDD and that symptomatology meeting the DSM-IV criteria for PMDD has been reported to occur in oral contraception users. It is therefore possible that fluoxetine may be extensively prescribed to a large sub-population of OC users with PMDD in whom efficacy and safety has not been investigated.

The DSM-IV diagnosis of PMDD requires the patient to have five or more of eleven diagnostic features including at least one of the four major criteria; depression, anxiety/tension, persistent anger/irritability, affective lability. CPMP noted that the primary efficacy measure in the six-cycle continuous trial (Study CO19) addressed only the first three of these major criteria (depression, anxiety and irritability) and did not address affective lability or any of the remaining seven minor criteria. Hence, the validity of the primary efficacy measure is questionable and does not allow any generalisable conclusions to be drawn from the results of this trial. Furthermore, a large number of drop-outs was observed (148 out of 320 patients randomised for the trial). The placebo effect (6%) was unusually low which may suggest that the population included in this trial were highly selected and may not represent the PMDD population seen in clinical practice. Therefore, the external validity of the trial is questionable.

As to the *three-cycle intermittent* trial (Study HCJN), the CPMP noted that neither a distinction between severe, moderate and mild PMDD nor a clear cut-off score for DRSP (Daily Record of Severity of Problems) determining a severe impairment, which might justify pharmacotherapy, were established.

PMDD is a chronic disorder: average onset of this disorder is 26 years of age and the symptoms often worsen over time. A relapse immediately after discontinuation of therapy would imply a very long treatment. Healthy women could be exposed to this treatment for up to 30 years, most of their reproductive lifetime. Therefore, in the view of the CPMP obtaining data on the efficacy and safety of fluoxetine from long term, randomized trials would be necessary. However, for the time being this data is lacking. Moreover, the development of tolerance to the effect of fluoxetine was not investigated in either of the two studies.

The outstanding issues regarding the indication PMDD were addressed by the MAH during a hearing before the CPMP on 24 July 2002. The major points addressed by the MAH were; the diagnosis and severity of PMDD, evidence of long term efficacy of fluoxetine in PMDD, relapses and withdrawal after cessation of fluoxetine therapy and concomitant use of oral contraceptives. Following the presentation, the representatives of the MAH and the CPMP members and experts discussed the outstanding issues.

The CPMP concluded that, since the two studies provided by the MAH did not allow definitive conclusions to be drawn particularly concerning the optimum dosing schedule (continuous versus intermittent dosing), the duration of treatment or the long-term efficacy and safety, the PMDD indication could not be included in the Therapeutic indications section. Nevertheless, the submitted two pivotal trials should be described under section 5.1. Pharmacodynamic properties of the harmonised SPC.

The CPMP considered that the following was the most suitable harmonised Section 4.1 indications text:

4.1 Therapeutic indications

Major depressive episodes.

Obsessive-compulsive disorder.

Bulimia nervosa: 'Tradename' is indicated as a complement of psychotherapy for the reduction of binge-eating and purging activity.

Section 4.2. Posology and method of administration

The MAH was requested to substantiate scientifically the divergent information across member states and justify a proposed common wording.

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Prozac (and associated names) the following was considered to be the most suitable harmonised Section 4.2 Posology text:

4.2 Posology and method of administration

For oral administration to adults only.

Major depressive episodes

Adults and the elderly: 20 mg/day to 60 mg/day. A dose of 20 mg/day is recommended as the initial dose. Although there may be an increased potential for undesirable-effects at higher doses, a dose increase may be considered after three weeks if there is no response.

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

Obsessive-compulsive disorder - Adults and the elderly: 20 mg/day to 60 mg/day. A dose of 20 mg/day is recommended as the initial dose. Although there may be an increased potential for side-effects at higher doses, a dose increase may be considered after two weeks if there is no response. If no improvement is observed within 10 weeks, treatment with fluoxetine should be reconsidered. If a good therapeutic response has been obtained, treatment can be continued at a dosage adjusted on an individual basis. While there are no 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 60 mg/day is recommended.
Long-term efficacy (more than 3 months) has not been demonstrated in bulimia nervosa.

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

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

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

The capsule and liquid dosage forms are bioequivalent.

