CPMP/1123/97-EN
EMEA/H/A/200

OPINION OF THE COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS PURSUANT TO ARTICLE 10 OF COUNCIL DIRECTIVE 75/319/EEC AS AMENDED, FOR

Medicinal product

Name:	**Fluoxetin NM** (see Annex A)
International non-proprietary name:	Fluoxetine
Pharmaceutical form:	Capsule, hard
Strength:	20 mg
Route of administration:	Oral use
Packaging and package size:	See Annex A

Basis for Opinion

Generics (UK) Ltd. submitted an application for Mutual Recognition of the Marketing Authorisation granted by Denmark for the above mentioned medicinal product in the framework of Article 9 of Council Directive 75/319/EEC as amended.

The Reference Member State is Denmark.

The Member State which has received an application for Mutual Recognition (Concerned Member State) is Germany.

Member States which have previously authorised the above mentioned medicinal product under a national procedure are Finland and Sweden.

The Concerned Member State has not been able to agree in respect of the Mutual Recognition of the Marketing Authorisation granted by the Reference Member State.

Detailed statements of the matters on which the above mentioned Member States have been unable to reach agreement and the reasons for their disagreement were submitted to the EMEA by Germany on 30 April 1997 and are appended to this opinion. The Reference Member State sent its report to the EMEA on 12 May 1997; this report is appended.

The matter was referred to the CPMP on 14 May 1997.

On the basis of the questions raised by Germany, the points to be considered by the CPMP were:

1. In view of fluoxetine's non-linear pharmacokinetic profile after multiple dosing and its long half-life especially of its active metabolite, the relevance of a single dose bioequivalence study and a possible lack of therapeutic equivalence should be explained.

2. With regards to a possible lack of therapeutic equivalence with the brand leader and concerns (increased depression and suicidality...) from the Australian Drug Evaluation Committee, all available post-marketing data from the actual generic product, particularly Australian post-marketing surveillance data should be provided.

3. A single SPC should be proposed and justified (differences with already approved SPCs in the EU for the brand leader should be highlighted).

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Switchboard: (+44-171) 418 8400 Fax: (+44-171) 418 8551
E_Mail: mail@emea.eudra.org http://www.eudra.org/emea.html

Written explanations were provided by the Marketing Authorisation Holder on 29 August 1997.
Supplementary information was provided by the Marketing Authorisation Holder on 11 December 1997.

Opinion

The CPMP, having considered the points of disagreement and the responses provided by the Marketing Authorisation Holder as set out in the appended Arbitration Assessment Report, is of the opinion that:

The objections raised by Germany should not prevent the granting of a Marketing Authorisation and the Summary of Product Characteristics of the Reference Member State should be amended. The amended Summary of Product Characteristics of the Reference Member State is set out in Annex I.

This opinion is forwarded to the European Commission, to Member States and to the Marketing Authorisation Holder, together with its annexes and appendices.

London, 17 December 1997

On behalf of the CPMP
Prof. J.-M. Alexandre, Chairman

ANNEX A

LIST OF THE NAMES OF THE MEDICINAL PRODUCT, MARKETING AUTHORISATION HOLDER, PACKAGING AND PACKAGE SIZES IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Name and Strength of the Medicinal Product	Packaging and pack sizes
Denmark	Generics [UK] Ltd. Station Close, Potters Bar Hertfordshire EN6 1TL, UK	Fluoxetin NM, 20 mg	Bottles containing 28 capsules Blister packs containing 28 capsules
Finland	Generics [UK] Ltd. Station Close, Potters Bar Hertfordshire EN6 1TL, UK	Fluoxetine Generics 20 mg Kaps	Bottles containing 30 or 100 capsules Blister packs containing 30 or 100 capsules
Sweden	Generics [UK] Ltd. Station Close, Potters Bar Hertfordshire EN6 1TL, UK	Seroscand Kapslar 20 mg	Bottles containing 30 or 100 capsules Blister packs containing 30 or 100 capsules

ANNEX B
SCIENTIFIC CONCLUSIONS PRESENTED BY THE EMEA
ON THE BASIS OF THE OPINION OF THE CPMP

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF FLUOXETIN NM
(see Annex A)

Quality issues

It has been clarified that the batch used in the bioequivalence study was similar to the industrial size batches. Therefore, all issues related to quality have been adequately addressed.

