CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18-936/S-060/S-062/S-063

ADMINISTRATIVE DOCUMENTS

REGULATORY PROJECT MANAGER
LABELING REVIEW

NOV 21 2000

Drug: Prozac Capsules (NDA 18-936)

Supplement	Date	Action Date	Status
SLR-060	7-6-99	5-2-00	AE
SLR-062	8-22-00	Pending	
SLR-063	8-31-00	Pending	

Note of interest:

- The last approved labeling supplement (Label Code: 69-4721-00-6) for Prozac, SLR-052, was approved in an Agency letter dated 10-7-99.
- This application has two product labels; one with the tradename Sarafem used to treat Premenstrual Dysphoric Disorder (PMDD), and the other with the tradename Prozac used for depression, OCD, and bulimia nervosa. All safety related changes will be placed into both product labelings.

REVIEW

18-936/S-060
Date: 7-6-99, and amended with a faxed submission dated 10-2-00, and an archival submission dated 11-8-00
CBE: No, Prior Approval
Label Code No: N/A, Draft Labeling
Reviewed by Medical Officer: An approvable letter issued on 5-2-00. Lilly responded with their proposed changes in a fax dated 10-2-00. This was reviewed by the medical officer and found to be acceptable. An amendment dated 11-8-00, submitted to this application, providing for Lilly's summary of total changes is also consistent with the 10-2-00 fax.

This supplemental application provides for revisions to the **ADVERSE REACTIONS-Other Events Observed in US Clinical Trials**, and **ADVERSE REACTIONS-Postintroduction Reports** sections of labeling [redacted]

18-936/S-062
Date: 8-22-00
CBE: No, Prior Approval
Label Code No: N/A, Draft Labeling
Reviewed by Medical Officer: Yes, recommends approval with minor edits. These minor revisions were agreed upon between Lilly and the Agency, and this is reflected in their amendment dated 11-8-00, to this supplemental application providing for Lilly's summary of total changes.

This supplemental application provides for a harmonization of the Prozac labeling with the approved labeling for Sarafem, the fluoxetine drug product for the treatment of PMDD. Specifically, these changes provide for the following revisions:

1. A cautionary statement in the **DESCRIPTIONS** section of labeling that Sarafem is the same product as Prozac.

2. A statement that thioridazine should not be used with Prozac in the **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS** sections of labeling.
3. The addition of two additional adverse event terms of "lupus-like syndrome" and "laryngospasm" into the **WARNINGS** section.
4. An addition of a subsection entitled **Sumatriptan** under **PRECAUTIONS-Drug Interactions** section.
5. The addition of a subsection entitled **Male and Female Sexual Dysfunction with SSRIs** under the **ADVERSE REACTIONS** section.
6. The addition of several terms to the **ADVERSE REACTIONS-Postintroduction Reports** section.
7. A complete revision of the **OVERDOSAGE** section.
8. An addition to the **HOW SUPPLIED** section of a "Protect from light." statement for Prozac capsules.

Note of interest: All of the above changes were acceptable except for the following two changes:

1) Under the Sexual Dysfunction section, the paragraph should include a statement similar to the one in the Sarafem labeling regarding orgasmic dysfunction. The Agency proposed the following sentence: "There have been spontaneous reports in women taking fluoxetine of orgasmic dysfunction, including anorgasmia."

2) Under the Sexual Dysfunction section, change "mood-related disorder", which was more appropriate for the PMDD indication, with the more general term "psychiatric disorder". The sentence would now read as follows: Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder..."

Lilly agreed to make the above two changes (see amendment dated 11-8-00).

Additionally, the Agency communicated to Lilly in a letter dated July 6, 2000, to monitor the drug product in photostability studies, to submit the results of such studies before January 6, 2001, and to remove the light protection instruction from labeling via a CBE-30 supplement if the stability studies demonstrate that light protection is not necessary. This commitment should, again, be reflected in this approval letter.