Children: The use of fluoxetine in children and adolescents (under the age of 18) is not recommended, as safety and efficacy have not been established.

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

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

- Safety issues

Section 4.3. Contra-indications
The MAH was requested to propose and scientifically justify a common EU wide approach as the contraindications text was considered to differ to a large extent between Member States especially relating to:

- The contraindication associated with pimozide (approved only in France).

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Prozac (and associated names), the most suitable harmonised Section 4.3 Contraindications text was approved (See Annex III). The text approved in the harmonised SPC is not so dissimilar to the currently approved SPCs that it will significantly change clinical practices.

Section 4.4. Special warnings and precautions for use

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Prozac (and associated names),, the most suitable harmonised Section 4.4 Special Warnings and Precautions for Use text was approved (See Annex III). The text in the harmonised SPC is not so dissimilar to the currently approved SPCs that it will significantly change clinical practices

All other sections of the SPC were harmonised as a result of the referral procedure (except See Below; Administrative Issues).

- Administrative issues

Other sections of the SPC which were not harmonised and which need to be introduced nationally by the Member States when implementing the harmonised SPC are the following: MAH, MA number, date of first authorisation/renewal of authorisation, Date of revision of the text.

Benefit/Risk considerations
Based on the documentation submitted by the MAH and the scientific discussion within the Committee, the CPMP considered that the benefit/risk ratio of Prozac (and associated names), is favourable for use relating to Major depressive episodes, Obsessive-compulsive disorder and Bulimia nervosa.

GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS

Whereas,

- the scope of the referral was the harmonisation of the Summaries of Products Characteristics,

- the Summary of Products Characteristic proposed by the Marketing Authorisation Holders has been assessed based on the documentation submitted and the scientific discussion within the Committee,

the CPMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics is set out in Annex III of the Opinion. The major divergences identified at the start of the referral have been resolved.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS

Note: This SPC is the one that was annexed to the Commission Decision concerning this referral for arbitration; the text was valid at that time. It is not subsequently maintained or updated by the EMEA, and therefore may not necessarily represent the current text.

1. NAME OF THE MEDICINAL PRODUCT

<Prozac and associated names – see Annex I> <strength> <pharmaceutical form>

(To be implemented nationally)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each <capsule> <dispersible tablet> contains <strength> fluoxetine.

Each 5 ml of <oral solution> <reconstituted powder for suspension> contains 20 mg fluoxetine

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Dispersible tablet

Capsule

Oral solution

Powder for oral suspension

(Description of pharmaceutical form to be implemented nationally)

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Major depressive episodes.

Obsessive-compulsive disorder.

Bulimia nervosa: 'Invented name' is indicated as a complement of psychotherapy for the reduction of binge-eating and purging activity.

4.2. Posology and method of administration

For oral administration to adults only.

Major depressive episodes
Adults and the elderly: 20 mg/day to 60 mg/day. A dose of 20 mg/day is recommended as the initial dose. Although there may be an increased potential for undesirable-effects at higher doses, a dose increase may be considered after three weeks if there is no response.

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

Obsessive-compulsive disorder - Adults and the elderly: 20 mg/day to 60 mg/day. A dose of 20 mg/day is recommended as the initial dose. Although there may be an increased potential for side-effects at higher doses, a dose increase may be considered after two weeks if there is no response. If no improvement is observed within 10 weeks, treatment with fluoxetine should be reconsidered. If a good therapeutic response has been obtained, treatment can be continued at a dosage adjusted on an

individual basis. While there are no 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 60 mg/day is recommended.
Long-term efficacy (more than 3 months) has not been demonstrated in bulimia nervosa.

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

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

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

The capsule and liquid dosage forms are bioequivalent.

Children: The use of fluoxetine in children and adolescents (under the age of 18) is not recommended, as safety and efficacy have not been established.

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

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

4.3. Contraindications

Hypersensitivity to fluoxetine or to any of its excipients.

Monoamine Oxidase Inhibitors : Cases of serious and sometimes fatal reactions have been reported in patients receiving an 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.

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 is not recommended. Treatment with fluoxetine can be initiated the following day after discontinuation of a reversible MAOI (e.g. moclobemide).

