CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75465

ADMINISTRATIVE DOCUMENTS

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 2, 2001

FROM: Gary J. Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

SUBJECT: ANDA 75-755
Fluoxetine Hydrochloride Tablets
Alphapharm Pty, Ltd.

TO: The Record Regarding U.S. Patent No. 6,258,853

July 10, 2001, U.S. Patent No. 6,258,853 (the '853 patent) was issued to Stowell, et.al. The abstract of the patent states " The present invention relates to novel pharmaceutical formulations and methods of using Form A of fluoxetine hydrochloride" .

On July 18, 2001, aai Pharma (aai) submitted a letter to the Agency under 21 C.F.R. 314.53(f) to advise the agency that the holder of NDA 18-936, Eli Lilly & Co. (Lilly) for Prozac® (fluoxetine hydrochloride) has failed to submit required patent information under 21 U.S.C. 355(c)(2) with respect to the '853 patent. aai claims that the patent meets all the legal requirements for listing and that Lilly must list the patent in Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book). aai requested that FDA contact Lilly to confirm the correctness of Lilly's omission of information with respect to the '853 patent. aai also stated that FDA has an obligation to effect the Congressional intent of protecting patent owner rights whether or not the patent owner or licensee is an NDA applicant.

On July 23, 2001, the FDA issued a letter to Lilly asking Lilly to review the patent challenge submitted under 314.53(f) and to confirm whether the patent information for NDA 18-936 was correct.

On July 31, 2001, Lilly replied to the FDA's July 23, 2001, letter and stated they reviewed the challenge and that the patent

information contained in the Orange Book is correct. Lilly stated that no changes need to be made to the patent and exclusivity information addendum of the Orange Book.

On August 2, 2001, the Agency fully approved applications for fluoxetine hydrochloride that were otherwise ready for approval. All scientific and regulatory issues had been resolved. All patent and exclusivity information currently listed in the Orange Book had been addressed.

The statute 21 U.S.C. 355(c)(2) states that the holder of an approved application shall file with the Secretary, the patent number and the expiration date of any patent which claims the drug for which the application was submitted, or which claims a method of using such drug, and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. Because the NDA holder, Lilly, declined to list the '853 patent, the Agency did not list the patent. The Agency's ministerial role in the patent listing process is limited. The statute requires the Agency to publish the patent after it is submitted to the Agency by the applicant. The Agency does not independently list patents, which are not submitted to it by the applicant for listing. The Agency fulfilled its ministerial role by forwarding the patent challenge submitted under 21 C.F.R. 314.53(f) for the '853 patent to the NDA applicant, Lilly.

alphapharm

Certification of the Field Copy of the Amendment to

ANDA # 75-755

Alphapharm Pty Ltd hereby certifies that the Field copies (Red and Burgundy folders) of the Amendment for Fluoxetine Hydrochloride Tablets 10 mg and 20 mg, ANDA #75-755, are a true copy of the Amendment.

Barry Spencer

Science Law Officer

Dated 18/5/01

Record of Telephone Conversation

The firm will do the following:

1) Revise the specifications in Exhibit IV of 12/15/00 amendment to include Melting Range and Bioburden.

2) Provide accelerated stability protocols to support major post-approval changes.

3) Remove the 5 mL vials from the title of the Marketed Product Stability Protocol for List 2308.

4) Request to disregard the stability summary data for 10 mL Add-Vantage vial.

Date: June 12, 2001
ANDA Number: 75-857
Product Name: Midazolam
Firm Name: Abbott
Firm Representative: Surendera Tyagi
Phone Number: 847-938-4369
FDA Representative: Jeen Min Tao-Chin Wang
Signatures: 6/18/01

CC: ANDA 75-857

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

ANDA Number: 75-755 Date of Submission: December 6, 1999 and February 11, 2000

Applicant's Name: Alphapharm Pty. Ltd.

Established Name: Fluoxetine Tablets 10 mg and 20 mg

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. Revise your storage temperature recommendations throughout your labels and labeling as follows:

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

   b. We note that this application has a shared insert with ANDA 75-577. These ANDAs must be approved together or further revisions to the insert labeling will be necessary.

2. CONTAINER 30s, 100s, 2000s (10 mg and 20 mg)

   See GENERAL COMMENT above.

3. INSERT

   a. GENERAL COMMENT

      "U.S." rather than "US" throughout the text of the insert labeling

   b. DESCRIPTION

      "molecular" rather than "empirical"

   c. CLINICAL PHARMACOLOGY

      i. Absorption, Distribution, Metabolism, and Excretion, Systemic Bioavailability, second paragraph, first sentence - The capsule, tablet, and oral solution dosage form ...

      ii. Clinical Trials, second paragraph

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

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

   d. INDICATIONS AND USAGE

      i. "reevaluate" rather than "re-evaluate" (three instances)

      ii. Second sentence - ... with depressed adult and geriatric outpatients ... to the DSM-III (currently DSM-IV) category ...

iii. Revise the second paragraph as follows:

A major depressive episode (DSM-IV) implies ...persistent (nearly every day for at least 2 weeks) depressed or ... daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood; loss of interest in usual activities; significant change in weight and/or appetite; insomnia or hypersomnia; psychomotor agitation or retardation; increased fatigue; feelings of guilt or worthlessness; slowed thinking or impaired concentration; a suicide attempt or suicidal ideation.