18-936/S-063
Date: 8-22-00
CBE: Yes
Label Code No: PV 3281 AMP
Reviewed by Medical Officer: Yes

This supplemental application provides for final printed labeling as requested in the Agency approval letter dated 7-6-00, providing for the approval of fluoxetine, under the tradename of Sarafem, for PMDD. The FPL is identical to the labeling attached in the 7-6-00 approval letter except for the revisions agreed upon in telephone conversation between myself and Lilly personnel dated 7-6-00. The revisions included changes to the **WARNINGS, ADVERSE REACTIONS-Female Sexual Dysfunction with SSRIs, ADVERSE REACTIONS-**

Postintroduction Reports, and **OVERDOSAGE** sections. It should be noted that most of these revisions were previously requested in Agency correspondence dated 6-7-00.

CONCLUSIONS

1. The supplements only provide for the labeling revisions listed above. It should also be noted that there are several minor editorial changes throughout the labeling. See highlighted labeling, submitted on 11-8-00, denoting revisions to the last approved Prozac labeling.

2. The labeling submitted for Sarafem is identical to the labeling attached to the approval letter dated 7-6-00 except for the changes as outlined in the memo of telephone call dated 7-6-00.

3. The medical officer concurs with the above revisions.

4. I recommend that an approval letter issue for these supplemental applications.

5. Lilly also needs to be notified that subsequent labeling revisions not only should be submitted to the capsule NDA, 18-936, but also to the tablet, NDA 20-974, and oral solution, NDA 20-101, applications. I will notify Lilly of this administrative issue via telephone.

Paul David. RPh
Regulatory Project Manager

11/21/2000
John Purvis
Supervisory Consumer Safety Officer

NDA 18-936
HFD-120/Div Files
HFD-120/T.Laughren/A.Mosholder/ P.David
11-9-00pd
rev:11-21-00pd
ft:11-21-00pd
LABELING REVIEW

www.lilly.com

ORIGINAL

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285 U.S.A.

Phone 317 276 2000

November 8, 2000

Correspondence

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological
Drug Products, HFD-120
Attn.: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857-1706

SLR-060- AL
SLR-062 AL

NDA SUPP AMEND

Re: NDA 18-936, Prozac® (fluoxetine hydrochloride)

Submitted herewith are labeling changes for Prozac that reflect final resolution of supplements S-060 and S-062. In addition, changes agreed between Lilly and FDA as a result of final labeling for Sarafem™ (fluoxetine hydrochloride) have also been incorporated into the Prozac labeling. Final agreement on all changes was reached in phone and electronic mail communications between Mr. Paul David, FDA, and Dr. David W. Johnson, Lilly, on November 7, 2000.

Please call Dr. David W. Johnson at (317) 277-1806 or me at (317) 277-3799 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

for Gregory T. Brophy, Ph.D.
Director
U.S. Regulatory Affairs

Enc.
cc: Mr. Paul David

Note to reviewer

The labeling changes included in the attached proposed labeling encompass those sent to FDA under Supplement S-062 on August 22, 2000. They also finalize changes for Supplement S-060. Finally, they are consistent with similar changes made to the Sarafem™ labeling in the original approval on July 6, 2000 and in Supplement S-063 filed on August 31, 2000. The basis for all the labeling changes is the current Prozac labeling, PV 3312, dated August 11, 1999. Details of the regulatory history of each change are given below.

1. **DESCRIPTION** section: a statement to disclose that Prozac® and Sarafem are both fluoxetine hydrochloride. This statement is similar, but not identical, to the one included in the Sarafem labeling in the original approval 7/6/00 and is the same as that included in Supplement S-062 for Prozac.

2. **CONTRAINDICATIONS, WARNINGS, & PRECAUTIONS** section: incorporation of the thioridazine information exactly as in the Sarafem labeling. These statements are identical to those included in the Sarafem labeling in the original approval 7/6/00 and the same as those included in Supplement S-062 for Prozac.

3. **WARNINGS** section: incorporation of two additional event terms, lupus-like syndrome and laryngospasm exactly as in the Sarafem labeling. These changes were made to the Sarafem labeling in Supplement S-063 and are the same as those included in Supplement S-062 for Prozac. The original approval for this labeling was in the letter from FDA to Lilly on June 7, 2000.

4. **PRECAUTIONS** section: incorporation of the sumatriptan precaution exactly as in the Sarafem labeling approved on 7/6/00 and the same as that included in Supplement S-062 for Prozac. Such a precaution was originally proposed by FDA on September 25, 1996 with response from Lilly on December 13, 1996. No separate supplement number was assigned to this change.

