

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-458

LABELING REVIEW(S)

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

ANDA Number: **76-458**

Dates of Submission: **July 15, 2002 and November 19, 2003**

Applicant's Name: **Par Pharmaceutical, Inc.**

Established Name: **Fluoxetine Oral Solution USP, 20 mg/5 mL**

Labeling Deficiencies:

1. GENERAL COMMENTS

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

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

- b. Please update your exclusivity statement regarding the New Patient Population (NPP) exclusivity [patients 6 to 11 years old] with an original expiration date of January 3, 2006 [extended to July 3, 2006 because of pediatric exclusivity].

- c. We note that you have filed a Paragraph 3 certification to the '549 patent and its associated use code U-154 [treatment of animals suffering from an appetite disorder]. Since this patent [and associated use code U-154] expire June 2, 2004 you must include all text relating to the bulimia indication in your insert as seen in the model labeling.

2. CONTAINER 120 mL

See GENERAL COMMENTS 1 (a) above.

3. INSERT

a. GENERAL COMMENTS

- i. "e.g." rather than "—" throughout the insert
- ii. "U.S." rather than "—" throughout the insert
- iii. "coadministration" and "coadministered" throughout the insert [delete "_____"]

b. DESCRIPTION

- i. "It also contains alcohol (0.17%), benzoic acid ..." [Ensure that the alcohol content is expressed in (v/v).]
- ii. You may delete "_____" from the listing of inactive ingredients.

c. CLINICAL PHARMACOLOGY

Pharmacodynamics, first sentence - "The antidepressant, antiobsessive-compulsive, and antibulimic actions of ..."

d. CLINICAL TRIALS

Add the bulimia information to the end of this section as seen in the labeling of the reference listed drug.

e. INDICATIONS AND USAGE

Add the bulimia information to the end of this section as seen in the labeling of the reference listed drug.

f. WARNINGS

Potential Interaction with Thioridazine, first sentence - "25 mg" rather than " — "

g. PRECAUTIONS

i. General

A). Anxiety and Insomnia

- 1). Add the following text as the third paragraph:

In U.S. placebo-controlled clinical trials for bulimia nervosa, insomnia was reported in 33% of patients treated with fluoxetine 60 mg, and 13% of patients treated with placebo. Anxiety and nervousness were reported respectively in 15% and 11% of patients treated with fluoxetine 60 mg, and in 9% and 5% of patients treated with placebo.

- 2). Fourth paragraph ("Among the ...) - "... insomnia (2% in bulimia), and nervousness ..."

B). Altered Appetite and Weight

- 1). First paragraph - "... in underweight depressed or bulimic patients may be ..."

- 2). Add the following text as the last paragraph:

In U.S. placebo-controlled clinical trials for bulimia nervosa, 8% of patients treated with fluoxetine, 60 mg, and 4% of patients treated with placebo reported anorexia (decreased appetite). Patients treated with fluoxetine, 60 mg, on average lost 0.45 kg compared with a gain of 0.16 kg by patients treated with placebo in the 16-week double-blind trial. Weight change should be monitored during therapy.

- C). Activation of Mania/Hypomania, second paragraph - Add the following as the second sentence:
 "... with placebo. No patients reported mania/hypomania in U.S. placebo-controlled clinical trials for bulimia. In all ..."
 - D). Seizures, second sentence - "... trials for either OCD or bulimia. In all ..."
 - E). Suicide, second paragraph - "... comorbidity between both OCD and major depressive disorder and bulimia and major depressive disorder, the same ... when treating patients with OCD or bulimia."
 - F). Drugs Metabolized by P450IID6, first paragraph, last sentence - "... its metabolite, the sum ..." (add comma)
- ii. Nursing Mothers, third sentence - "295 ng/mL" (delete _____)
 - iii. Pediatric Use, fourth paragraph, penultimate sentence - "... the growth, development, and ..." (add comma)

h. ADVERSE REACTIONS

- i. Incidence in Major Depressive Disorder, OCD and Bulimia Placebo-Controlled Clinical Trials ...
 - A). Add "Bulimia" to the title as seen above.
 - B). Last sentence - "... of major depressive disorder, OCD, and bulimia in U.S. controlled ..."
 - C). Table 1
 - 1). Title - "... MAJOR DEPRESSIVE DISORDER, OCD AND BULIMIA PLACEBO-CONTROLLED ..."
 - 2). Add all the bulimia data to the table as seen in the labeling of the reference listed drug.
 - 3). *Footnote - "... depressive disorder, OCD and bulimia clinical trials."
 - 4). +Footnote - "... N=43 placebo OCD; N=14 fluoxetine bulimia; N=1 placebo bulimia)"
- ii. Association with Discontinuation in Major Depressive Disorder, OCD and Bulimia Placebo-Controlled Clinical Trials ...
 - A). Title
 - 1). Note the upper case letters in the title as seen above.
 - 2). Add "Bulimia" to the title.
 - B). Last sentence - "... in major depressive disorder, OCD and bulimia clinical trials."

- C). Table 2
- 1). Title
 - a). "... MAJOR DEPRESSIVE DISORDER, OCD AND BULIMIA PLACEBO-CONTROLLED ..."
 - b). "... CLINICAL TRIALS*" (add asterisk)
 - 2). Add "bulimia" to the title of the first column.
 - 3). Add the bulimia data column with appropriate title to the table as seen in the labeling of the reference listed drug.
 - 4). Delete _____.
 - 5). Footnote - "... major depressive disorder, OCD and bulimia clinical trials."
- D). Other Adverse Events in Pediatric Patients ..., second paragraph, first sentence - Delete the word _____
- E). Male and Female Sexual Dysfunction with SSRIs, first paragraph, fifth sentence - "... major depressive disorder, OCD, and bulimia placebo-controlled ..."

i. DOSAGE AND ADMINISTRATION

- i. Obsessive-Compulsive Disorder, Initial Treatment, Adult, second sentence - "... dose response relationship for ..." (delete _____)
- ii. Add the bulimia information subsection as seen in the labeling of the reference listed drug to follow the OCD subsection.
- iii. Switching Patients to a Tricyclic ..., last sentence - "... under PRECAUTIONS, Drug Interactions)."

j. HOW SUPPLIED

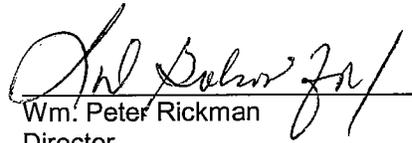
See GENERAL COMMENTS (1) (a) above.

Please revise your insert labeling, as instructed above, and submit in final print

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

<http://www.fda.gov/cder/cdernew/listserv.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.



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

**APPEARS THIS WAY
ON ORIGINAL**

BASIS OF APPROVAL:

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: 120 mL

Satisfactory in FPL as of November 19, 2003 submission [vol 2.1].

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 Liquid

NDA Number: 20-101

NDA Drug Name: Prozac Liquid (fluoxetine oral solution USP)

NDA Firm: Eli Lilly and Company

Date of Approval of NDA Insert and supplement #: 1-03-03 (S-064)(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: The RLD - Prozac Liquid - shares an insert with Prozac capsules and tablets - the capsules NDA (18-936) has the most recently approved labeling supplement.

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 26 | X | | |
| Is this name different than that used in the Orange Book? | | 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 | |
| Inactive Ingredients: (FTR: List page # in application where inactives are listed) | | | |
| Does the product contain alcohol? TRACE AMOUNT IN ONE OF THE FLAVORING. If so, has the accuracy of the | X | | |

| | | | |
|--|---|---|---|
| statement been confirmed? Firm has not mentioned the fact that the product contains alcohol - I have asked them to mention it in the DESCRIPTION section. See calculations in FTR for %v/v | | | |
| 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 | |
| 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 |
| 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 | |
| Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD? | | 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? | | | |
| 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? YES If so, was a food study done? NO - WAIVER GRANTED - SEE PAGE 163 7-15-02 SUBMISSION | X | 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:

Is there any ethyl alcohol in the final product? There is a small amount in the Natural Peppermint Extract. See calculations below.

FOR THE RECORD:

- Review based on the labeling of Prozac (NDA 18-936/S064) Capsules, approved 1-3-03. The RLD - Prozac Liquid - shares an insert with Prozac capsules and tablets - the capsules NDA (18-936) has the most recently approved labeling supplement. The last approved supplement for the RLD NDA 20-101 (Prozac Liquid) is S-027 approved 7-29-02.

2. Patent/ Exclusivities

Patent Data - 20-101

| No | Expiration | Use Code | Use | File | Labeling Impact |
|---------|---|----------|--|------|---|
| 4626549 | 6-2-04 (6 months ped exclusivity added on) | U-154 | Method of treating animals suffering from an appetite disorder | III | Because of PIII certification all the bulimia information must remain in the insert |

Exclusivity Data - 20-101

| Code/sup | Expiration | Use Code | Description | Labeling Impact |
|----------|------------|----------|--|---------------------------------------|
| I-362 | 7-29-05 | | Treatment of panic disorder, with or without agoraphobia | All panic disorder info removed |
| NPP | 1-3-06 | | Use in 6 to 11 year olds | Peds info modified due to exclusivity |
| PED | 7-3-06 | | Use in 6 to 11 year olds | Peds info modified due to exclusivity |