e. PRECAUTIONS

i. Drug Interactions

A). "coadministration" (three instances) and "coadministered" (two instances) [delete hyphen]

B). First sentence - "etc." (add period)

C). Potential Effects of Coadministration of Drugs Tightly Bound to Plasma Proteins - "warfarin" rather than "Coumadin"

D). Warfarin - "anticoagulant" (delete hyphen)

ii. Carcinogenesis, Mutagenesis, Impairment of Fertility, Carcinogenicity - ... (approximately 1.2 and 0.7 times, ...

iii. Retitle the "Usage in the Elderly" subsection "Geriatric Use" and revise as follows:

Geriatric Use
U.S. fluoxetine clinical trials (10,782 patients) included 687 patients $\geq$ 65 years of age and 93 patients $\geq$ 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

A). First sentence - Cases of ... (delete "Several")

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

f. ADVERSE REACTIONS

i. Table 2, first column - "Vasodilatation" (spelling)

ii. Paragraph after Table 2 - ... on placebo ... (rather than "of")

g. DOSAGE AND ADMINISTRATION

i. "Geriatric Use" rather than "Usage in the Elderly" (3 instances)

ii. Switching Patients to a Tricyclic Antidepressant (TCA)

A). "coadministered" (delete hyphen)

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

h. HOW SUPPLIED

See GENERAL COMMENTS (a) above.

Please revise your container labels 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

(this supersedes the TENTATIVE APPROVAL SUMMARY dated 2-16-01)
TENTATIVE APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-755** Dates of Submission: **March 6 and March 23, 2001** and March 26, 2001

Applicant's Name: **Alphapharm Pty. Ltd.**

Established Name: **Fluoxetine Hydrochloride Tablets 10 mg and 20 mg**

4/2/01

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 30s, 100s and 2000s

Satisfactory in FPL as of March 6, 2001 submission.

Professional Package Insert Labeling:

Satisfactory in FPL as of March 6, 2001 submission.
(Insert which references Tablets only)

Revisions needed post approval: None

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Prozac® Tablets

NDA Number: 20-974

NDA Drug Name: Prozac® (fluoxetine hydrochloride) Tablets

NDA Firm: Lilly Research Laboratories

Date of Approval of NDA Insert and supplement #: 11/28/00 (S-062) [for NDA 18-936]

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side by sides

Other Comments: There are no approved supplements for NDA 20-974 (the RLD). It has a shared insert with the capsule (NDA 18-936) and the oral solution (NDA 20-101). The firm did not submit S-052, the supplement for revision to the Geriatric Use subsection to NDA 20-974 (they should have). I used this supplement to do my review. Also, I called the U.S. Agent for the firm (Michelle Bonomi) on 10-4-00 about having the bulk container labels revised to include the statement that the fluoxetine present is in the form of the hydrochloride as seen on the container labels. I stated that since we do not approve bulk container labels that the firm would not have to submit the revised bulk container labels. The firm has submitted two sets of PI's, one is combined with the capsules and the other is just the tablets. The latter will be used during the 180 day exclusivity period for the capsules. After that time the combined insert will be used. The firm sent in a telephone amendment withdrawing the combined insert. We cannot approve this application with that labeling (because the capsules will be approved at a later date).

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24		X	
Is this name different than that used in the Orange Book?	X		
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
		X	

Do any of the inactives differ in concentration for this route of administration?			
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement? Three ingredients in the DESCRIPTION section not in the C&C statement - They could be ingredients of the Opadry - I WILL ASK THE CHEMIST	X		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

The DESCRIPTION section lists hydroxypropyl methylcellulose, polyethylene glycol, and titanium dioxide as inactive ingredients yet they are not listed in the C & C statement. Are they components of the Opadry?

FOR THE RECORD:

1. This review was based on the labeling for Prozac® (Lilly; Approved 11/28/00; Revised 10/00 [in draft]. There are no approved supplements for NDA 20-974 (the RLD). It has a shared insert with the capsule (NDA 18-936) and the oral solution (NDA 20-101). The firm did not submit S-062, the supplement for revisions throughout the insert to NDA 20-974 (they should have). I used this supplement to do my review.

2. The inactives are listed accurately in the DESCRIPTION section except see NOTES TO THE CHEMIST (p 2655 v 1.7 and p 68 v B 2.1).

3. Two patents are still in effect for the innovator:

   4626549 - A method of blocking the uptake of monoamines by brain neurons in animals (use code U-84) expires 12/2/03. Use code U-154 - method of treating animals suffering from an appetite disorder - is also associated with this patent

   4314081 - For the chemical entity - expires 2/2/01

   The firm has filed a Paragraph 4 to both patents. Unlike other firms, e.g. Teva and Zenith-Goldline, they have retained reference to the bulimia indication associated with the first above referenced patent. Other firms are "not claiming" bulimia.

4. Storage/dispensing recommendations:

NDA - Store at CRT 59° to 86°F (15° to 30°C). Dispense in a tight, light-resistant container.

ANDA - Store at CRT 15° to 30°C (59° to 86°F)(see USP). Dispense in a tight, light-resistant container.

