ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration
Austria	Eli Lilly Ges.m.b.H. Kölblgasse 8-10 A-1030 Wien Austria	Fluctine	20mg/5ml	Oral solution	Oral use
Austria	Eli Lilly Ges.m.b.H. Kölblgasse 8-10 A-1030 Wien Austria	Fluctine	20 mg	Capsule, hard	Oral use
Belgium	Eli Lilly Benelux S.A. rue de l'Etuve 52 Stoofstraat B-1000 Brussels Belgium	Prozac	20 mg	Capsule, hard	Oral use
Belgium	Eli Lilly Benelux S.A. rue de l'Etuve 52 Stoofstraat 1000 Brussels Belgium	Prozac	20mg/5ml	Oral solution	Oral use
Belgium	Eli Lilly Benelux S.A. rue de l'Etuve 52 Stoofstraat 1000 Brussels Belgium	Fontex	20 mg	Capsule, hard	Oral use
Belgium	Eli Lilly Benelux S.A. rue de l'Etuve 52 Stoofstraat B-1000 Brussels Belgium	Fluoxetine ‘Lilly’	20 mg	Capsule, hard	Oral use
France	Lilly France S.A.S. 13 rue Pagès 92158 Suresnes Cedex France	Prozac	20 mg	Capsule, hard	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration
France	Lilly France S.A.S. 13 rue Pagès 92158 Suresnes Cedex FRANCE	Prozac	20mg/5ml	Oral solution	Oral use
France	LICO SARL 203, Bureaux de la Colline 92213 Saint Cloud, FRANCE	Fluoxétine RPG	20 mg	Capsule, hard	Oral use
France	Lilly France S.A.S 13 rue Pagès 92158 Suresnes Cedex, FRANCE	Fluoxétine Lilly	20 mg	Capsule, hard	Oral use
Germany	Lilly Deutschland GmbH Saalburgstr. 153 D-61350 Bad Homburg Germany	Fluctin	20 mg	Capsule, hard	Oral use
Germany	Lilly Deutschland GmbH Saalburgstr. 153 D-61350 Bad Homburg Germany	Fluctin	20 mg/5ml	Oral solution	Oral use
Greece	Pharmaserve-Lilly S.A.C.I 15th KLM National Road Athens-Lamia, 145 64 Kifissia, GREECE	Ladose	20mg/5ml	Oral Solution	Oral use
Greece	Pharmaserve-Lilly S.A.C.I 15th KLM National Road Athens-Lamia, 145 64 Kifissia, GREECE	Ladose	20 mg	Capsule, hard	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration
Ireland	Eli Lilly & Co Ltd Kingsclere road Basingstoke Hampshire RG21 6XA United Kingdom	Prozac	20mg/5mg	Oral solution	Oral use
Ireland	Eli Lilly & Co Ltd Kingsclere road Basingstoke Hampshire RG21 6XA United Kingdom	Prozac	20 mg	Capsule, hard	Oral use
Italy	Eli Lilly Italia S.p.A., Via Gramsci 731/733, 50019 Sesto Fiorentino (Fi), ITALY	Prozac	20mg/5ml	Oral Solution	Oral use
Italy	Eli Lilly Italia S.p.A., Via Gramsci 731/733, 50019 Sesto Fiorentino (Fi), ITALY	Prozac	20 mg	Capsule, hard	Oral use
Luxembourg	Eli Lilly Benelux S.A, Rue de l'Etuve 52 Stoofstraat, 1000 Brussels, BELGIUM	Prozac	20 mg	Capsule, hard	Oral use
Luxembourg	Eli Lilly Benelux S.A, Rue de l'Etuve 52 Stoofstraat, 1000 Brussels, BELGIUM	Fontex	20 mg	Capsule, hard	Oral use
Luxembourg	Eli Lilly Benelux S.A, Rue de l'Etuve 52 Stoofstraat, 1000 Brussels, BELGIUM	Prozac	20 mg/5 ml	Oral Solution	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration
Portugal	Lilly Portugal - Produtos Farmacêuticos, Lda. Rua Dr. António Loureiro Borges 1, Piso 1 - Arquiparque - Miraflores 1499-016 Algés - Portugal	Prozac	20 mg	Capsule, hard	Oral use
Portugal	Lilly Portugal - Produtos Farmacêuticos, Lda. Rua Dr. António Loureiro Borges 1, Piso 1 - Arquiparque - Miraflores 1499-016 Algés - Portugal	Prozac	20mg/5ml	Oral Solution	Oral use
Spain	Dista S.A., Avenida Industria 30 28108 Alcobendas – Madrid SPAIN	Prozac	20 mg/5 ml	Oral solution	Oral use
Spain	Dista S.A., Avenida Industria 30 28108 Alcobendas – Madrid SPAIN	Prozac	20 mg	Capsule, hard	Oral use
Sweden	Eli Lilly Sweden AB Gustav III:s boulevard 42, P.O. Box 721 S-16927 Solna, SWEDEN	Fontex	20mg/5ml	Oral Solution	Oral use
The Netherlands	Eli Lilly Nederland B.V. Grootslag 1-5 3991 RA Houten The Netherlands	Prozac	20mg/5ml	Oral solution	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration
The Netherlands	Eli Lilly Nederland B.V. Grootslag 1-5 3991 RA Houten The Netherlands	Prozac	20 mg	Capsule, hard	Oral use
UK	Eli Lilly and Co Ltd, Kingsclere road, Basingstoke, Hampshire RG21 6XA, ENGLAND	Prozac	20mg/5ml	Oral Solution	Oral use
UK	Eli Lilly and Co Ltd, Kingsclere road, Basingstoke, Hampshire RG21 6XA, ENGLAND	Prozac	20 mg	Capsule, hard	Oral use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLETS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF PROZAC AND ASSOCIATED NAMES (SEE ANNEX I)

Prozac is currently approved for the treatment of major depressive episodes, obsessive-compulsive disorder and bulimia nervosa, in adults. The current procedure is a referral following a Mutual Recognition Procedure variation application, which concerned an extension of the indication for Prozac to include the treatment of major depressive episodes in children aged 8 to 17 years.

EFFICACY ISSUES

Efficacy of fluoxetine in children and adolescents in the treatment of moderate to severe major depressive episodes has been demonstrated in three short-term (8-12 weeks duration) placebo-controlled studies.

Two of these trials were sponsored by the MAH (HCJE and X065) and were reviewed during the MR variation procedure. The third was a trial sponsored by the National Institute of Mental Health (NIMH) – the Treatment of Adolescents with Depression trial (TADS).

In two studies (HCJE and TADS), the starting dose 10 mg/d was increased to 20mg/d after one week with an optional further increase to 40 mg/d in one study. In study X065, the starting dose was 20 mg/d, which, in case of intolerance, could be decreased to every second day of administration.

The clinical studies in children and adolescents moderate to severe major depressive episodes showed a modest but positive effect, comparable to what has been seen in adults. Stratified analysis by age on children and adolescents indicated no difference in effect sizes between these two groups. Pharmacokinetic data indicate that given a similar dosage, children have twice the serum levels as adolescents. This difference was largely accounted for by weight.

In one of the short-term studies, responders (in total 40 patients) were included in a 32-week placebo-controlled relapse prevention study. Significantly more patients (twice as many) relapsed on placebo compared to fluoxetine. However, data on maintenance of effect is limited.