3. Storage Conditions:
 NDA – Store at controlled room temperature, 59° to 86°F (15° to 30°C)
 ANDA – Store at controlled room temperature, 59° to 86°F (15° to 30°C) (see USP). I have asked the firm to revise to read: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].
 USP -
4. Dispensing Recommendations:
 NDA – Dispense in a tight, light-resistant container.
 ANDA - Dispense in a tight, light-resistant container as defined in USP. Protect from light.
 USP - Dispense in a tight, light-resistant container.
5. Par Pharmaceutical is the manufacturer [p 323 v 1.1 section IX].
6. Product Line:
 The innovator markets their product in bottles of 120 mL.
 The applicant proposes to market their product in bottles (amber — with CRC closure) of 120 mL.
7. The flavor and color of this drug product have been accurately described in the HOW SUPPLIED section [p 24 v 1.1 – 1-13-03 submission].
8. Inactive Ingredients:
 The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 166 (Volume 1.1 - section VII). However the firm has failed to indicate that the product contains alcohol. The innovator's product has 0.23% while this product has 0.17% (see calculations below).
 I have asked the firm to indicate the alcohol concentration (v/v) in the DESCRIPTION section as does the innovator. The innovator's container label does not indicate that there is alcohol present in their drug product so I have not asked this generic to declare it on their container label.

ALCOHOL CALCULATION:

The natural peppermint flavoring is — % (w/w) alcohol. Each 5 mL contains — of natural peppermint flavoring

————— mg density of alcohol = 0.789

————— = 0.17% (v/v)

This calculation was verified by U. Venkataran (chemistry team leader)

Date of Review: 12-5-03

Dates of Submission: 7-15-02 and 11-19-03

Primary Reviewer: Adolph Vezza

Date:

A. Vezza

12/17/03

Team Leader: Captain Lillie Golson

Date:

L. Golson

12/17/03

cc: ANDA: 76-458
 DUP/DIVISION FILE
 HFD-613/AVezza/LGolson (no cc)
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 Review

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

ANDA Number: **76-458** Dates of Submission: **December 31, 2003 and January 28, 2004**

Applicant's Name: **Par Pharmaceutical, Inc.**

Established Name: **Fluoxetine Oral Solution USP, 20 mg/5 mL**

BASIS OF APPROVAL:

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: 120 mL

Satisfactory in FPL as of December 31, 2003 submission [vol 2.1].

Professional Package Insert Labeling:

Satisfactory in FPL as of January 28, 2004 submission [vol 2.1 - 010699-01 - rev 01/04].

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 Liquid**

NDA Number: **20-101**

NDA Drug Name: **Prozac Liquid (fluoxetine oral solution USP)**

NDA Firm: **Eli Lilly and Company**

Date of Approval of NDA Insert and supplement #: **1-03-03 (S-064)(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: **The RLD - Prozac Liquid - shares an insert with Prozac capsules and tablets - the capsules NDA (18-936) has the most recently approved labeling supplement.**

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 26 | X | | |
| Is this name different than that used in the Orange Book? | | 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 cartooned? 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 | |
| Inactive Ingredients: (FTR: List page # in application where inactives are listed) | | | |
| Does the product contain alcohol? TRACE AMOUNT IN ONE OF THE FLAVORING. If so, has the accuracy of the statement been confirmed? Firm has not mentioned the fact that the product contains alcohol - I have asked them to mention it in the DESCRIPTION section and they have with this submission. See calculations in FTR for %v/v | 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 | |
| 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 |
| 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 | |
| Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD? | | 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? | | | |
| 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? YES If so, was a food study done? NO - WAIVER GRANTED - SEE PAGE 163 7-15-02 SUBMISSION | X | 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:

Is there any ethyl alcohol in the final product? YES - There is a small amount in the Natural Peppermint Extract. See calculations below. Verified by chemistry team leader U. Venkataran.

FOR THE RECORD: (portions taken from previous review)

- Review based on the labeling of Prozac (NDA 18-936/S064) Capsules, approved 1-3-03. The RLD - Prozac Liquid - shares an insert with Prozac capsules and tablets - the capsules NDA (18-936) has the most recently approved labeling supplement. The last approved supplement for the RLD NDA 20-101 (Prozac Liquid) is S-027 approved 7-29-02.

Date of Review: 2-20-04

Dates of Submission: 12-31-03 and 1-28-04

Primary Reviewer: Adolph Vezza

Date:

Team Leader: *A. Vezza*
Captain Lillje Golson

Date:

cc: ANDA: 76-458
DUP/DIVISION FILE
HFD-613/AVezza/LGolson (no cc)
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Review

APPEARS THIS WAY
ON ORIGINAL