5. This is the first generic for this drug product. This is a non-USP drug product and it is not listed in the PF. Re: the established name, it was decided to use "Fluoxetine Tablets" since the USP capsule form of the drug and the oral solution (not USP) both drop the salt (HCl) from the name. This decision was reversed since the product is not USP - I asked the firm to revise their labels and labeling to read "Fluoxetine Hydrochloride Tablets" and they have.

6. The innovator markets this drug product (10 mg) in bottles of 30s and 100s. The 20 mg tablets were withdrawn. The firm submitted a copy of a Citizen's Petition to determine whether or not the 20 mg tablets were withdrawn for safety reasons. The applicant proposes bottle sizes of 30s (CRC), 100s (CRC), and 2000s for both the 10 mg and 20 mg tablets. The applicant's proposed containers are all made of HDPE.

7. The tablets are accurately described in the HOW SUPPLIED section (p 3367 v 1.8 and p 729 v B 2.3).

8. Both the innovator and this ANDA's 10 mg drug product is scored (NOTE: I don't know why because there is no indication for a 5 mg dose in the labeling.) The ANDA'S 20 mg tablet is also scored.

9. Alphapharm is the manufacturer (p 2927 v 1.7).

10. The February 11, 2000 submission is for the addition of a 20 mg tablet.

11. This ANDA shares an insert with ANDA 75-577 (capsules) but the firm submitted both a combined insert and a separate one, the separate one to be used during the 180 day exclusivity period for the capsules then the combined one will be used after this period. The firm was informed that this plan won't work because the combined insert cannot be approved before the capsules application is approved. The firm has withdrawn the combined insert (3/23/01).

Date of Review: 3-22-01 **Dates of Submission:** 3-6-01 & 3-23-01

Primary Reviewer: Adolph Vezza A. Vezza **Date:** 3/26/01

Team Leader: Charlie Hoppes **Date:** 3/26/01

cc:

ANDA: 75-755
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev/3/22/01|V:\FIRMSAM\Alphapharm\LTRS&REV\75755TAP3.L
Review

Record of Telephone Conversation

FDA requested the firm (ESI) to do the following:

1. Please confirm that the sum of the 2 peaks, for 527 & 537 is NMT %

2. The firm stated 6 months stability for the bulk drug but only sent in 3 months of data. Please send in the 6 months data and any other up-to-date stability data.

3. Since the bulk containers are being sold to the repackager, the bulk container is considered to be a market container so the firm needs to do USP 661 testing. In particular we would like light and moisture testing.

4. The firm will acknowledge that they will update the labeling in an annual report for any repackagers.

Date:
March 6, 2001

ANDA Number:
75-755

Product Name:
Fluoxetine

Firm Name:
Par Pharmaceutical (US Agent for Alphapharm)

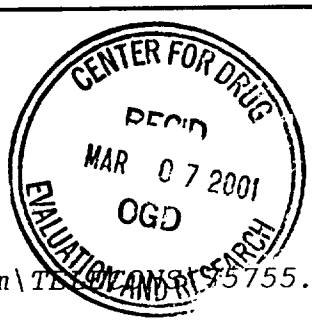
Firm Representative:
Michelle Bonomi-Huvlal

Phone Number:
845-469-6170

FDA Representative:
Jeen Min
Tao-chin Wang
Glen Smith

Signatures:

/S/



CC: ANDA 75-755

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TENTATIVE APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-755** Date of Submission: **February 9, 2001**

Applicant's Name: **Alphapharm Pty. Ltd.**

Established Name: **Fluoxetine Hydrochloride Tablets 10 mg and 20 mg**

NOTE: Do not approve before application for capsules in this labeling.

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 30s, 100s and 2000s

Satisfactory in FPL as of September 8, 2000 submission.

Professional Package Insert Labeling:

Satisfactory in FPL as of February 9, 2001 submission.

Revisions needed pre full approval:

1. GENERAL COMMENTS

   a. Please note that the established name for this drug product is "Fluoxetine Hydrochloride Tablets". Please revise your labels and labeling accordingly.

   b. Submit 12 copies of revised container labels and insert labeling before full approval of this application.

2. CONTAINER 30s, 100s and 2000s

   See GENERAL COMMENTS above.

3. INSERT

   a. GENERAL COMMENT

      See GENERAL COMMENTS above.

   b. TITLE

      See GENERAL COMMENTS (a) above

   b. DESCRIPTION

      First sentence - "... oral administration; it is also marketed for the treatment of premenstrual dysphoric disorder (Sarafem™, fluoxetine hydrochloride). It is chemically unrelated ..."

   c. PRECAUTIONS

      i. General, Suicide, first paragraph, last sentence - Delete "of capsules".

ii. Pediatric Use - Upper case "U"

iii. Geriatric Use, fourth sentence - "... safety or effectiveness ..." rather than "and"

iv. Hyponatremia, first sentence - "Cases of ..." (delete "Several")

d. DOSAGE AND ADMINISTRATION

i. Bulimia Nervosa, Maintenance/Continuation, sentence two - "... have been continued ..."

ii. Switching Patients to a Tricyclic Antidepressant (TCA) - "... *under* PRECAUTIONS, Drug Interactions)."

e. HOW SUPPLIED

i. See GENERAL COMMENTS (a) above.

ii. Add the statement "Protect from light."

iii. Add the statement "Sarafem™ is a trademark of Eli Lilly."