Efficacy issues

The single dose bioequivalence study was of high quality. Based on this study, the test product and the reference product were regarded to be bioequivalent. It was not considered that a multiple dose bioequivalence study would provide additional useful information.

Safety issues

The applicant has provided all available post marketing safety reports from first launch up to 30 August 1997. These reports indicate a side effect profile (types of adverse events and frequency) as expected and acceptable for fluoxetine. There was no evidence of true therapeutic inefficacy related to the generic fluoxetine. Furthermore, there was no evidence of therapeutic inefficacy related to the switch from the brand leader.

However, due to the uncertainties of the database, the potential risk of suicidal attempts associated with therapeutic inefficacy and the previous discussions of a risk for suicides associated with fluoxetine, the applicant should during post marketing surveillance closely monitor adverse effects and provide safety reviews of this concern.

Benefit/risk ratio

It was concluded that the benefit / risk ratio for Fluoxetin NM is positive. However, a number of changes of the SPC are required. These are outlined in Annex I.

ANNEX I
THE AMENDED SUMMARY OF PRODUCT CHARACTERISTICS
OF THE REFERENCE MEMBER STATE

1. NAME OF THE MEDICINAL PRODUCT (INN)

Fluoxetine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fluoxetine hydrochloride 22.36 mg equivalent to 20 mg of fluoxetine

3. PHARMACEUTICAL FORM

Capsule, hard

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fluoxetine is indicated for the treatment of major depressive episodes.

4.2 Posology and method of administration

For oral administration in adults.

For major depressive episodes, a dose of 20 mg/day is recommended and a maximum daily dose should not exceed 80 mg/day.

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

- Patients with renal or liver disease:
In cases of liver dysfunction or renal failure (GFR 10-50 ml/min), the dose should be reduced, e.g. to 20 mg every second day.

- Children: Fluoxetine capsules are not indicated for use in children. Fluoxetine efficacy and safety have not been studied in children and below the age of 18.

- Elderly: there are not enough data available on fluoxetine efficacy and safety in this population, therefore caution is recommended when increasing the dose which should rarely exceed 40 mg and should not exceed 60 mg.

4.3 Contraindications

- Fluoxetine is contraindicated in patients with a known hypersensitivity to fluoxetine.

- Concurrent treatment of fluoxetine with irreversible non-selective and B selective monoamine oxidase inhibitors (MAOIs) is contraindicated and could result in severe sometimes fatal disorders (see section 4.5).

- Fluoxetine should normally not be used concomitantly with reversible and A selective MAOIs (see section 4.5).

For combination of fluoxetine and other antidepressants, see section 4.5.

- Fluoxetine should not be administered to patients with severe renal failure (GFR < 10 ml/min).

- Fluoxetine should not be used in patients with unstable or uncontrolled epilepsy.
- Fluoxetine should not be used in nursing mothers (see section 4.6).

4.4 Special warnings and special precautions for use

Special Warning
As with all antidepressant treatment, there is a risk of suicide particularly at the beginning of treatment, due to the delay between treatment and clinical improvement: as for all antidepressants, the full therapeutic effect may not manifest itself until 3-4 weeks.

Withdrawal reactions have been reported in association with selective serotonin reuptake inhibitors (SSRIs). Symptoms typically include nausea and dizziness. Avoid abrupt discontinuation of treatment.

In patients receiving fluoxetine in combination with tryptophan, adverse reactions, including agitation, gastrointestinal disorders and restlessness have been reported.

Precautions for Use
Rash and allergic reactions such as urticaria and angioneurotic oedema have been reported. Administration of fluoxetine should therefore be stopped when no other cause for such effects can be established.

Fluoxetine should be used with caution in patients with epilepsy. Patients should be treated and monitored sufficiently before initiation of fluoxetine (see also section 4.5). Treatment should be stopped in patients who develop fits or seizures. Prolonged seizures in patients who were also receiving electroconvulsive therapy (ECT) have been infrequently reported.

Psychosis and mood shift towards manic phase have been reported. This may require treatment discontinuation.

In some patients, a serotonin syndrome has been observed which can be life-threatening. Medication should be stopped and supporting measures taken.

Due to limited clinical information, caution should be taken when treating patients with cardiovascular disease or recently recovered from a myocardial infarct.