In order to warrant a restriction of treatment to patients who are similar to those that were included in the study, the indication was restricted to patients non-responsive to several sessions of psychological therapy and to be treated in combination with psychological therapy.

The starting dose was agreed to be 10mg/day given as 2.5ml of the Prozac liquid formulation. Dose adjustments should be made carefully, on an individual basis, to maintain the patient at the lowest effective dose. Only after one to two weeks, the dose may be increased to 20mg/day.

SAFETY ISSUES

In terms of non-clinical data, the studies in rats and mice identified several areas of concern, including effects on sexual development, growth, testicular toxicity and potential long-term neurobehavioural effects. The relevance of these data for a depressed child cannot be established, however the MAH has committed to perform additional studies to further explore the mechanism of these effects.

In relation to **emotional behaviour**, the difficulties in conducing a clinical study include problems related to defining and measuring the outcome variable (emotional behaviour), and problems related to identifying an adequate control group. The MAH committed therefore to study further the characterisation of effects on specified emotional behaviours in juvenile rats.

The available pre-clinical data on **growth** suggested an impairment of bone development/growth in young rodents exposed to fluoxetine. However, the CHMP considered that the impact of the marked toxicity observed in the juvenile study, as well as the relevance of these data for children and adolescents were difficult to assess. In addition, the evaluation of the study HCLS designed to examine the growth of fluoxetine-treated children/adolescents as compared to untreated patients with the same diagnosis provided some reassurance regarding the effect of fluoxetine on growth, as fluoxetine did not have a clinically significant impact on this parameter.

In relation to **testicular toxicity**, effects were observed in juvenile rats in conjunction with other clinical signs of toxicity (at a dose exceeding the maximum tolerated dose) and at an exposure level that would not be tolerated chronically in humans. However, following the request by CHMP and in order to further investigate the mechanisms of testicular toxicity in rats the MAH agreed to perform a new study in rats intended to further explore the mechanism for the testicular effects in rats. Results from this study will characterize the development of testicular lesions, and the reversibility of these findings at multiple time points; and potentially identify specific cellular targets and/or neurohormonal mechanisms involved in the development of these lesions.

In relation to **sexual maturation,** in animal studies there were indications of dose-related delay in both male and female sexual development. The MAH suggested the involvement of fluoxetine-induced inhibition of GnRH, so that fluoxetine would act as an endocrine disrupter. However, the CHMP requested the MAH to undertake an additional study in young rats, to assess the neurohormonal status of hypothalamic-pituitary-gonadal (HPG) axis during sexual maturation of juvenile male and female rats.
Results from this study would demonstrate whether fluoxetine is associated with an effect on the HPG axis in juvenile rats.

The MAH also undertook to participate in a prospective placebo-controlled study, which will explore possible effects of fluoxetine treatment on sexual maturation.

The MAH also committed to use registries in some Member States that could be used to provide data on the effects of fluoxetine on sexual maturation.

In relation to **suicidality**, the CHMP concluded that the current warning of the product information already informs doctors and parents to monitor patients carefully for the appearance of suicidal behaviour, self-harm or hostility, particularly at the beginning of treatment.

In conclusion, some concerns in relation to growth, pubertal development, hostility and suicide related behaviour in children and adolescents treated with fluoxetine remain. However, the product information was strengthened with appropriate warnings to inform doctors and parents about the need to monitor patients for the appearance of these events.

The CHMP concluded that the data evaluated on fluoxetine has shown this medicinal product to be effective in children and adolescents with moderate to severe major depressive episodes. The balance of benefits and risks for fluoxetine in the treatment of depression in children and adolescents in this condition is judged to be favourable.

Having considered the overall submitted data provided by the MAH in writing and in the oral explanation, the CHMP recommended the granting of the variation to the terms of the Marketing Authorisations for which the Summaries of Product Characteristics, labelling and package leaflets.

GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLETS

Whereas,

- the CHMP considered the referral made under Article 6(12) of Commission Regulation EC No 1084/2003, for Prozac and associated names (see Annex I),

- the CHMP agreed that fluoxetine is effective in children and adolescents aged 8 years and above in the indication of moderate to severe major depressive episodes, 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,

- the CHMP agreed that appropriate warnings to inform doctors and parents about the need to monitor patients for the appearance of events in relation to growth, pubertal development, hostility and suicide related behaviour should be strengthen in the product information,

- the MAH committed to perform additional pre-clinical studies to explore further the mechanism of the effects on sexual development, testicular toxicity and emotional behaviour seen in rats, and to discuss any necessary follow up measures needed as a result of these studies,

- the CHMP agreed that the benefits/risk balance for fluoxetine in the treatment of moderate to severe major depressive episode in children and adolescents aged 8 to 18 is favourable,

The CHMP recommended the granting of the variation of the Marketing Authorisations for which the Summaries of Product Characteristics, Labelling and Package Leaflets are set out in Annex III and under the conditions set out in Annex IV.

ANNEX III

SUMMARIES OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLETS

Note: This Product Information is the one that was Annexed to the Commission Decision on this Article 6(12) referral for fluoxetine containing medicinal products.
The text was valid at that time.

After the CD, the Member State competent authorities will update the product information as required. Therefore, this Product Information may not necessarily represent the current text.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICAL PRODUCT

(Invented name)® 20 mg hard capsules
<[See Annex I - To be completed nationally]>

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains fluoxetine hydrochloride equivalent to 20mg of fluoxetine.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules.

<[To be completed nationally]>

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Adults:

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.

Children and adolescents aged 8 years and above:

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

4.2. Posology and method of administration

For oral administration.

Major depressive episodes

Adults and the elderly: The recommended dose is 20mg daily. Dosage should be reviewed and adjusted if necessary within 3 to 4 weeks of initiation of therapy and thereafter as judged clinically appropriate. Although there may be an increased potential for undesirable effects at higher doses, in some patients, with insufficient response to 20 mg, the dose may be increased gradually up to a maximum of 60 mg (see section 5.1). Dosage adjustments should be made carefully on an individual patient basis, to maintain the patients at the lowest effective dose.

Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are 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 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 60 mg/day is recommended. Long-term efficacy (more than 3 months) has not been demonstrated in bulimia nervosa.

Adults - All indications: The recommended dose may be increased or decreased. Doses above 80 mg/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 given as 2.5ml of the (Invented name)® liquid formulation. 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 Pharmacokinetic properties).

For paediatric patients who respond to treatment, the need for continued treatment after 6 months should be reviewed. If no clinical benefit is achieved within 9 weeks, treatment should be reconsidered.

Elderly: Caution is recommended when increasing the dose and the daily dose should generally 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).

Withdrawal symptoms seen on discontinuation of (Invented name)®: Abrupt discontinuation should be avoided. When stopping treatment with (Invented name)® 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 Special warnings and precautions for use and section 4.8 Undesirable Effects). 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 to any of the 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 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. (Invented name)® 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 prescribers discusses carefully the risks and benefits of treatment with the child/young person and/or their parents.

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

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

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

*Hepatic/Renal Functio*n: 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 Los*s: 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/suicidal thoughts: Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which (Invented name)® 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, those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. In addition, there is a possibility of an increased risk of suicidal behaviour in young adults.

Patients (and caregivers of patients) should be alerted about the need to monitor for the emergence of such events and to seek medical advice immediately if these symptoms present.