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Prozac® Tablets

NDA Number: 20-974

NDA Drug Name: Prozac® (fluoxetine hydrochloride) Tablets

NDA Firm: Lilly Research Laboratories

Date of Approval of NDA Insert and supplement #: 11/28/00 (S-062) [for NDA 18-936]

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side by sides

Other Comments: There are no approved supplements for NDA 20-974 (the RLD). It has a shared insert with the capsule (NDA 18-936) and the oral solution (NDA 20-101). The firm did not submit S-052, the supplement for revision to the Geriatric Use subsection to NDA 20-974 (they should have). I used this supplement to do my review. Also, I called the U.S. Agent for the firm (Michelle Bonomi) on 10-4-00 about having the bulk container labels revised to include the statement that the fluoxetine present is in the form of the hydrochloride as seen on the container labels. I stated that since we do not approve bulk container labels that the firm would not have to submit the revised bulk container labels. The labeling deficiencies listed above were related to the U.S. Agent for the firm by fax on 2-16-01.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24		X	
Is this name different than that used in the Orange Book?	X		

If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement? Three ingredients in the DESCRIPTION section not in the C&C statement - They could be ingredients of the Opadry - I WILL ASK THE CHEMIST	X		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be			

listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

The DESCRIPTION section lists hydroxypropyl methylcellulose, polyethylene glycol, and titanium dioxide as inactive ingredients yet they are not listed in the C & C statement. Are they components of the Opadry?

FOR THE RECORD:

1. This review was based on the labeling for Prozac® (Lilly; Approved 11/28/00; Revised 10/00 [in draft]. There are no approved supplements for NDA 20-974 (the RLD). It has a shared insert with the capsule (NDA 18-936) and the oral solution (NDA 20-101). The firm did not submit S-062, the supplement for revisions throughout the insert to NDA 20-974 (they should have). I used this supplement to do my review.

2. The inactives are listed accurately in the DESCRIPTION section except see NOTES TO THE CHEMIST (p 2655 v 1.7 and p 68 v B 2.1).

3. Two patents are still in effect for the innovator:

   4626549 - A method of blocking the uptake of monoamines by brain neurons in animals (use code U-84) expires 12/2/03. Use code U-154 - method of treating animals suffering from an appetite disorder - is also associated with this patent

   4314081 - For the chemical entity - expires 2/2/01

   The firm has filed a Paragraph 4 to both patents. Unlike other firms, e.g. Teva and Zenith-Goldline, they have retained reference to the bulimia indication associated with the first above referenced patent. Other firms are "not claiming" bulimia.

4. Storage/dispensing recommendations:

   NDA - Store at CRT 59° to 86°F (15° to 30°C). Dispense in a tight, light-resistant container.

   ANDA - Store at CRT 15° to 30°C (59° to 86°F)(see USP). Dispense in a tight, light-resistant container.

5. This is the first generic for this drug product. This is a non-USP drug product and it is not listed in the PF. Re: the established name, it was decided to use "Fluoxetine Tablets" since the USP capsule form of the drug and the oral solution (not USP) both drop the salt (HCl) from the name. This decision was reversed since the product is not USP - I have asked the firm to revise their labels and labeling to read "Fluoxetine Hydrochloride Tablets".

6. The innovator markets this drug product (10 mg) in bottles of 30s and 100s. The 20 mg tablets were withdrawn. The firm submitted a copy of a Citizen's Petition to determine whether or not the 20 mg tablets were withdrawn for safety reasons. The applicant proposes bottle sizes of 30s (CRC), 100s (CRC), and 2000s for both the 10 mg and 20 mg tablets. The applicant's proposed containers are all made of HDPE.

7. The tablets are accurately described in the HOW SUPPLIED section (p 3367 v 1.8 and p 729 v B 2.3).

8. Both the innovator and this ANDA's 10 mg drug product is scored (NOTE: I don't know why because there is no indication for a 5 mg dose in the labeling.) The ANDA'S 20 mg tablet is also scored.

9. Alphapharm is the manufacturer (p 2927 v 1.7).

10. The February 11, 2000 submission is for the addition of a 20 mg tablet.

11. This ANDA shares an insert with ANDA 75-577 (capsules).

Date of Review: 2-15-01 **Date of Submission:** 2-9-01

Primary Reviewer: Adolph Vezza **Date:** 2/16/01

A. Vezza

Team Leader: Charlie Hoppes **Date:** 2/16/01

/S/

cc:

ANDA: 75-755
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev/2/15/01|V:\FIRMSAM\Alphaph.arm\LTRS&REV\75755TAP2.L
Review

TELEPHONE MEMO

TO: **Christine M. Markus**
King & Spalding (US Agent for Alphapharm Pty Limited)
202-626-2926

REF# **ANDA 75-755**

FROM: **Krista M. Scardina**

DATE: **January 10, 2001**

SUBJECT: **Fluoxetine Tablets, 10 mg and 20 mg**

REQUESTED BY: **Christine M. Markus**

The firm sent a letter to the Agency January 3, 2001 regarding ANDA 75-755. King & Spalding wanted formal clarification that we received both the hard copy and the computer diskette following a telephone amendment. The ANDA originally included the hard copy of the data. The firm was only asked during the teleconference to submit that data on diskette. It was therefore clarified with the firm that DBE has both the hard copy and the computer diskette containing the bio study data for PK statistical analysis. Please refer to the Telephone Memo dated December 12, 2000 for the original teleconference.