5. **ADVERSE REACTIONS** section: incorporation of a paragraph concerning male and female sexual dysfunction with SSRIs. This paragraph is identical to the approved Sarafem labeling from 7/6/00 in the initial part of the paragraph, but differs in the data included since it reflects the database on Prozac for all patients, males and females, while the Sarafem labeling only includes information on female patients. The statements concerning the specific data are similar to those used in the labeling of other SSRIs. The labeling for Prozac was proposed in Supplement S-062. In further electronic messages between Mr. Paul David, FDA, and Dr. David W. Johnson, Lilly, two suggested editorial changes to this section were agreed, as of 10/30/00. The labeling included here reflects that contained in Supplement S-062 with the addition of the changes agreed by electronic mail.

6. **ADVERSE REACTIONS** section, Other Events subsection: On July 6, 1999, Lilly proposed changes to the Prozac labeling to reflect the current understanding of the

terms neuroleptic malignant syndrome and serotonin syndrome with respect to the Prozac labeling. FDA responded to that request on May 2, 2000, agreeing with some, but not all of the proposed changes. Lilly confirmed acceptance of FDA's suggested labeling in a fax from Dr. Reed Tarwater, Lilly, to Mr. Paul David, on October 2, 2000. Mr. David responded with agreement to those changes in an electronic message on October 4, 2000. The changes included here reflect the results of that agreement. Please note that the original proposal by Lilly included changes in the **CONTRAINDICATIONS** section. These have not been made per the agreement described above.

7. **ADVERSE REACTIONS** section: incorporation of additional postintroduction reports event terms exactly as in the Sarafem labeling as modified in Supplement S-063. These changes are identical to those in Supplement S-062. The original approval for this labeling was in the letter from FDA to Lilly on June 7, 2000.

8. **OVERDOSE** section: incorporation of the new overdose language exactly as in the Sarafem labeling in Supplement S-063 and as proposed for Prozac in Supplement S-062. The original approval for this labeling was in the letter from FDA to Lilly on June 7, 2000.

9. **HOW SUPPLIED** section: incorporation of the statement "Protect from light", exactly as in the Sarafem labeling and as proposed in Supplement S-062.

10. **ALL** sections: minor editorial changes throughout the labeling as proposed in Supplements S-062 and S-063.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-936/S-063

SEP 11 2000

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Attention: Gregory T. Brophy, Ph.D.
Director
U.S. Regulatory Affairs

Dear Dr. Brophy:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Sarafem (fluoxetine hydrochloride)

NDA Number: 18-936

Supplement Number: S-063

Date of Supplement: August 31, 2000

Date of Receipt: September 1, 2000

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on October 31, 2000 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation I
Attention: Document Control Room 4008
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

John S. Purvis 11 SEP 2000
Chief, Project Management Staff
Division of Neuropharmacological Drug Prducts, 120
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 18-936/063
HFD-120/Div. Files
HFD-120/CSO/David

filename: C:\WPWIN61\TEMPLATE\FDA\18-936.WPD

SUPPLEMENT ACKNOWLEDGEMENT

www.lilly.com

NDA SUPPLEMENT

Lilly

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285
U.S.A.

Phone 317 276 2000

August 31, 2000 ORIGINAL **SPECIAL SUPPLEMENT-CHANGES BEING EFFECTED**

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological
Drug Products, HFD-120
Attn.: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857-1706

CENTER FOR DRUG EVALUATION AND RESE
SEP 01 2000
RECEIVED HFD-120

NDA NO. 18-936 REF NO. SLR-063
NDA SUPPL FOR LABELING

Re: NDA 18-936, SARAFEM™ (fluoxetine hydrochloride)

Please refer to phone conversations between Mr. Paul David and Dr. Doris Bates, FDA, and Dr. David W. Johnson, Lilly concerning the approved labeling for Sarafem. In those conversations, it was agreed that several updates to the Sarafem labeling would be made by Lilly at the next printing of the Sarafem labeling, as outlined in the attached note to reviewer. It was also agreed in that conversation that Lilly would submit the changes for the Sarafem labeling under 314.70(c).