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 Undesirable effects). In clinical trials adverse events seen on treatment discontinuation occurred in approximately 60% of patients in both the fluoxetine and placebo groups. Of these adverse events, 17% in the fluoxetine group and 12% in the placebo group were severe in nature.

The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), 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 (Invented name)® 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 (Invented name)®", Section 4.2 Posology and Method of Administration).

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

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 '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 when prescribing to pregnant women, especially during late pregnancy or just prior to the onset of labour since the following effects have been reported in neonates: irritability, tremor, hypotonia, persistent crying, difficulty in sucking or in sleeping. These symptoms may indicate either serotonergic effects

or a withdrawal syndrome. The time to occur and the duration of these symptoms may be related to the long half-life of fluoxetine (4-6 days) and its active metabolite, norfluoxetine (4-16 days).

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

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

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

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 rarely psychomotor restlessness/akathisia (see section 4.4 Special warning and precautions for use). Hallucinations, manic reaction, confusion, agitation, anxiety and associated symptoms (e.g. nervousness), impaired concentration and thought process (e.g. depersonalisation), panic attacks, suicidal thoughts and behaviour (these symptoms may be due to the underlying disease), very rarely serotonin syndrome.

*Urogenital syste*m: 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', *Haemorrhag*e).

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.

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 Special warnings and precautions for use). It is therefore advised that when (Invented name)® treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 Posology and Method of Administration and section 4.4 Special warnings and precautions for use).

Children and adolescents (see section 4.4 Special warnings and precautions for use):

In paediatric clinical trials suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility were more frequently observed among children and adolescents treated with antidepressants compared to those treated with placebo.

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

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

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

Isolated cases of adverse events potentially indicating delayed sexual maturation or sexual dysfunction have been reported from paediatric clinical use. (see also section 5.3)

In paediatric clinical trials, 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 inhibitors, ATC code: N06A B03.

Fluoxetine is a selective inhibitor of serotonin reuptake, and this probably accounts for the mechanism of action. Fluoxetine has practically no affinity to other receptors such as 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.

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 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.

Major depressive episodes (children and adolescents): Clinical trials in children and adolescents aged 8 years and above have been conducted versus placebo. (Invented name)®, 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 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 (desmethylfluoxetine), by desmethylation.

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

At-risk populations
- Elderly: Kinetic parameters are not altered in healthy elderly when compared to younger subjects
- Children and adolescents: The mean fluoxetine concentration in children is approximately 2-fold higher than that observed in adolescents and the mean norfluoxetine concentration 1.5-fold higher. Steady state plasma concentrations are dependent on body weight and are higher in lower weight children (see 4.2 Posology and method of administration). As in adults, fluoxetine and norfluoxetine accumulated extensively following multiple oral dosing; steady-state concentrations were achieved within 3 to 4 weeks of daily dosing.
- Hepatic insufficiency: In case of hepatic insufficiency (alcoholic cirrhosis), fluoxetine and norfluoxetine half-lives are increased to 7 and 12 days, respectively. A lower or less frequent dose should be considered.
- Renal insufficiency: After single-dose administration of fluoxetine in patients with mild, moderate or complete (anuria) renal insufficiency, kinetic parameters have not been altered when compared to healthy volunteers. However, after repeated administration, an increase in steady-state plateau of plasma concentrations may be observed.

5.3. Preclinical safety data

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

In a juvenile toxicology study in CD rats, administration of 30 mg/kg/day of fluoxetine hydrochloride on postnatal days 21 to 90 resulted in irreversible testicular degeneration and necrosis, epididymal epithelial vacuolation, immaturity and inactivity of the female reproductive tract and decreased fertility. Delays in sexual maturation occurred in males (10 and 30 mg/kg/day) and females (30 mg/kg/day). The significance of these findings in humans is unknown. Rats administered 30 mg/kg also had decreased femur lengths compared with controls and skeletal muscle degeneration, necrosis and regeneration. At 10 mg/kg/day, plasma levels achieved in animals were approximately 0.8 to 8.8 fold (fluoxetine) and 3.6 to 23.2 fold (norfluoxetine) those usually observed in paediatric patients. At 3 mg/kg/day, plasma levels achieved in animals were approximately 0.04 to 0.5 fold (fluoxetine) and 0.3 to 2.1 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

Starch flowable
Dimeticone

Capsule components:
Patent blue V (E 131)
Yellow iron oxide (E172)
Titanium dioxide (E 171)
Gelatin

Pharmaceutical grade edible printing ink components:

Formulation 1:
Shellac
Propylene Glycol
Ammonium Hydroxide
Black Iron Oxide E172

Formulation 2:
Shellac
Soya Lecithin
Antifoam DC 1510
Black Iron Oxide E172

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

Three years.

6.4. Special precautions for storage

Do not store above 25˚C.

6.5. Nature and contents of container

<[To be completed nationally]>
Not all pack sizes may be marketed

6.6. Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

<[See Annex I - To be completed nationally]>

8. MARKETING AUTHORIZATION NUMBER

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

<[To be completed nationally]>

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

(Invented name)® 20mg per 5ml oral liquid.
<[To be completed nationally]>

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml of oral liquid contains fluoxetine hydrochloride equivalent to 20mg of fluoxetine.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral liquid.

<[To be completed nationally]>

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Adults:

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.
Children and adolescents aged 8 years and above:

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

4.2. Posology and method of administration

For oral administration.

Major depressive episodes

Adults and the elderly: The recommended dose is 20mg daily. Dosage should be reviewed and adjusted if necessary within 3 to 4 weeks of initiation of therapy and thereafter as judged clinically appropriate. Although there may be an increased potential for undesirable effects at higher doses, in some patients, with insufficient response to 20 mg, the dose may be increased gradually up to a maximum of 60 mg (see section 5.1). Dosage adjustments should be made carefully on an individual patient basis, to maintain the patients at the lowest effective dose.

Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are 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 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 60 mg/day is recommended. Long-term efficacy (more than 3 months) has not been demonstrated in bulimia nervosa.

Adults - All indications: The recommended dose may be increased or decreased. Doses above 80 mg/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 given as 2.5ml of the (Invented name)® liquid formulation. 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 Pharmacokinetic properties).

For paediatric patients who respond to treatment, the need for continued treatment after 6 months should be reviewed. If no clinical benefit is achieved within 9 weeks, treatment should be reconsidered.

Elderly: Caution is recommended when increasing the dose and the daily dose should generally 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).

Withdrawal symptoms seen on discontinuation of (Invented name)®: Abrupt discontinuation should be avoided. When stopping treatment with (Invented name)® 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 Special warnings and precautions for use and section 4.8 Undesirable Effects). 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 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 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. (Invented name)® 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 prescribers discusses carefully the risks and benefits of treatment with the child/young person and/or their parents.

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

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

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

*Hepatic/Renal Functio*n: 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 Los*s: 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/suicidal thoughts: Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which (Invented name)® 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, those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. In addition, there is a possibility of an increased risk of suicidal behaviour in young adults.

Patients (and caregivers of patients) should be alerted about the need to monitor for the emergence of such events and to seek medical advice immediately if these symptoms present.

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 Undesirable effects). In clinical trials adverse events seen on treatment discontinuation occurred in approximately 60% of patients in both the fluoxetine and placebo groups. Of these adverse events, 17% in the fluoxetine group and 12% in the placebo group were severe in nature.