4.4. Special warnings and special precautions for use

Warnings

Rash and allergic reactions: Rash, anaphylactoid events and progressive systemic events, sometimes serious (involving skin, kidney, liver or lung) have been reported. Upon the appearance of rash or of other allergic phenomena for which an alternative aetiology cannot be identified, fluoxetine should be discontinued.

Precautions

Seizures: Seizures are a potential risk with antidepressant drugs. Therefore, as with other antidepressants, fluoxetine should be introduced cautiously in patients who have a history of seizures. Treatment should be discontinued in any patient who develops seizures or where there is an increase in seizure frequency. Fluoxetine should be avoided in patients with unstable seizure disorders/epilepsy and patients with controlled epilepsy should be carefully monitored.

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

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

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

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

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

Suicide: As improvement may not occur during the first few weeks of treatment, in common with all antidepressants, patients should be closely monitored during this period. The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. It is general clinical experience with all therapies for depression that the risk of suicide may increase in the early stages of recovery.

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

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.

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

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

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

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

Phenytoin: Changes in blood levels have been observed when combined with fluoxetine. In some cases manifestations of toxicity have occurred. Consideration should be given to using conservative titration schedules of the concomitant drug and to monitoring clinical status.

Serotonergic drugs: Co-administration with serotonergic drugs (e.g. tramadol, triptans) may increase the risk of serotonin syndrome. Use with triptans carries the additional risk of coronary vasoconstriction and hypertension.

Lithium and tryptophan: There have been reports of serotonin syndrome when SSRIs have been given with lithium or tryptophan and, therefore, the concomitant use of fluoxetine with these drugs should be undertaken with caution. When fluoxetine is used in combination with lithium, closer and more frequent clinical monitoring is required.

CYP2D6 isoenzyme: Because fluoxetine's metabolism (like tricyclic antidepressants and other selective serotonin antidepressants) involves the hepatic cytochrome CYP2D6 isoenzyme system, concomitant therapy with drugs also metabolised by this enzyme system may lead to drug interactions. Concomitant therapy with drugs predominantly metabolised by this isoenzyme, and which have a narrow therapeutic index (such as flecainide, encainide, carbamazepine and tricyclic antidepressants), should be initiated at or adjusted to the low end of their dose range. This will also apply if fluoxetine has been taken in the previous 5 weeks.

Oral anticoagulants: Altered anti-coagulant effects (laboratory values and/or clinical signs and symptoms), with no consistent pattern, but including increased bleeding, have been reported uncommonly when fluoxetine is co-administered with oral anticoagulants. Patients receiving warfarin therapy should receive careful coagulation monitoring when fluoxetine is initiated or stopped. (see 'Precautions', 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, which may result in an increase of undesirable effects.

4.6. Pregnancy and lactation

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

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

4.7. Effects on ability to drive and use machines

Although fluoxetine has been shown not to affect psychomotor performance in healthy volunteers, any psychoactive drug may impair judgement or skills. Patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.

4.8. Undesirable effects

Undesirable effects may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.

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

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

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

Nervous system: Headache, sleep abnormalities (e.g. abnormal dreams, insomnia), dizziness, anorexia, fatigue (e.g. somnolence, drowsiness), euphoria, transient abnormal movement (e.g., twitching, ataxia, tremor, myoclonus), seizures and psychomotor restlessness. Hallucinations, manic reaction, confusion, agitation, anxiety and associated symptoms (e.g. nervousness), impaired concentration and thought process (e.g. depersonalisation), panic attacks (these symptoms may be due to the underlying disease), very rarely serotonin syndrome.

Urogenital system: Urinary retention, urinary frequency

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

Miscellaneous: Alopecia, yawn, abnormal vision (e.g., blurred vision, mydriasis), sweating, vasodilatation, arthralgia, myalgia, postural hypotension, ecchymosis. Other haemorrhagic

manifestations (e.g., gynaecological haemorrhages, gastrointestinal bleedings and other cutaneous or mucous bleedings) have been reported rarely (see 'Precautions', Haemorrhage).