Initiation and cessation of fluoxetine treatment may affect glycaemic homeostasis. In diabetic patients, glycaemic monitoring should be reinforced and insulin and/or oral hypoglycaemic dosage may need to be adjusted.

Fluoxetine may cause weight loss that is undesirable in underweight depressed patients.

In some cases, inappropriate secretion of antidiuretic hormone has been reported (see also section 4.8).

Fluoxetine has not shown evidence of potentiating the effects of alcohol. However, as during other CNS medicinal product treatment, alcohol use should be avoided.

Fluoxetine should be used with great caution in patients with hepatic insufficiency since the half-lives of fluoxetine and norfluoxetine are prolonged.

Fluoxetine should be used with great caution in patients with renal insufficiency since the half-life of norfluoxetine is prolonged (see also section 4.3).

The medicinal product should be prescribed in small quantities in order to reduce the risk of overdosing with the product.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combination
Irreversible non-selective and B selective MAOIs (see section 4.3).
This combination can result in severe, sometimes fatal reactions (**serotonin syndrome**) including sudden or progressive occurrence of the following symptoms which impose immediate discontinuation of

treatment: hyperthermia, rigidity, myoclonus, tachycardia, autonomic instability, diarrhoea, and mental status changes, e.g. confusion, agitation progressing to delirium and coma.
Fluoxetine should not be used for at least 2 weeks after irreversible non-selective and B selective MAOI-medication. MAOI treatment should not be started for at least 5 weeks after cessation of fluoxetine treatment.

Inadvisable combination
Reversible and A selective MAOIs (see section 4.3)
If the combination must be used, the patient should be monitored closely and treatment initiated with the minimal dose (see also irreversible MAOIs).

Fluoxetine should not be used for at least some days after reversible and A selective MAOI-medication. MAOI treatment should not be started for at least 5 weeks after cessation of fluoxetine treatment.

Precautions for use during combination:
Patients receiving stable doses of phenytoin, or carbamazepine have developed raised plasma levels of phenytoin, or carbamazepine and clinical toxicity following initiation of concomitant fluoxetine treatment.

The risk of using fluoxetine in combination with other CNS active medicinal products has not been fully evaluated. Therefore, caution is advised if the concomitant administration of fluoxetine and such medicinal products is required. Cases of lithium toxicity have been reported. When used concomitantly, lithium levels should be monitored.

There have been increases in previously stable plasma levels of other antidepressants (for example tricyclic antidepressants) with a potentially increased incidence of adverse effects when fluoxetine has been administered concomitantly with these agents. If necessary, doses should be adjusted. When fluoxetine is substituted by a tricyclic antidepressant, the latter should be initiated with caution due to the long half-life of fluoxetine and norfluoxetine. There are no data to show the usefulness of combination of fluoxetine and other antidepressants.

Oral anticoagulants. Concomitant use of fluoxetine may result in increased anticoagulant activity and haemorragic risk. The prothrombin time and INR level should be checked more frequently and if necessary the doses should be adjusted.

Generally, concomitant treatment with medicinal products known to be metabolised in the liver by cytochrome CYP 2D6, especially those with a narrow therapeutic index, should be conducted with care due to possible interaction. Lower doses of such medicinal products should therefore be considered (and for up to 5 weeks after cessation of fluoxetine treatment).

Since fluoxetine is tightly bound to plasma protein, the concomitant use of fluoxetine with another highly protein-bound medicinal product may cause a shift in plasma concentrations of either product, thus potentially resulting in an adverse effect.

4.6 Use during pregnancy and lactation

In animal studies, fluoxetine has not demonstrated teratogenic effects or fetotoxicity but studies were limited by maternal toxicity. In humans, the number of exposed pregnancies is too low to conclude. Therefore, as a precautionary measure, fluoxetine use is not recommended during pregnancy.

Breast-feeding: Fluoxetine has been shown to pass into human milk. Therefore, breast-feeding is not recommended. See also section 4.3.

4.7 Effects on ability to drive and use machines

Fluoxetine may impair judgement, thinking, or motor skills. Patients should be advised to avoid driving motor vehicles or operating hazardous machinery.

4.8 Undesirable Effects

Anorexia, weight loss, appetite loss, nausea, vomiting, diarrhoea, dry mouth, dyspepsia, constipation.
Headache, restlessness, insomnia, anxiety, dizziness, visual disturbance, drowsiness, confusion, tremor, sweating, sedation. Suicide and suicidal attempts (see section 4.4).
Withdrawal reactions have been reported in association with SSRIs. Symptoms typically include nausea and dizziness (see section 4.4)
Serotonin syndromes have exceptionally been reported (see section 4.5)
Small increases in diastolic blood pressure and tachycardia as well as bradycardia have been reported.
Rash and allergic reactions: urticaria, exceptionally Quincke edema, have been reported (see section 4.4).
Rarely, vasculitis, erythema polymorph, or exceptionally Lyell syndrome, and rare cases of fever, rash and arthralgia as in serum sickness.
Hyperprolactinemia with galactorrhea.
Hyponatremias have been reported. In some cases, plasma sodium was less than 100 mmol/l. Hyponatremia may be revealed by confusion or seizures and was reversible on discontinuation of treatment. Most of the cases have been described in elderly or patients with diuretics or hypovolemia.
Rare cases of increased ALTs and exceptional cytolytic or mixed hepatitis have been reported.

4.9 Overdose

Nausea, vomiting, seizures and signs of CNS excitations have been reported with overdose.
No specific antidote is known. Appropriate elimination of ingested product and/or prevention of absorption should be performed when indicated. Management should include general symptomatic and supportive measures including a clear airway and monitoring cardiac and vital signs until stable. Extra-renal elimination techniques are likely to be of no benefit in the view of the large distribution volume.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Antidepressant
ATC code: N06 AB03
Fluoxetine is a selective competitive inhibitor of 5HT (serotonin) uptake in the presynaptic cleft and exerts little or no effect on re-uptake mechanisms for norepinephrine, dopamine or acetylcholine. The major metabolite norfluoxetine is similar in efficacy to the parent molecule.

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
It is highly protein bound (about 95%) and has a high volume of distribution (Vd: 20-40 l/kg).

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 primarily metabolised by the liver to the active metabolite norfluoxetine (demethylfluoxetine), by demethylation.

Elimination
The elimination half-life of fluoxetine is about 4 days (2-7 days) and for norfluoxetine about 7-9 days (4-15 days). These long half-lives are responsible for persistance of the drug for 5-6 weeks after discontinuation (see section 4.5). Excretion is mainly (about 65%) via the kidneys. Fluoxetine is secreted into breast milk.

t-risk populations

- Elderly: Kinetic parameters are not altered in healthy elderly as compared with younger subjects.
- Hepatic insufficiency: In case of hepatic insufficiency (alcoholic cirrhosis), fluoxetine and norfluoxetine half-lives are increased up to 7 and 12 days, respectively. This should lead to decrease the dose.
- Renal insufficiency: After single-dose administration of fluoxetine in patients with mild, moderate or complete (anuria) renal insufficiency, kinetic parameters have not been altered as 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

Fluoxetine was of low acute toxicity. Chronic toxicity studies have shown inducible reversible phospholipidosis, similar to that observed with other amphophilic cationic substances (e.g. amiodarone, imipramine). The clinical relevance of this effect has not been established. However, this should be taken into consideration, should respiratory disorders occur. Fluoxetine did not show evidence of mutagenicity, carcinogenicity nor teratogenicity in animal studies. Fertility studies conducted in rats at dose levels of up to 9 to 12.5 mg/kg/day showed that fluoxetine had no adverse effects on fertility but that neonatal survival rate was slightly decreased (probably associated with depressed maternal food consumption and suppressed weight gain).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, maize starch, colloidal anhydrous silica, talc, magnesium stearate, brilliant blue (E133), quinoleine yellow (E104), erythrosine (E127), indigo carmine (E132), sodium lauryl sulphate, gelatin, shellac, potassium hydroxide, iron oxide black (E172) and titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

2 years

6.4 Special precautions for storage

Store below 25ºC.

6.5 Nature and content of container

HDPE bottles with polypropylene screw caps (with a pressure sensitive wad) containing, 20, 28, 30, 50, 100 capsules.

PVC/PVDC/Al blister packs containing 20, 28, 30, 50, 100 capsules.

6.6 Instructions for use and handling, and disposal (if appropriate)

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Generics (UK) Ltd.
Station Close
Potters Bar
Hertfordshire
EN6 1TL
UK

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF (PARTIAL) REVISION OF THE TEXT