The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), 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 (Invented name)® 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 (Invented name)®", section 4.2 Posology and Method of Administration).

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.

(Invented name)® oral liquid contains sucrose: Patients with rare hereditary problems of fructose intolerance, glucosegalactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

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

Half-life: The long elimination half-lives of 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 when prescribing to pregnant women, especially during late pregnancy or just prior to the onset of labour

since the following effects have been reported in neonates: irritability, tremor, hypotonia, persistent crying, difficulty in sucking or in sleeping. These symptoms may indicate either serotonergic effects or a withdrawal syndrome. The time to occur and the duration of these symptoms may be related to the long half-life of fluoxetine (4-6 days) and its active metabolite, norfluoxetine (4-16 days).

*Lactatio*n: 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 rarely psychomotor restlessness/akathisia (see section 4.4 Special warning and precautions for use). Hallucinations, manic reaction, confusion, agitation, anxiety and associated symptoms (e.g. nervousness), impaired concentration and thought process (e.g. depersonalisation), panic attacks, suicidal thoughts and behaviour (these symptoms may be due to the underlying disease), very rarely serotonin syndrome.

*Urogenital syste*m: 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', *Haemorrhag*e).

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.

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 Special warnings and precautions for use). It is therefore advised that when (Invented name)® treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 Posology and Method of Administration and section 4.4 Special warnings and precautions for use).

Children and adolescents (see section 4.4 Special warnings and precautions for use):

In paediatric clinical trials suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility were more frequently observed among children and adolescents treated with antidepressants compared to those treated with placebo.

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

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

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

Isolated cases of adverse events potentially indicating delayed sexual maturation or sexual dysfunction have been reported from paediatric clinical use. (see also section 5.3)

In paediatric clinical trials, 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 inhibitors, ATC code: N06A B03.

Fluoxetine is a selective inhibitor of serotonin reuptake, and this probably accounts for the mechanism of action. Fluoxetine has practically no affinity to other receptors such as 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.

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 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.

Major depressive episodes (children and adolescents): Clinical trials in children and adolescents aged 8 years and above have been conducted versus placebo. (Invented name)®, 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 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 (desmethylfluoxetine), by desmethylation.

Elimination

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

At-risk populations

- Elderly: Kinetic parameters are not altered in healthy elderly when compared to younger subjects
- Children and adolescents: The mean fluoxetine concentration in children is approximately 2-fold higher than that observed in adolescents and the mean norfluoxetine concentration 1.5-fold higher. Steady state plasma concentrations are dependent on body weight and are higher in lower weight children (see 4.2 Posology and method of administration). As in adults, fluoxetine and norfluoxetine accumulated extensively following multiple oral dosing; steady-state concentrations were achieved within 3 to 4 weeks of daily dosing.
- Hepatic insufficiency: In case of hepatic insufficiency (alcoholic cirrhosis), fluoxetine and norfluoxetine half-lives are increased to 7 and 12 days, respectively. A lower or less frequent dose should be considered.
- Renal insufficiency: After single-dose administration of fluoxetine in patients with mild, moderate or complete (anuria) renal insufficiency, kinetic parameters have not been altered when compared to healthy volunteers. However, after repeated administration, an increase in steady-state plateau of plasma concentrations may be observed.

5.3. Preclinical safety data

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

In a juvenile toxicology study in CD rats, administration of 30 mg/kg/day of fluoxetine hydrochloride on postnatal days 21 to 90 resulted in irreversible testicular degeneration and necrosis, epididymal epithelial vacuolation, immaturity and inactivity of the female reproductive tract and decreased fertility. Delays in sexual maturation occurred in males (10 and 30 mg/kg/day) and females (30 mg/kg/day). The significance of these findings in humans is unknown. Rats administered 30 mg/kg

also had decreased femur lengths compared with controls and skeletal muscle degeneration, necrosis and regeneration. At 10 mg/kg/day, plasma levels achieved in animals were approximately 0.8 to 8.8 fold (fluoxetine) and 3.6 to 23.2 fold (norfluoxetine) those usually observed in paediatric patients. At 3 mg/kg/day, plasma levels achieved in animals were approximately 0.04 to 0.5 fold (fluoxetine) and 0.3 to 2.1 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

Benzoic Acid
Sucrose
Glycerin
Mint flavour (containing 0.23% alcohol)
Purified Water

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

Two years.

6.4. Special precautions for storage

Do not store above 25ºC.

6.5. Nature and contents of container

<[To be completed nationally]>
The pack may include a measuring cup or syringe.
Not all pack sizes may be marketed

6.6. Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

<[See Annex I - To be completed nationally]>

8. MARKETING AUTHORIZATION NUMBER

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

<[To be completed nationally]>

LABELLING AND PACKAGE LEAFLET

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTONS FOR (Invented name)® 20 MG HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

(Invented name)® 20 mg hard capsules
<[See Annex I - To be completed nationally]>
fluoxetine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

<[See Annex I - To be completed nationally]>

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25˚C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[See Annex I - To be completed nationally]>

12. MARKETING AUTHORISATION NUMBER(S)

<[See Annex I - To be completed nationally]>

13. MANUFACTURER'S BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

(Invented name)® 20 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
20 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

(Invented name)® 20 mg hard capsules
<[See Annex I - To be completed nationally]>
fluoxetine hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

<[See Annex I - To be completed nationally]>

3. EXPIRY DATE

Exp.

4. BATCH NUMBER

Lot.

5. OTHER

(the days of the week will be printed on the foil in abbreviated form).

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTONS FOR (Invented name)® 20 mg per 5 ml oral liquid

1. NAME OF THE MEDICINAL PRODUCT

(Invented name)® 20 mg per 5 ml oral liquid
<[See Annex I - To be completed nationally]>
fluoxetine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 5ml of oral liquid contains fluoxetine hydrochloride equivalent to 20mg of fluoxetine

3. LIST OF EXCIPIENTS

Also contains sucrose. Read the leaflet for more information.

4. PHARMACEUTICAL FORM AND CONTENTS

<[See Annex I - To be completed nationally]>

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25˚C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[See Annex I - To be completed nationally]>

12. MARKETING AUTHORISATION NUMBER(S)

<[See Annex I - To be completed nationally]>

13. MANUFACTURER'S BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

(Invented name)® 20 mg per 5 ml

PARTICULARS TO APPEAR ON THE BOTTLE
CARTONS FOR PROZAC 20 mg per 5 ml oral liquid

1. NAME OF THE MEDICINAL PRODUCT

(Invented name)® 20 mg per 5 ml oral liquid
<[See Annex I - To be completed nationally]>
fluoxetine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 5ml of oral liquid contains fluoxetine hydrochloride equivalent to 20mg of fluoxetine

3. LIST OF EXCIPIENTS

Also contains sucrose. Read the leaflet for more information.

4. PHARMACEUTICAL FORM AND CONTENTS

<[See Annex I - To be completed nationally]>

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25˚C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[See Annex I - To be completed nationally]>

12. MARKETING AUTHORISATION NUMBER(S)

<[See Annex I - To be completed nationally]>

13. MANUFACTURER'S BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

(Invented name)® 20mg hard capsules
<[See Annex I - To be completed nationally]>
fluoxetine (as hydrochloride)

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What (Invented name)® is and what it is used for
2. Before you take (Invented name)®
3. How to take (Invented name)®
4. Possible side effects
5. How to store (Invented name)®
6. Further information

1. WHAT (Invented name)® IS AND WHAT IT IS USED FOR

(Invented name)® is one of a group of medicines called selective serotonin re-uptake inhibitor (SSRI) antidepressants.

This medicine is used to treat the following conditions:

Adults:
- Major depressive episodes
- Obsessive-compulsive disorder
- Bulimia nervosa: (Invented name)® is used alongside psychotherapy for the reduction of binge-eating and purging

Children and adolescents aged 8 years and above:

- Moderate to severe major depressive disorder, if the depression does not respond to psychological therapy after 4–6 sessions. (Invented name)® should be offered to a child or young person with moderate to severe major depressive disorder only in combination with psychological therapy.

2. BEFORE YOU TAKE (Invented name)®

Do not take (Invented name)® and tell your doctor or pharmacist if the following apply:
- If you are allergic (hypersensitive) to fluoxetine or any of the other ingredients of (Invented name)®. An allergy may include rash, itching, swollen face or lips or shortness of breath.
- If you are taking medicines known as non-selective monoamine oxidase inhibitors or reversible monoamine oxidase inhibitors type A (also called MAOIs) which are also used to treat depression), since serious or even fatal reactions can occur.

Treatment with fluoxetine should only be started 2 weeks after discontinuation of an irreversible MAOI (for instance tranylcypromine).

However treatment with fluoxetine can be started the following day after discontinuation of certain MAOIs called reversible MAOI-A (for instance moclobemide)

Do not take any MAOIs for at least five weeks after you stop taking (Invented name)®. If (Invented name)® has been prescribed for a long period and/or at a high dose, a longer interval needs to be considered by your doctor. Examples of MAOIs include nialamide, iproniazide, selegeline, moclobemide, phenelzine, tranylcypromine, isocarboxazid and toloxatone.

Take special care with (Invented name)® and tell your doctor or pharmacist if you:

- develop a rash or other allergic reactions (like itching, swollen lips or face or shortness of breath), stop taking the capsules straight away and contact your doctor immediately .
- have epilepsy or have had a fit in the past; if you have a fit (seizure) or experience an increase in seizure frequency, contact your doctor immediately, the use of fluoxetine might need to be discontinued.
- have suffered from mania in the past; if you have a manic episode, contact your doctor immediately, the use of fluoxetine might need to be discontinued.
- have diabetes your doctor may need to adjust your dose of insulin or other antidiabetic treatment);
- have liver problems (your doctor may need to adjust your dosage)
- have heart problems
- are taking diuretics (water tablets), especially when you are elderly;
- are having ECT (electro-convulsive therapy) treatment;
- have a history of bleeding disorders or you develop bruises or unusual bleeding.
- are using medicinal products that effect the coagulation of blood (see 'Taking other medicines').
- start to experience fever, muscle stiffness or tremor, changes in your mental state like confusion, irritability and extreme agitation; you may suffer from the so called serotonin syndrome or neuroleptic malignant syndrome. Although this syndrome occurs rarely it may result in potentially life threatening conditions, contact your doctor immediately, the use of fluoxetine might need to be discontinued.
- have suicidal thoughts or want to harm your self. Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide related events). This risk persists until improvements of your illness occurs. Since it can take 3 to 4 weeks before your illness improves following treatment with fluoxetine, your doctor will monitor you closely at the start of the treatment. Other psychiatric conditions for which (Invented name)® is prescribed can also be associated with an increased risk of suicide-related events. The same precautions should therefore be observed when treating patients with other psychiatric disorders.

Use in children and adolescents aged 8 to 18 years of age:

Patients under 18 have an increased risk of side-effects such as suicide attempt, suicidal thoughts and hostility (predominantly aggression, oppositional behaviour and anger) when they take this class of medicines. (Invented name)® should only be used in children and adolescents aged 8 to 18 years for the treatment of moderate to severe major depressive episodes (in combination with psychological therapy) and it should not be used in other indications.

Additionally, only limited information concerning the long-term safety of (Invented name)® on growth, puberty, mental, emotional and behavioural development in this age group is available. Despite this, your doctor may prescribe (Invented name)® for patients under 18 for moderate to severe major depressive episode in combination with psychological therapy because he/she decides that this is in their best interests. If your doctor has prescribed (Invented name)® for a patient under 18 and you want to discuss this, please go back to your doctor. You should inform your doctor if any of the symptoms listed above develop or worsen when patients under 18 are taking (Invented name)®.

(Invented name)® should not be used in the treatment of children under the age of 8 years.

Taking Other Medicines with (Invented name)®

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, (up to five weeks ago) including medicines obtained without prescription. This medicine may affect the way some other medicines work (interaction). An interaction could occur with:

- MAO-inhibitors (used to treat depression). Non-selective MAO-inhibitors and MAO-inhibitors type A (moclobemide) should not be used with (Invented name)® as serious or even fatal reactions (serotonin syndrome) can occur (see section "Do not take (Invented name)®"). MAO-inhibitors type B (selegeline) can be used with (Invented name)® provided that your doctor monitors you closely.
- lithium, tryptophan; there is an increased risk of serotonin syndrome when these drugs are co-administered with (Invented name)®. When fluoxetine is used in combination with lithium your doctor will carry out more frequent check-ups.
- phenytoin (for epilepsy); because (Invented name)® may influence the blood levels of this drug, your doctor may need to introduce phenytoin more carefully and carry out check-ups when given with (Invented name)®.
- clozapine, (used to treat certain mental disorders), tramadol (a painkiller) or triptans (for migraine); there is an increased risk of hypertension.
- flecainide or encainide (for heart problems), carbamazepine (for epilepsy), tricyclic antidepressants (for example imipramine, desipramine and amitriptyline); because (Invented name)® may possibly change the blood levels of these medicines, your doctor may need to lower their dose when administered with (Invented name)®.
- warfarin or other medicines used to thin the blood; (Invented name)® may alter the effect of these medicines on the blood. If (Invented name)® treatment is started or stopped when you are taking warfarin, your doctor will need to perform certain tests.
- You should not start to take the herbal remedy St John's wort while you are being treated with (Invented name)® since this may result in an increase of undesirable effects. If you are already taking St John's wort when you start on (Invented name)®, stop taking the St John's wort and tell your doctor at your next visit.

Taking (Invented name)® with food or drink

- You can take (Invented name)® with or without food, whichever you prefer.
- You should avoid alcohol while you are taking this medicine.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.
Pregnancy

Information collected to date does not indicate a increased risk when used during pregnancy. However caution should be exercised when used during pregnancy, especially during late pregnancy or just before giving birth since the following effects have been reported in new born children: irritability, tremor, muscle weakness, persistent crying, difficulty in sucking or in sleeping.

Breast-feeding

Fluoxetine is excreted in breast milk and can cause side effects in babies. You should only breast-feed if it is clearly necessary. If breastfeeding is continued, your doctor may prescribe a lower dose of fluoxetine.

Driving and using machines

This medicine may affect your judgment or co-ordination. Do not drive or use machinery without advice from your physician or pharmacist.

3. HOW TO TAKE (Invented name)®

Always take (Invented name)® exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose is:

- Depression: The recommended dose is 20 mg daily. Your doctor will review and adjust your dosage if necessary within 3 to 4 weeks of the start of treatment. When appropriate the dosage can be gradually increased up to a maximum of 60 mg. The dose should be increased carefully to ensure that you receive the lowest effective dose. You may not feel better immediately when you first start taking your medicine for depression. This is usual because an improvement in depressive symptoms may not occur until after the first few weeks. Patients with depression should be treated for a period of at least 6 months.
- Bulimia nervosa: The recommended dose is 60 mg daily.
- OCD: The recommended dose is 20 mg daily. Your doctor will review and adjust your dosage if necessary after 2 weeks of treatment. When appropriate the dosage can be gradually increases up to a maximum of 60 mg. If no improvement is noted within 10 weeks, treatment with (Invented name)® should be reconsidered.
- Children and adolescents aged 8 to 18 years with depression: Treatment should be started and be supervised by a specialist. The starting dose is 10mg/day (given as 2.5ml of (Invented name)® oral liquid). After one to two weeks, your doctor may increase the dose to 20mg/day. The dose should be increased carefully to ensure that you receive the lowest effective dose. Lower weight children may need lower doses. Your doctor should review the need for continuing treatment beyond 6 months. If you have not improved, your treatment should be reassessed.

If you are elderly, your doctor will increase the dose with more caution and the daily dose should generally not exceed 40 mg. The maximum dose is 60 mg per day.

If you have a liver problem or are using other medication that might have an influence on fluoxetine, your doctor may decide to prescribe a lower dose or instruct you to use (Invented name)® every other day.

Method of administration:

- Swallow the capsules with a drink of water. Do not chew the capsules.

If you take more (Invented name)® than you should

- If you take too many capsules, go to your nearest hospital emergency department (or casualty) or tell your doctor straight away.
- Take the pack of (Invented name)® with you if you can.

Symptoms of overdose include: nausea, vomiting, seizures, heart problems (like irregular heart beat and cardiac arrest), lung problems and change in mental condition ranging from agitation to coma.

If you forget to take (Invented name)®

- If you miss a dose, do not worry. Take your next dose the next day at the usual time. Do not take a double dose to make up for a forgotten dose.
- Taking your medicine at the same time each day may help you to remember to take it regularly.

If you stop taking (Invented name)®

Do not stop taking (Invented name)® until your doctor tells you to. It is important that you keep taking your medicine.

- Do not stop taking your medicine without asking your doctor first, even when you start to feel better.
- Make sure you do not run out of capsules.

You may notice the following effects when you stop taking (Invented name)®: dizziness; tingling feelings like pins and needles; sleep disturbances (vivid dreams, nightmares, inability to sleep); feeling restless or agitated; unusual tiredness or weakness; feeling anxious; nausea/vomiting (feeling sick or being sick); tremor (shakiness); headaches.

Most people find that any symptoms on stopping (Invented name)® are mild and go away on their own within a few weeks. If you experience symptoms when you stop treatment, contact your doctor.

When stopping (Invented name)®, your doctor will help you to reduce your dose slowly over one or two weeks - this should help reduce the chance of withdrawal effects.

If you have any further questions on the use of (Invented name)®, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, (Invented name)® can cause side effects, although not everybody gets them.

- If you get a rash or allergic reaction such as itching, swollen lips/tongue or wheezing/shortness of breath, stop taking the capsules straight away and tell your doctor immediately.
- If you feel restless and feel like you cannot sit or stand still, you may have something called akathisia; increasing your dose of (Invented name)® may make you feel worse. If you feel like this, **contact your doctor.**
- **Tell your doctor immediately** if your skin starts to turn red and then blister or peel. This is very rare.

Some patients have had:

- a combination of symptoms (know as serotonin syndrome) including unexplained fever with faster breathing or heart rate, sweating, muscle stiffness or tremor, confusion, extreme agitation or sleepiness (only rarely);
- feelings of weakness, drowsiness or confusion mostly in elderly people and in (elderly) people on diuretics (water tablets);
- prolonged and painful erection;
- irritability and extreme agitation.

If you have any of the above side effects, you should tell your doctor immediately.

If you have any of the following symptoms and they bother you, or last for some time, tell your doctor or a pharmacist.

Whole body - chills, sensitivity to sunlight, weight loss.

Digestive system - diarrhoea and stomach upsets, vomiting, indigestion, difficulty swallowing or a change in taste, or a dry mouth. Abnormal liver function has been reported rarely, with very rare cases of hepatitis.

Nervous system - headache, sleep problems or unusual dreams, dizziness, poor appetite, tiredness, abnormally high mood, uncontrollable movements, fits, extreme restlessness, hallucinations, untypical wild behaviour, confusion, agitation, anxiety, nervousness, not being able to concentrate or think properly, panic attacks; or thoughts of suicide or harming yourself.

Urogenital system and reproductive disorders - difficulty passing urine or passing urine too frequently, poor sexual performance, prolonged erections, and producing breastmilk.

Respiratory System - sore throat, shortness of breath. Lung problems (including inflammatory processes of varying histopathology and/or fibrosis) have been reported rarely.

Other - hair loss, yawning, blurred vision, unexplained bruising or bleeding, sweating, hot flushes, feeling dizzy when you stand up, or joint or muscle pain, low levels of sodium in the blood.

Most of these side effects are likely to go away with continued treatment.

Additionally in Children and Adolescents (8-18 years) – fluoxetine may slow growth or possibly delay sexual maturity.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE (Invented name)®

Keep out of the reach and sight of children.

- Do not take (Invented name)® after the expiry date which is stated on the pack.
- Do not store your capsules above 25°C.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What (Invented name)® 20mg capsules contain:

The active substance is fluoxetine hydrochloride.

Other ingredients inside the capsule are: starch flowable and dimeticone.

The capsule shell is made of gelatin, patent blue V (E131), yellow iron oxide (E172), titanium dioxide (E171). The black edible printing ink consists of shellac, propylene glycol, ammonium hydroxide, black iron oxide (E172) (formulation 1) or shellac, soya lecithin, antifoam DC 1510, black iron oxide (E172) (formulation 2).

What (Invented name)® looks like and contents of the pack

<[To be completed nationally]>

Marketing Authorisation Holder and Manufacturer

<[See Annex I - To be completed nationally]>

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria: Fluctine

Belgium: Prozac, Fontex, Fluoxetine 'Lilly'

France: Prozac, Fluoxétine Lilly

Germany: Fluctin

Greece: Ladose

Ireland, Italy, Netherlands, Portugal, Spain, UK: Prozac

Luxembourg: Prozac, Fontex

<[See Annex I - To be completed nationally]>

This leaflet was last approved in {MM/YYYY}.

<[To be completed nationally]>

PACKAGE LEAFLET: INFORMATION FOR THE USER

(Invented name)® 20mg oral liquid
<[See Annex I - To be completed nationally]>
fluoxetine (as hydrochloride)

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What (Invented name)® is and what it is used for
2. Before you take (Invented name)®
3. How to take (Invented name)®
4. Possible side effects
5. How to store (Invented name)®
6. Further information

1. WHAT (Invented name)® IS AND WHAT IT IS USED FOR

(Invented name)® is one of a group of medicines called selective serotonin re-uptake inhibitor (SSRI) antidepressants.

This medicine is used to treat the following conditions:

Adults:
- Major depressive episodes
- Obsessive-compulsive disorder
- Bulimia nervosa: (Invented name)® is used alongside psychotherapy for the reduction of binge-eating and purging

Children and adolescents aged 8 years and above:

- Moderate to severe major depressive disorder, if the depression does not respond to psychological therapy after 4–6 sessions. (Invented name)® should be offered to a child or young person with moderate to severe major depressive disorder only in combination with psychological therapy.

2. BEFORE YOU TAKE (Invented name)®

Do not take (Invented name)® and tell your doctor or pharmacist if the following apply:

- If you are allergic (hypersensitive) to fluoxetine or any of the other ingredients of (Invented name)®. An allergy may include rash, itching, swollen face or lips or shortness of breath.
- If you are taking medicines known as non-selective monoamine oxidase inhibitors or reversible monoamine oxidase inhibitors type A (also called MAOIs) which are also used to treat depression), since serious or even fatal reactions can occur.

Treatment with fluoxetine should only be started 2 weeks after discontinuation of an irreversible MAOI (for instance tranylcypromine).

However treatment with fluoxetine can be started the following day after discontinuation of certain MAOIs called reversible MAOI-A (for instance moclobemide)

Do not take any MAOIs for at least five weeks after you stop taking (Invented name)®. If (Invented name)® has been prescribed for a long period and/or at a high dose, a longer interval needs to be considered by your doctor. Examples of MAOIs include nialamide, iproniazide, selegeline, moclobemide, phenelzine, tranylcypromine, isocarboxazid and toloxatone.

Take special care with (Invented name)® and tell your doctor or pharmacist if you:

- develop a rash or other allergic reactions (like itching, swollen lips or face or shortness of breath), stop taking (Invented name)® straight away and contact your doctor immediately .
- have epilepsy or have had a fit in the past; if you have a fit (seizure) or experience an increase in seizure frequency, contact your doctor immediately, the use of fluoxetine might need to be discontinued.
- have suffered from mania in the past; if you have a manic episode, contact your doctor immediately, the use of fluoxetine might need to be discontinued.
- have diabetes your doctor may need to adjust your dose of insulin or other antidiabetic treatment);
- have liver problems (your doctor may need to adjust your dosage)
- have heart problems
- are taking diuretics (water tablets), especially when you are elderly;
- are having ECT (electro-convulsive therapy) treatment;
- have a history of bleeding disorders or you develop bruises or unusual bleeding.
- are using medicinal products that effect the coagulation of blood (see 'Taking other medicines').
- start to experience fever, muscle stiffness or tremor, changes in your mental state like confusion, irritability and extreme agitation; you may suffer from the so called serotonin syndrome or neuroleptic malignant syndrome. Although this syndrome occurs rarely it may result in potentially life threatening conditions, contact your doctor immediately, the use of fluoxetine might need to be discontinued.
- have suicidal thoughts or want to harm your self. Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide related events). This risk persists until improvements of your illness occurs. Since it can take 3 to 4 weeks before your illness improves following treatment with fluoxetine, your doctor will monitor you closely at the start of the treatment. Other psychiatric conditions for which (Invented name)® is prescribed can also be associated with an increased risk of suicide-related events. The same precautions should therefore be observed when treating patients with other psychiatric disorders.
- have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Use in children and adolescents aged 8 to 18 years of age:

Patients under 18 have an increased risk of side-effects such as suicide attempt, suicidal thoughts and hostility (predominantly aggression, oppositional behaviour and anger) when they take this class of medicines. (Invented name)® should only be used in children and adolescents aged 8 to 18 years for the treatment of moderate to severe major depressive episodes (in combination with psychological therapy) and it should not be used in other indications.

Additionally, only limited information concerning the long-term safety of (Invented name)® on growth, puberty, mental, emotional and behavioural development in this age group is available. Despite this, your doctor may prescribe (Invented name)® for patients under 18 for moderate to severe major depressive episode in combination with psychological therapy because he/she decides that this is in their best interests. If your doctor has prescribed (Invented name)® for a patient under 18 and you

want to discuss this, please go back to your doctor. You should inform your doctor if any of the symptoms listed above develop or worsen when patients under 18 are taking (Invented name)®.

(Invented name)® should not be used in the treatment of children under the age of 8 years.

Taking Other Medicines with (Invented name)®

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, (up to five weeks ago) including medicines obtained without prescription. This medicine may affect the way some other medicines work (interaction). An interaction could occur with:

- MAO-inhibitors (used to treat depression). Non-selective MAO-inhibitors and MAO-inhibitors type A (moclobemide) should not be used with (Invented name)® as serious or even fatal reactions (serotonin syndrome) can occur (see section "Do not take (Invented name)®"). MAO-inhibitors type B (selegeline) can be used with (Invented name)® provided that your doctor monitors you closely.
- lithium, tryptophan; there is an increased risk of serotonin syndrome when these drugs are co-administered with (Invented name)®. When fluoxetine is used in combination with lithium your doctor will carry out more frequent check-ups.
- phenytoin (for epilepsy); because (Invented name)® may influence the blood levels of this drug, your doctor may need to introduce phenytoin more carefully and carry out check-ups when given with (Invented name)®.
- clozapine, (used to treat certain mental disorders), tramadol (a painkiller) or triptans (for migraine); there is an increased risk of hypertension.
- flecainide or encainide (for heart problems), carbamazepine (for epilepsy), tricyclic antidepressants (for example imipramine, desipramine and amitriptyline); because (Invented name)® may possibly change the blood levels of these medicines, your doctor may need to lower their dose when administered with (Invented name)®.
- warfarin or other medicines used to thin the blood; (Invented name)® may alter the effect of these medicines on the blood. If (Invented name)® treatment is started or stopped when you are taking warfarin, your doctor will need to perform certain tests.
- You should not start to take the herbal remedy St John's wort while you are being treated with (Invented name)® since this may result in an increase of undesirable effects. If you are already taking St John's wort when you start on (Invented name)®, stop taking the St John's wort and tell your doctor at your next visit.

Taking (Invented name)® with food or drink

- You can take (Invented name)® with or without food, whichever you prefer.
- You should avoid alcohol while you are taking this medicine.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Pregnancy

Information collected to date does not indicate a increased risk when used during pregnancy. However caution should be exercised when used during pregnancy, especially during late pregnancy or just before giving birth since the following effects have been reported in new born children: irritability, tremor, muscle weakness, persistent crying, difficulty in sucking or in sleeping.

Breast-feeding

Fluoxetine is excreted in breast milk and can cause side effects in babies. You should only breast-feed if it is clearly necessary. If breastfeeding is continued, your doctor may prescribe a lower dose of fluoxetine.

Driving and using machines

This medicine may affect your judgment or co-ordination. Do not drive or use machinery without advice from your physician or pharmacist.

3. HOW TO TAKE (Invented name)®

Always take (Invented name)® exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose is:

- Depression: The recommended dose is 20 mg daily. Your doctor will review and adjust your dosage if necessary within 3 to 4 weeks of the start of treatment. When appropriate the dosage can be gradually increased up to a maximum of 60 mg. The dose should be increased carefully to ensure that you receive the lowest effective dose. You may not feel better immediately when you first start taking your medicine for depression. This is usual because an improvement in depressive symptoms may not occur until after the first few weeks. Patients with depression should be treated for a period of at least 6 months.
- Bulimia nervosa: The recommended dose is 60 mg daily.
- OCD: The recommended dose is 20 mg daily. Your doctor will review and adjust your dosage if necessary after 2 weeks of treatment. When appropriate the dosage can be gradually increases up to a maximum of 60 mg. If no improvement is noted within 10 weeks, treatment with (Invented name)® should be reconsidered.
- Children and adolescents aged 8 to 18 years with depression: Treatment should be started and be supervised by a specialist. The starting dose is 10mg/day (given as 2.5ml of (Invented name)® oral liquid). After one to two weeks, your doctor may increase the dose to 20mg/day. The dose should be increased carefully to ensure that you receive the lowest effective dose. Lower weight children may need lower doses. Your doctor should review the need for continuing treatment beyond 6 months. If you have not improved, your treatment should be reassessed.

If you are elderly, your doctor will increase the dose with more caution and the daily dose should generally not exceed 40 mg. The maximum dose is 60 mg per day.
If you have a liver problem or are using other medication that might have an influence on fluoxetine, your doctor may decide to prescribe a lower dose or instruct you to use (Invented name)® every other day.

Method of administration:

- Measure the right amount of medicine using the measuring cup, syringe or a measuring spoon, then drink it.

If you take more (Invented name)® than you should

- If you take too much, go to your nearest hospital emergency department (or casualty) or tell your doctor straight away.
- Take the bottle of (Invented name)® with you if you can.

Symptoms of overdose include: nausea, vomiting, seizures, heart problems (like irregular heart beat and cardiac arrest), lung problems and change in mental condition ranging from agitation to coma.

If you forget to take (Invented name)®

- If you miss a dose, do not worry. Take your next dose the next day at the usual time. Do not take a double dose to make up for a forgotten dose.
- Taking your medicine at the same time each day may help you to remember to take it regularly.

If you stop taking (Invented name)®

Do not stop taking (Invented name)® until your doctor tells you to. It is important that you keep taking your medicine.

- Do not stop taking your medicine without asking your doctor first, even when you start to feel better.
- Make sure you do not run out of medicine.

You may notice the following effects when you stop taking (Invented name)®: dizziness; tingling feelings like pins and needles; sleep disturbances (vivid dreams, nightmares, inability to sleep); feeling restless or agitated; unusual tiredness or weakness; feeling anxious; nausea/vomiting (feeling sick or being sick); tremor (shakiness); headaches.

Most people find that any symptoms on stopping (Invented name)® are mild and go away on their own within a few weeks. If you experience symptoms when you stop treatment, contact your doctor.

When stopping (Invented name)®, your doctor will help you to reduce your dose slowly over one or two weeks - this should help reduce the chance of withdrawal effects.

If you have any further questions on the use of (Invented name)®, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, (Invented name)® can cause side effects, although not everybody gets them.

- If you get a rash or allergic reaction such as itching, swollen lips/tongue or wheezing/shortness of breath, stop taking (Invented name)® straight away and tell your doctor immediately.
- If you feel restless and feel like you cannot sit or stand still, you may have something called akathisia; increasing your dose of (Invented name)® may make you feel worse. If you feel like this, **contact your doctor.**
- **Tell your doctor immediately** if your skin starts to turn red and then blister or peel. This is very rare.

Some patients have had:

- a combination of symptoms (know as serotonin syndrome) including unexplained fever with faster breathing or heart rate, sweating, muscle stiffness or tremor, confusion, extreme agitation or sleepiness (only rarely);
- feelings of weakness, drowsiness or confusion mostly in elderly people and in (elderly) people on diuretics (water tablets);
- prolonged and painful erection;
- irritability and extreme agitation.

If you have any of the above side effects, you should tell your doctor immediately.

If you have any of the following symptoms and they bother you, or last for some time, tell your doctor or a pharmacist.

Whole body - chills, sensitivity to sunlight, weight loss.

Digestive system - diarrhoea and stomach upsets, vomiting, indigestion, difficulty swallowing or a change in taste, or a dry mouth. Abnormal liver function has been reported rarely, with very rare cases of hepatitis.

Nervous system - headache, sleep problems or unusual dreams, dizziness, poor appetite, tiredness, abnormally high mood, uncontrollable movements, fits, extreme restlessness, hallucinations, untypical wild behaviour, confusion, agitation, anxiety, nervousness, not being able to concentrate or think properly, panic attacks; or thoughts of suicide or harming yourself.

Urogenital system and reproductive disorders - difficulty passing urine or passing urine too frequently, poor sexual performance, prolonged erections, and producing breastmilk.

Respiratory System - sore throat, shortness of breath. Lung problems (including inflammatory processes of varying histopathology and/or fibrosis) have been reported rarely.

Other - hair loss, yawning, blurred vision, unexplained bruising or bleeding, sweating, hot flushes, feeling dizzy when you stand up, or joint or muscle pain, low levels of sodium in the blood.
Most of these side effects are likely to go away with continued treatment.

Additionally in Children and Adolescents (8-18 years) – fluoxetine may slow growth or possibly delay sexual maturity.

(Invented name)® oral liquid contains sugar which may be harmful to the teeth.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE (Invented name)®

Keep out of the reach and sight of children.

- Do not take (Invented name)® after the expiry date which is stated on the pack.
- Do not store your (Invented name)® above 25°C.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What (Invented name)® oral liquid contains:

The active substance is fluoxetine hydrochloride.

Other ingredients are: Benzoic Acid, Sucrose, Glycerin, Mint flavour (containing 0.23% alcohol) and Purified Water.

What (Invented name)® looks like and contents of the pack

<[To be completed nationally]>

Marketing Authorisation Holder and Manufacturer

<[See Annex I - To be completed nationally]>

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria: Fluctine

Belgium, France, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, UK: Prozac

Germany: Fluctin

Greece: Ladose

Sweden: Fontex

<[See Annex I - To be completed nationally]>

This leaflet was last approved in {MM/YYYY}.

<[To be completed nationally]>

ANNEX IV

CONDITIONS OF THE MARKETING AUTHORISATION

National Competent Authorities, coordinated by the Reference Member State (RMS), shall ensure that the following conditions are fulfilled by the Marketing Authorisation Holders:

1. Toxicological Studies:

The MAH should perform the following studies and report the results to the RMS:

- Juvenile rat study to evaluate neurohormonal status of hypothalamic-pituitary-gonadal (HPG) axis during sexual maturation of juvenile CD male and female rats administered fluoxetine.

- Juvenile rat study to characterize the development and potential reversibility of testicular toxicity (ie, neurohormonal and histopathologic evaluations) in male juvenile CD rats administered fluoxetine.

- Juvenile rat study to characterize the effects on specified emotional behaviours. In this study, fluoxetine would be administered to CD rats from postnatal day 33 to postnatal day 62 with evaluations in the elevated zero maze, forced swimming test and prepulse inhibition test, once during treatment and 2 months post-treatment.

2. Clinical evaluation of the effect of fluoxetine on sexual maturation

- NIMH Prospective placebo-controlled study: The MAHs committed to assess the possibilities to include the evaluation of the effect of fluoxetine on sexual maturation in children aged 8 – 12 years old within the protocol being developed under the auspices of National Institute of Mental Health (NIMH) in United States as well as to discuss with the study investigators the improvement of the trial design by extending the duration of the follow-up and increasing of the upper age range of patients in this study during. The MAHs committed to provide this protocol to the RMS as soon as it is made available to them.

- The MAHs committed to further investigate whether or not the existing in Member States can be used to provide evaluable data on the effects of fluoxetine on sexual maturation.