Hyponatraemia: Hyponatraemia (including serum sodium below 110 mmol/l) has been rarely reported and appeared to be reversible when fluoxetine was discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone secretion. The majority of reports were associated with older patients, and patients taking diuretics or otherwise volume depleted.

Respiratory system: Pharyngitis, dyspnoea. Pulmonary events (including inflammatory processes of varying histopathology and/or fibrosis) have been reported rarely. Dyspnoea may be the only preceding symptom.

When stopping treatment, withdrawal symptoms have been reported in association with SSRIs, although the available evidence does not suggest this is due to dependence. Common symptoms include dizziness, paraesthesia, headache, anxiety and nausea, the majority of which are mild and self-limiting. Fluoxetine has been only rarely associated with such symptoms. Plasma fluoxetine and norfluoxetine concentrations decrease gradually at the conclusion of therapy, which makes dosage tapering unnecessary in most patients.

4.9. Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Fluoxetine is a selective inhibitor of serotonin reuptake, and this probably accounts for the mechanism of action. Fluoxetine has practically no affinity to other receptors such as α_1-, α_2-, and β-adrenergic serotonergic; dopaminergic; histaminergic$_1$; muscarinic; and GABA receptors.

Major depressive episodes: Clinical trials in patients with major depressive episodes have been conducted versus placebo and active controls. 'Invented name' has been shown to be significantly more effective than placebo as measured by the Hamilton Depression Rating Scale (HAM-D). In these studies, 'Invented name' produced a significantly higher rate of response (defined by a 50% decrease in the HAM-D score) and remission, compared to placebo.

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

Bulimia nervosa: In short term trials (under 16 weeks), in out-patients fulfilling DSM-III-R-criteria for bulimia nervosa, fluoxetine 60 mg/day was shown to be significantly more effective than placebo for

the reduction of bingeing and purging activities. However, for long-term efficacy no conclusion can be drawn.

Two placebo-controlled studies were conducted in patients meeting Pre-Menstrual Dysphoric Disorder (PMDD) diagnostic criteria according to DSM-IV. Patients were included if they had symptoms of sufficient severity to impair social and occupational function and relationships with others. Patients using oral contraceptives were excluded. In the first study of continuous 20 mg daily dosing for 6 cycles, improvement was observed in the primary efficacy parameter (irritability, anxiety and dysphoria). In the second study, with intermittent luteal phase dosing (20 mg daily for 14 days) for 3 cycles, improvement was observed in the primary efficacy parameter (Daily Record of Severity of Problems score). However, definitive conclusions on efficacy and duration of treatment cannot be drawn from these studies.

5.2. Pharmacokinetic properties

Absorption
Fluoxetine is well absorbed from the gastrointestinal tract after oral administration. The bioavailability is not affected by food intake.

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

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

Elimination
The elimination half-life of fluoxetine is 4 to 6 days and for norfluoxetine 4 to16 days. These long half-lives are responsible for persistance of the drug for 5-6 weeks after discontinuation. Excretion is mainly (about 60%) via the kidney. Fluoxetine is secreted into breast milk.

At-risk populations
- Elderly:
  Kinetic parameters are not altered in healthy elderly when compared to younger subjects
- Hepatic insufficiency:
  In case of hepatic insufficiency (alcoholic cirrhosis), fluoxetine and norfluoxetine half-lives are increased to 7 and 12 days, respectively. A lower or less frequent dose should be considered.
- Renal insufficiency:
  After single-dose administration of fluoxetine in patients with mild, moderate or complete (anuria) renal insufficiency, kinetic parameters have not been altered when compared to healthy volunteers. However, after repeated administration, an increase in steady-state plateau of plasma concentrations may be observed.

5.3. Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

(to be implemented nationally)

6.2. Incompatibilities

(to be implemented nationally)

6.3. Shelf life

(to be implemented nationally)

6.4. Special precautions for storage

(to be implemented nationally)

6.5. Nature and contents of container

(See Annex I - to be implemented nationally)

Not all pack sizes may be marketed.

6.6. Instructions for use and handling

(to be implemented nationally)

7. MARKETING AUTHORISATION HOLDER

(See Annex I - to be implemented nationally)

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT