CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75465

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-465** Date of Submission: **May 9, 2000**

Applicant's Name: **CHEMINOR DRUGS LIMITED**

Established Name: **Fluoxetine Capsules USP, 10 mg, 20 mg and 40 mg**

Labeling Deficiencies:

1. CONTAINER 30s and 100s (10 mg, 20 mg and 40 mg) - 500s (40 mg) - 1000s (20 mg)

   Please note that for computer generated labels to be acceptable as final print, they must be of actual size, color and clarity. Please assure that these criteria are met prior to submission of final print.

2. INSERT

   We acknowledge your amendment dated May 9, 2000. We note that you are not claiming the indication, Obsessive Compulsive Disorder (OCD), and that you have deleted reference to that indication in your insert labeling.

   The regulations for generic drug labeling, 21 CFR 314.94(a)(8)(iv), state in relevant part, that labeling proposed by the applicant, "... must be the same as the labeling approved for the reference listed drug except for ... omission of an indication or other aspect of labeling protected by patent or accorded exclusivity ...". Unless there is a patent or exclusivity that covers OCD, you must retain that indication in your labeling.

   Our Office does not have expertise in the interpretation of patents. Since no patent listed in the Orange Book specifically claims OCD, we ask that you request clarification as to whether that indication is the subject of any patent.

   We acknowledge your Paragraph IV certification to patent 4,626,549 and we believe there should be clarification regarding this patent, and that it should be specifically associated (or not associated) with the indications appearing in the labeling for the referenced listed drug.

   To clarify whether OCD is specifically claimed by a patent, we refer you to 21 CFR 314.53(f) "Correction of patent information errors". Please follow the procedure outlined by that regulation to request clarification through HFD-90, Division of Data Management.

   Please copy your application with your letter to HFD-90. Please also provide a desk copy to Adolph Vezza.

/S/

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-465 Date of Submission: September 14 and September 20, 1999

Applicant's Name: CHEMINOR DRUGS LIMITED

Established Name: Fluoxetine Capsules USP, 10 mg, 20 mg and 40 mg

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Labeling Deficiencies:

1. GENERAL COMMENT

   Please revise your storage temperature recommendations throughout your labels and labeling as follows:

   Store at controlled room temperature 15°-30°C (59°-86°F)(see USP).

2. CONTAINER

   a. 30s and 100s (10 mg, 20 mg and 40 mg) - 500s (40 mg) - 1000s (20 mg)

      See GENERAL COMMENT above.

   b. 30s, 100s and 500s

      Dispense in a tight, light-resistant container with a child-resistant closure. (add "container")

3. UNIT DOSE CARTON 100s (40 mg)

   See GENERAL COMMENT above.

4. INSERT (Revised 9/99)

   a. DESCRIPTION

      i. "pregelatinized corn starch"

      ii. Include the ingredients of the imprinting ink in the listing of inactive ingredients.

   b. CLINICAL PHARMACOLOGY

      i. **Absorption, Distribution, Metabolism, and Excretion**, *Accumulation and Slow Elimination,* Second paragraph, last sentence - following the discontinuation of fluoxetine.

      ii. Clinical Trials, Second paragraph

         A). First sentence - ... controlled studies (N = 671 randomized) comparing ...

         B). Penultimate sentence - ... HAM-D score of ≤ 8. Fluoxetine ...

c. INDICATIONS AND USAGE

Second sentence - ... with depressed adult and geriatric outpatients ...

d. PRECAUTIONS

i. **General**, *Anxiety and Insomnia*, second paragraph

A). First sentence - Among the most common adverse events associated ...

B). Last sentence - (see Table 2 below).

ii. Drug Interactions, first sentence - ... etc. ... (add period)

iii. Usage in the Elderly

A). Revise this title to read "Geriatric Use".

B). Revise the text of this subsection as follows:

Geriatric Use
U.S. fluoxetine clinical trials (10,782 patients) included 687 patients ≥ 65 years of age and 93 patients ≥ 75 years of age. The efficacy in geriatric patients has been established (see Clinical Trials under CLINICAL PHARMACOLOGY). For pharmacokinetic information in geriatric patients see Age under CLINICAL PHARMACOLOGY. No overall differences in safety and effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other SSRIs, fluoxetine has been associated with cases of clinically significant hyponatremia in elderly patients (see Hyponatremia under PRECAUTIONS).

iv. Hyponatremia

Revise the fifth sentence as follows - ... depleted. In two 6-week controlled studies in patients ≥ 60 years of age, 10 of 323 fluoxetine and 6 of 327 placebo recipients ...

e. ADVERSE REACTIONS

i. Incidence in US Placebo-Controlled Clinical Trials (excluding data from extensions of trials)

A). Delete the second paragraph

B). Delete Table 2 and the asterisked and hyphenated text beneath it.

ii. Associated with Discontinuation in US Placebo-Controlled Clinical Trials (excluding data from extensions of trials) - Retitle "Table 3" as "Table 2"

iii. Other Events Observed In All US Clinical Trials

A). First paragraph -... of Table 1 above ... (delete

B). *Endocrine System*, Infrequent - "hypothyroidism" rather than

f. OVERDOSAGE

Management of Overdose

i. Revise the first 4 paragraphs as follows:

Treatment should consist of those general measures employed in the management of overdosage with any antidepressant.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for fluoxetine are known.

A specific caution involves patients who are taking fluoxetine and might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (see Other Antidepressants under PRECAUTIONS).

Based on experience in animals, which may not be relevant to humans, fluoxetine-induced seizures that fail to remit spontaneously may respond to diazepam.

In managing overdosage, ...

ii. Penultimate paragraph - Delete all the text save for the first sentence.

iii. Last paragraph

A). Combine with the penultimate paragraph.

B). ... a poison control center for additional information on the treatment ...

g. DOSAGE AND ADMINISTRATION

Depression, *Initial Treatment*, fourth paragraph - **"Geriatric Use"** rather than

h. HOW SUPPLIED

i. We encourage the use of the NDC numbers in this section.

ii. ... unit-dose packages of 100 (10 x 10).

iii. See GENERAL COMMENT above.

Please revise your container labels and unit dose carton and insert labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes –

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-465** Date of Submission: **September 24, 1998**

Applicant's Name: **CHEMINOR DRUGS LIMITED**

Established Name: **Fluoxetine Capsules USP, 10 mg and 20 mg**

Labeling Deficiencies:

1. CONTAINER 30s, 100s (10 mg and 20 mg) 1000s (20 mg)

   a. Each capsule contains:

      Fluoxetine Hydrochloride equivalent to ___ mg Fluoxetine.

   b. "**Usual Dosage:**" rather than "**Dosage:**".

2. INSERT

   a. GENERAL COMMENTS

      i. Delete "hydrochloride" throughout the text of the insert except in the DESCRIPTION section.

      ii. Italicize "*in vivo*" and "*in vitro*" throughout the text of the insert.

      iii. We acknowledge your comment that you have included only the depression indication in your labeling at this time due to ongoing patent litigation between the patent holder and other companies. However, we ask you to include information regarding the obsessive-compulsive disorder in your labeling as this exclusivity has expired.

      Also, you will be required to include information on the bulimia nervosa disorder if your drug product is approved after the expiration date of the exclusivity for this indication (November 21, 1999).

iv. Since you have elected to leave out the bulimia indication from your insert labeling, please delete all references to bulimia throughout the text of the insert.

b. CLINICAL PHARMACOLOGY

Absorption, Distribution, Metabolism, and Excretion - Age, second sentence -
... nonlinear ... (one word)

c. INDICATIONS AND USAGE

Please include the indications for "Obsessive-Compulsive Disorder" as seen below:

... (see **Clinical Trials** under **CLINICAL PHARMACOLOGY**).

Obsessive-Compulsive Disorder

Fluoxetine is indicated for the treatment of obsessions and compulsions in patients with obsessive-compulsive disorder (OCD), as defined in the DSM-III-R; i.e., the obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of fluoxetine was established in 13-week trials with obsessive-compulsive outpatients whose diagnoses corresponded most closely to the DSM-III-R category of obsessive-compulsive disorder (see **Clinical Trials** under **CLINICAL PHARMACOLOGY**).

Obsessive-compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses, or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

The effectiveness of fluoxetine in long-term use, i.e., for more than 13 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use fluoxetine for extended periods should periodically reevaluate the long-term usefulness

of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

d. PRECAUTIONS

i. General, Anxiety and Insomnia, last paragraph - ... with discontinuation (incidence at least twice that for placebo and at least 1% for fluoxetine in clinical trials collecting only a primary event associated with discontinuation) in US placebo-controlled fluoxetine clinical trials were anxiety (2% in OCD), insomnia (1% in combined indications), and nervousness (1% in depression)(see Table 3, below).

ii. Drug Interactions

A). CNS Active Drugs - The subsections "Anticonvulsants" through "Other Antidepressants" are all subsections of "CNS Active Drugs". Please distinguish the titles as such.

B). Antipsychotics, last sentence - "pimozide" rather than "primozide"

C). Potential Effects of Coadministration of Drugs Tightly Bound to Plasma Proteins, first sentence - delete "sodium"

e. ADVERSE REACTIONS

i. First paragraph - "i.e.," rather than "ie,"

ii. Associated with Discontinuation in US Placebo-Controlled Clinical Trials (excluding data from extensions of trials) - ... in clinical trials collecting along a primary event associated with discontinuation) in depression and OCD.

iii. Table 3

A). Place (N=1108) under the title in the first column.

B). Delete "Nervousness (1%)" from the first column.

C). Place (N=392) under the title in the second column.

D). Delete "Insomnia (1%)" from the second column.

E). Delete "Nausea (1%)" from the second column.

F). Place (N=266) under the title of the third column.

G). Third column - "Rash (1%)" rather than "Rash (3%)".

iv. Postintroduction Reports - ...epidermal necrolysis, erythema nodosum, exfoliative dermatitis, ...

f. DRUG ABUSE AND DEPENDENCE

Physical and Psychological Dependence, second sentence - ... drug seeking ... CNS active (delete the two hyphens)

g. DOSAGE AND ADMINISTRATION

i. Please add the information concerning dosage and administration for the obsessive-compulsive disorder as shown below:

... under **CLINICAL PHARMACOLOGY**).

Obsessive-Compulsive Disorder

Initial Treatment

In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of obsessive-compulsive disorder, patients were administered fixed daily doses of 20, 40, or 60 mg of fluoxetine or placebo (see **Clinical Trials** under **CLINICAL PHARMACOLOGY**). In one of these studies, no dose response relationship for effectiveness was demonstrated. Consequently, a dose of 20 mg/day, administered in the morning, is recommended as the initial dose. Since there was a suggestion of a possible dose response

relationship for effectiveness in the second study, a dose increase may be considered after several weeks if insufficient clinical improvement is observed. The full therapeutic effect may be delayed until 5 weeks of treatment or longer.

Doses above 20 mg/day may be administered on a once a day (i.e., morning) or b.i.d. schedule (i.e., morning and noon). A dose range of 20 to 60 mg/day is recommended, however, doses of up to 80 mg/day have been well tolerated in open studies of OCD. The maximum fluoxetine dose should not exceed 80 mg/day.

As with the use of fluoxetine in depression, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (see **Usage in the Elderly** under **PRECAUTIONS**), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (see *Liver Disease* and *Renal Disease* under **CLINICAL PHARMACOLOGY**, and *Use in Patients with Concomitant Illness* under **PRECAUTIONS**).

Maintenance/Continuation Treatment

While there are no systematic studies that answer the question of how long to continue fluoxetine, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of fluoxetine after 13 weeks has not been documented in controlled trials, patients have been continued in therapy under double-blind conditions for up to an additional 6 months without loss of benefit. However, dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment.

ii. Switching Patients to a Tricyclic Antidepressant (TCA)

A). "may" rather than "mat"

B). ... under **PRECAUTIONS, Drug Interactions**).

h. HOW SUPPLIED

We encourage the use of the NDC number in this section.

i. ANIMAL TOXICOLOGY

We encourage you to relocate the "Rx only" symbol to immediately below the title of the insert.

Please revise your labels and labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

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