TELEPHONE MEMO

TO: **Eugene Pfiefer**
King and Spalding (Agent for Alphapharm PTY. Ltd.)
202-737-0500

REF# **ANDA 75-555**

FROM: **Krista Scardina**

DATE: **12 December 2000**

SUBJECT: **Fluoxetine HCl Tablets, 20 mg**

REQUESTED BY: **Chandra Chaurasia**

The firm was requested to submit computer diskettes containing the bio study data for PK statistical analysis. The firm will have ten business days to submit the diskettes (28 December 2000).

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

ANDA Number: 75-755 Date of Submission: December 6, 1999 and February 11, 2000

Applicant's Name: Alphapharm Pty. Ltd.

Established Name: Fluoxetine Tablets 10 mg and 20 mg

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. Revise your storage temperature recommendations throughout your labels and labeling as follows:

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

   b. We note that this application has a shared insert with ANDA 75-577. These ANDAs must be approved together or further revisions to the insert labeling will be necessary.

2. CONTAINER 30s, 100s, 2000s (10 mg and 20 mg)

   See GENERAL COMMENT above.

3. INSERT

   a. GENERAL COMMENT

      "U.S." rather than "US" throughout the text of the insert labeling

   b. DESCRIPTION

      "molecular" rather than "empirical"

   c. CLINICAL PHARMACOLOGY

      i. Absorption, Distribution, Metabolism, and Excretion, Systemic Bioavailability, second paragraph, first sentence - The capsule, tablet, and oral solution dosage form ...

      ii. Clinical Trials, second paragraph

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

         B). Penultimate sentence - ... HAM-D score of $\leq$ 8. Fluoxetine ...

   d. INDICATIONS AND USAGE

      i. "reevaluate" rather than "re-evaluate" (three instances)

      ii. Second sentence - ... with depressed adult and geriatric outpatients ... to the DSM-III (currently DSM-IV) category ...

iii. Revise the second paragraph as follows:

A major depressive episode (DSM-IV) implies ...persistent (nearly every day for at least 2 weeks) depressed or ... daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood; loss of interest in usual activities; significant change in weight and/or appetite; insomnia or hypersomnia; psychomotor agitation or retardation; increased fatigue; feelings of guilt or worthlessness; slowed thinking or impaired concentration; a suicide attempt or suicidal ideation.

e. PRECAUTIONS

i. Drug Interactions

A). "coadministration" (three instances) and "coadministered" (two instances) [delete hyphen]

B). First sentence - "etc." (add period)

C). Potential Effects of Coadministration of Drugs Tightly Bound to Plasma Proteins - "warfarin" rather than "Coumadin"

D). Warfarin - "anticoagulant" (delete hyphen)

ii. Carcinogenesis, Mutagenesis, Impairment of Fertility, Carcinogenicity - ... (approximately 1.2 and 0.7 times, ...

iii. Retitle the "Usage in the Elderly" subsection "Geriatric Use" and revise as follows:

Geriatric Use
U.S. fluoxetine clinical trials (10,782 patients) included 687 patients $\geq$ 65 years of age and 93 patients $\geq$ 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

A). First sentence - Cases of ... (delete "Several")

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

f. ADVERSE REACTIONS

i. Table 2, first column - "Vasodilatation" (spelling)

ii. Paragraph after Table 2 - ... on placebo ... (rather than "of")

g. DOSAGE AND ADMINISTRATION

i. "Geriatric Use" rather than "Usage in the Elderly" (3 instances)

ii. Switching Patients to a Tricyclic Antidepressant (TCA)

A). "coadministered" (delete hyphen)

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

h. HOW SUPPLIED

See GENERAL COMMENTS (a) above.

Please revise your container labels 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

(this supersedes the TENTATIVE APPROVAL SUMMARY dated 3-26-01)
TENTATIVE APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-755** Date of Submission: **April 26, 2001**

Applicant's Name: **Alphapharm Pty. Ltd.**

Established Name: **Fluoxetine Hydrochloride Tablets 10 mg and 20 mg**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 30s, 100s and 2000s
Satisfactory in FPL as of March 6, 2001 submission.

Professional Package Insert Labeling:
Satisfactory in FPL as of April 26, 2001 submission.

Revisions needed post approval: PI – ADVERSE REACTIONS (1) "Associated with Discontinuation ..." – "... in depression and OCD." (delete comma) (2) Table 2 – Delete the second row (the two dashes)

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Prozac® Tablets

NDA Number: 20-974

NDA Drug Name: Prozac® (fluoxetine hydrochloride) Tablets

NDA Firm: Lilly Research Laboratories

Date of Approval of NDA Insert and supplement #: 11/28/00 (S-062) [for NDA 18-936]