Thus, Lilly is herewith submitting revised labeling in final printed form for the referenced product. For your convenience, the changes are highlighted with a blue marker. Enclosed are twelve copies of the revised final printed labeling (identified as PV 3281), ten of which are individually mounted on heavy weight paper or similar material. The labeling is dated July 11, 2000.

Please call Dr. David W. Johnson at (317) 277-1806 or me at (317) 277-3799 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Gregory T. Brophy, Ph.D.
Director
U.S. Regulatory Affairs

cc: Dr. Doris Bates

All changes agreed upon are present

CENTER FOR DRUG EVALUATION AND RESE
SEP 01 2000
RECEIVED HFD-120

9/7/00

ORIGINAL

www.lilly.com

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285
U.S.A.

Phone 317 276 2000

August 22, 2000 LABELING SUPPLEMENT

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological
Drug Products, HFD-120
Attn.: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA NO. 18-936 REF NO. SLR-062
NDA SUPPL FOR Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH
AUG 23 2000
RECEIVED HFD-120

Re: NDA 18-936, Prozac® (fluoxetine hydrochloride) - Pulvule

Please refer to a phone conversation between Mr. Paul David, FDA, and Dr. David W. Johnson, Lilly, on July 6, 2000. In that phone conversation, it was agreed that the relevant sections of the labeling for Sarafem™ (fluoxetine hydrochloride) for PMDD agreed to in the approval letter for Sarafem would be incorporated into the Prozac labeling. It was also agreed in that conversation that Lilly would submit the changes for the Prozac labeling as a 314.70(b) supplement to allow the FDA an opportunity to review the specific language to be incorporated into the Prozac labeling. Thus, Lilly is herewith submitting revised labeling for Prozac to incorporate these changes.

These changes will bring to conclusion several pending supplements for Prozac. Upon approval by FDA, Lilly will send the final printed labeling reflecting these changes and implement them for use in the Prozac labeling.

Please call Dr. David W. Johnson at (317) 277-1806 or me at (317) 277-3799 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Gregory T. Brophy, Ph.D.
Director
U.S. Regulatory Affairs

cc: Mr. Paul David

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-936/S-062

AUG 29 2000

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Attention: Gregory T. Brophy. Ph.D.

Dear Dr Brophy:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Prozac

NDA Number: 18-936

Supplement Number: S-062

Date of Supplement: August 22, 2000

Date of Receipt: August 23, 2000

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on October 22, 2000 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation I
Attention: Document Control Room 4008
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

8-29-00

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Prducts, 120
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 18-936/S-062
HFD-120/Div. Files
HFD-120/CSO/David

filename: C:\WPWIN61\TEMPLATE\FDA\18936S62.WPD

SUPPLEMENT ACKNOWLEDGEMENT

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-936/S-060

JUL 16 1999

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Attention: Gregory T. Brophy, Ph.D.
Director U.S. Regulatory Affairs

Dear Dr. Brophy:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Prozac (fluoxetine HCL)

NDA Number: 18-936

Supplement Number: 060

Date of Supplement: 06-Jul-99

Date of Receipt: 07-Jul-99

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on 05-Sep-99 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation I
Attention: Document Control Room 4008
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 18-936/060
HFD-120/Div. Files
HFD-120/CSO/David

filename:

SUPPLEMENT ACKNOWLEDGEMENT

Lilly

NDA SUPPLEMENT

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

NDA NO. 18-936 REF NO. SLR-060
NDA SUPPL FOR Draft Labeling

July 6, 1999

LABELING SUPPLEMENT

ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological
Drug Products, HFD-120
Attn.: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857-1706

CENTER FOR DRUG EVALUATION AND RESEARCH

JUL 07 1999

RECEIVED HFD-120

Re: NDA 18-936, Prozac® (fluoxetine hydrochloride) - Pulvule®

Lilly submits the attached Labeling Supplement to NDA 18-936 under 21 CFR §314.70(b).

Please call Dr. David W. Johnson at (317) 277-1806 or me at (317) 277-3799 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Gregory T. Brophy, Ph.D.
Director
U.S. Regulatory Affairs

cc: Mr. Paul David