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side by sides

Other Comments: There are no approved supplements for NDA 20-974 (the RLD). It has a shared insert with the capsule (NDA 18-936) and the oral solution (NDA 20-101). The firm did not submit S-052, the supplement for revision to the Geriatric Use subsection to NDA 20-974 (they should have). I used this supplement to do my review. Also, I called the U.S. Agent for the firm (Michelle Bonomi) on 10-4-00 about having the bulk container labels revised to include the statement that the fluoxetine present is in the form of the hydrochloride as seen on the container labels. I stated that since we do not approve bulk container labels that the firm would not have to submit the revised bulk container labels. The firm had submitted two sets of PI's, one is combined with the capsules and the other is just the tablets. The latter will be used during the 180 day exclusivity period for the capsules. After that time the combined insert will be used. The firm sent in a telephone amendment withdrawing the combined insert. We cannot approve this application with that labeling (because the capsules will be approved at a later date). With the 4-26-01 amendment the firm deleted all references to bulimia in their insert.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24		X	
Is this name different than that used in the Orange Book?	X		
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	

Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement? Three ingredients in the DESCRIPTION section not in the C&C statement - They could be ingredients of the Opadry - I WILL ASK THE CHEMIST	X		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

The DESCRIPTION section lists hydroxypropyl methylcellulose, polyethylene glycol, and titanium dioxide as inactive ingredients yet they are not listed in the C & C statement. Are they components of the Opadry?

FOR THE RECORD:

1. This review was based on the labeling for Prozac® (Lilly; Approved 11/28/00; Revised 10/00 [in draft]. There are no approved supplements for NDA 20-974 (the RLD). It has a shared insert with the capsule (NDA 18-936) and the oral solution (NDA 20-101). The firm did not submit S-062, the supplement for revisions throughout the insert to NDA 20-974 (they should have). I used this supplement to do my review.

2. The inactives are listed accurately in the DESCRIPTION section except see NOTES TO THE CHEMIST (p 2655 v 1.7 and p 68 v B 2.1).

3. Two patents are still in effect for the innovator:

   4626549 - A method of blocking the uptake of monoamines by brain neurons in animals (use code U-84) expires 12/2/03. Use code U-154 - method of treating animals suffering from an appetite disorder - is also associated with this patent

   4314081 - For the chemical entity - expires 2/2/01

   The firm has filed a Paragraph 4 to both patents and an MOU statement to patent "549. They have deleted all information related to the bulimia indication associated with the first above referenced patent.

4. Storage/dispensing recommendations:

   NDA - Store at CRT 59° to 86°F (15° to 30°C). Dispense in a tight, light-resistant container.

   ANDA - Store at CRT 15° to 30°C (59° to 86°F)(see USP). Dispense in a tight, light-resistant container.

5. This is the first generic for this drug product. This is a non-USP drug product and it is not listed in the PF. Re: the established name, it was decided to use "Fluoxetine Tablets" since the USP capsule form of the drug and the oral solution (not USP) both drop the salt (HCl) from the name. This decision was reversed since the product is not USP - I asked the firm to revise their labels and labeling to read "Fluoxetine Hydrochloride Tablets" and they have.

6. The innovator markets this drug product (10 mg) in bottles of 30s and 100s. The 20 mg tablets were withdrawn. The firm submitted a copy of a Citizen's Petition to determine whether or not the 20 mg tablets were withdrawn for safety reasons. The applicant proposes bottle sizes of 30s (CRC), 100s (CRC), and 2000s for both the 10 mg and 20 mg tablets. The applicant's proposed containers are all made of HDPE.

7. The tablets are accurately described in the HOW SUPPLIED section (p 3367 v 1.8 and p 729 v B 2.3).

8. Both the innovator and this ANDA's 10 mg drug product is scored (NOTE: I don't know why because there is no indication for a 5 mg dose in the labeling.) The ANDA'S 20 mg tablet is also scored.

9. Alphapharm is the manufacturer (p 2927 v 1.7).

10. The February 11, 2000 submission is for the addition of a 20 mg tablet.

11. This ANDA originally shared an insert with ANDA 75-577 (capsules) but the firm submitted both a combined insert and a separate one, the separate one to be used during the 180 day exclusivity period for the capsules then the combined one will be used after this period. The firm was informed that this plan won't work because the combined insert cannot be approved before the capsules application is approved. The firm has withdrawn the combined insert (3/23/01) and they submitted a "tablets only" insert minus all bulimia information with the 4-26-01 amendment.

Date of Review: 5-8-01 **Date of Submission:** 4-26-01

Primary Reviewer: Adolph Vezza **Date:** 5/8/01

Team Leader: Charlie Hoppes /SI **Date:** 5/8/01

/SI

cc:

ANDA: 75-755
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev/5/8/01|V:\FIRMSAM\Alphapharm\LTRS&REV\75755TAP4.L
Review

RECORD OF TELEPHONE CONVERSATION

I spoke to Michelle Bonomi, the U.S. Agent for Alphapharm, regarding the bulk container labels Alphapharm submitted to their ANDA 75-755 for Fluoxetine Tablets. I asked them to revise these labels so that it would be clear that the fluoxetine present in the tablets was present as the hydrochloride as seen on their container labels. I told Michelle that we do not approve bulk container labels but that if submitted we do review them. I also told her that since we don't approve them that it would not be necessary for Alphapharm to submit the revised bulk container labels so long as they make the requested revision.

DIVISION OF LABELING AND PROGRAM SUPPORT

DATE
October 4, 2000

ANDA NUMBER
75-755

IND NUMBER

TELECON

INITIATED BY APPLICANT/ SPONSOR X

MADE BY TELE.

X FDA

IN PERSON _

PRODUCT NAME
FLUOXETINE TABS

FIRM NAME
ALPHAPHARM

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Michelle Bonomi
U.S. Agent

TELEPHONE NUMBER
(914) 573-5503

SIGNATURE
Adolph Vezza

10/4/00

TENTATIVE APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-755** Date of Submission: **September 8, 2000**

Applicant's Name: **Alphapharm Pty. Ltd.**

Established Name: **Fluoxetine Tablets 10 mg and 20 mg**

NOTE: Do not approve before application for capsules in this labeling.

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 30s, 100s and 2000s

Satisfactory in FPL as of September 8, 2000 submission.

Professional Package Insert Labeling:

Satisfactory in FPL as of September 8, 2000 submission.

Revisions needed post-approval: PI - PRECAUTIONS, Geriatric Use "safety and effectiveness" rather than "safety or effectiveness"

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Prozac® Tablets

NDA Number: 20-974

NDA Drug Name: Prozac® (fluoxetine) Tablets

NDA Firm: Lilly Research Laboratories

Date of Approval of NDA Insert and supplement #: 10/7/99 (S-052) [for NDA 18-936]

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side by sides

Other Comments: There are no approved supplements for NDA 20-974 (the RLD). It has a shared insert with the capsule (NDA 18-936) and the oral solution (NDA 20-101). The firm did not submit S-052, the supplement for revision to the Geriatric Use subsection to NDA 20-974 (they should have). I used this supplement to do my review. Also, I called the U.S. Agent for the firm (Michelle Bonomi) on 10-4-00 about having the bulk container labels revised to include the statement that the fluoxetine present is in the form of the hydrochloride as seen on the container labels. I stated that since we do not approve bulk container labels that the firm would not have to submit the revised bulk container labels.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24		X	
Is this name different than that used in the Orange Book?	X		
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?	X		

Three ingredients in the DESCRIPTION section not in the C&C statement - They could be ingredients of the Opadry - I WILL ASK THE CHEMIST			
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
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Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
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Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

The DESCRIPTION section lists hydroxypropyl methylcellulose, polyethylene glycol, and titanium dioxide as inactive ingredients yet they are not listed in the C & C statement. Are they components of the Opadry?

FOR THE RECORD:

1. This review was based on the labeling for Prozac® (Lilly; Approved 10/7/99; Revised 8/11/99. There are no approved supplements for NDA 20-974 (the RLD). It has a shared insert with the capsule (NDA 18-936) and the oral solution (NDA 20-101). The firm did not submit S-052, the supplement for revision to the Geriatric Use subsection to NDA 20-974 (they should have). I used this supplement to do my review.

2. The inactives are listed accurately in the DESCRIPTION section except see NOTES TO THE CHEMIST (p 2655 v 1.7 and p 68 v B 2.1).

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   4626549 - A method of blocking the uptake of monoamines by brain neurons in animals (use code U-84) expires 12/2/03. Use code U-154 - method of treating animals suffering from an appetite disorder - is also associated with this patent

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   The firm has filed a Paragraph 4 to both patents. Unlike other firms, e.g. Teva and Zenith-Goldline, they have retained reference to the bulimia indication associated with the first above referenced patent. Other firms are "not claiming" bulimia.

4. Storage/dispensing recommendations:

   NDA - Store at CRT 59° to 86°F (15° to 30°C). Dispense in a tight, light-resistant container.

   ANDA - Store at CRT 15° to 30°C (59° to 86°F). Dispense in a tight, light-resistant container.

5. This is the first generic for this drug product. This is a non-USP drug product and it is not listed in the PF. Re: the established name, it was decided to use "Fluoxetine Tablets" since the USP capsule form of the drug and the oral solution (not USP) both drop the salt (HCl) from the name.

6. The innovator markets this drug product (10 mg) in bottles of 30s and 100s. The 20 mg tablets were withdrawn. The firm submitted a copy of a Citizen's Petition to determine whether or not the 20 mg tablets were withdrawn for safety reasons. The applicant proposes bottle sizes of 30s (CRC), 100s (CRC), and 2000s for both the 10 mg and 20 mg tablets. The applicant's proposed containers are all made of HDPE.

7. The tablets are accurately described in the HOW SUPPLIED section (p 3367 v 1.8 and p 729 v B 2.3).

8. Both the innovator and this ANDA's 10 mg drug product is scored (NOTE: I don't know why because there is no indication for a 5 mg dose in the labeling.) The ANDA'S 20 mg tablet is also scored.

9. Alphapharm is the manufacturer (p 2927 v 1.7).

10. The February 11, 2000 submission is for the addition of a 20 mg tablet.

Date of Review: 9-21-00 **Date of Submission:** 9-8-00

Primary Reviewer: Adolph Vezza /S/ **Date:** 10/4/00

Team Leader: Charlie Hoppes /S/ **Date:** 10/4/00

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ANDA: 75-755
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
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Review

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

ANDA Number: 75-755 Date of Submission: December 6, 1999 and February 11, 2000

Applicant's Name: Alphapharm Pty. Ltd.

Established Name: Fluoxetine Tablets 10 mg and 20 mg

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. Revise your storage temperature recommendations throughout your labels and labeling as follows:

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

   b. We note that this application has a shared insert with ANDA 75-577. These ANDAs must be approved together or further revisions to the insert labeling will be necessary.

2. CONTAINER 30s, 100s, 2000s (10 mg and 20 mg)

   See GENERAL COMMENT above.

3. INSERT

   a. GENERAL COMMENT

      "U.S." rather than "US" throughout the text of the insert labeling

   b. DESCRIPTION

      "molecular" rather than "empirical"

   c. CLINICAL PHARMACOLOGY

      i. Absorption, Distribution, Metabolism, and Excretion, Systemic Bioavailability, second paragraph, first sentence - The capsule, tablet, and oral solution dosage form ...

      ii. Clinical Trials, second paragraph

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

         B). Penultimate sentence - ... HAM-D score of $\leq$ 8. Fluoxetine ...

   d. INDICATIONS AND USAGE

      i. "reevaluate" rather than "re-evaluate" (three instances)

      ii. Second sentence - ... with depressed adult and geriatric outpatients ... to the DSM-III (currently DSM-IV) category ...

iii. Revise the second paragraph as follows:

A major depressive episode (DSM-IV) implies ...persistent (nearly every day for at least 2 weeks) depressed or ... daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood; loss of interest in usual activities; significant change in weight and/or appetite; insomnia or hypersomnia; psychomotor agitation or retardation; increased fatigue; feelings of guilt or worthlessness; slowed thinking or impaired concentration; a suicide attempt or suicidal ideation.

e. PRECAUTIONS

i. Drug Interactions

A). "coadministration" (three instances) and "coadministered" (two instances) [delete hyphen]

B). First sentence - "etc." (add period)

C). Potential Effects of Coadministration of Drugs Tightly Bound to Plasma Proteins - "warfarin" rather than "Coumadin"

D). Warfarin - "anticoagulant" (delete hyphen)

ii. Carcinogenesis, Mutagenesis, Impairment of Fertility, Carcinogenicity - ... (approximately 1.2 and 0.7 times, ...

iii. Retitle the "Usage in the Elderly" subsection "Geriatric Use" and revise 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

A). First sentence - Cases of ... (delete "Several")

B). 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 ...

f. ADVERSE REACTIONS

i. Table 2, first column - "Vasodilatation" (spelling)

ii. Paragraph after Table 2 - ... on placebo ... (rather than "of")

g. DOSAGE AND ADMINISTRATION

i. "Geriatric Use" rather than "Usage in the Elderly" (3 instances)

ii. Switching Patients to a Tricyclic Antidepressant (TCA)

A). "coadministered" (delete hyphen)

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

h. HOW SUPPLIED

See GENERAL COMMENTS (a) above.

Please revise your container labels 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.

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

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling?

Container Labels: 30s, 100s and 2000s

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Prozac® Tablets

NDA Number: 20-974

NDA Drug Name: Prozac® (fluoxetine) Tablets

NDA Firm: Lilly Research Laboratories

Date of Approval of NDA Insert and supplement #: 10/7/99 (S-052) [for NDA 18-936]

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side by sides

Other Comments: There are no approved supplements for NDA 20-974 (the RLD). It has a shared insert with the capsule (NDA 18-936) and the oral solution (NDA 20-101). The firm did not submit S-052, the supplement for revision to the Geriatric Use subsection to NDA 20-974 (they should have). I used this supplement to do my review.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24		X	
Is this name different than that used in the Orange Book?	X		
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or			

cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement? Three ingredients in the DESCRIPTION section not in the C&C statement - They could be ingredients of the Opadry - I WILL ASK THE CHEMIST	X		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	

Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

The DESCRIPTION section lists hydroxypropyl methylcellulose, polyethylene glycol, and titanium dioxide as inactive ingredients yet they are not listed in the C & C statement. Are they components of the Opadry?

FOR THE RECORD:

1. This review was based on the labeling for Prozac® (Lilly; Approved 10/7/99; Revised 8/11/99. There are no approved supplements for NDA 20-974 (the RLD). It has a shared insert with the capsule (NDA 18-936) and the oral solution (NDA 20-101). The firm did not submit S-052, the supplement for revision to the Geriatric Use subsection to NDA 20-974 (they should have). I used this supplement to do my review.

2. The inactives are listed accurately in the DESCRIPTION section except see NOTES TO THE CHEMIST (p 2655 v 1.7 and p 68 v B 2.1).

3. Two patents are still in effect for the innovator:

   4626549 - A method of blocking the uptake of monoamines by brain neurons in animals (use code U-84) expires 12/2/03. Use code U-154 - method of treating animals suffering from an appetite disorder - is also associated with this patent

   4314081 - For the chemical entity - expires 2/2/01

   The firm has filed a Paragraph 4 to both patents. Unlike other firms, e.g. Teva and Zenith-Goldline, they have retained reference to the bulimia indication associated with the first above referenced patent. Other firms are "not claiming" bulimia.

4. Storage/dispensing recommendations:

   NDA - Store at CRT 59° to 86°F (15° to 30°C). Dispense in a tight, light-resistant container.

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Date of Review: 2-23-00 **Date of Submission:** 12-6-99 and 2-11-00

Primary Reviewer: Adolph Vezza **Date:** 2/24/00

Team Leader: Charlie Hoppes /S/ /S/ **Date:** 4/24/00

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ANDA: 75-755
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Review