CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18-936/S-052
20-101/S-024

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

NDA 18-936/S-052
NDA 20-101/S-024

Lilly Research Laboratories
Attention: Gregory T. Brophy, Ph.D.
Senior Director U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, Indiana 46285

OCT 7 1999

Dear Dr. Brophy:

Please refer to your supplemental New Drug Applications submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prozac (fluoxetine hydrochloride) pulvules (NDA 18-936/S-052) and solution (NDA 20-101/S-024).

Reference is also made to an Agency approvable letter dated August 11, 1999, for the above supplemental applications requesting revisions to your proposed labeling and 20 copies of final printed labeling (FPL).

We acknowledge receipt of your amendment dated September 16, 1999, providing for 20 copies of FPL as requested in our August 11, 1999 approvable letter (Label Code PV 3312DPP).

We additionally note that you have incorporated revisions made in 18-936/S-059 and 20-101/S-026 (approved on June 16, 1999) and revisions made in 18-936/S-054 (approved on June 15, 1999). We note that the FPL for these approved supplemental applications was submitted on July 21, 1999.

These supplemental applications, 18-936/S-052 and 20-101/S-024, provide for revisions to the Precautions-Geriatric Use section of labeling as well as some other minor changes.

We note that the FPL differs from the labeling as requested in our August 11, 1999, approvable letter in that you have added the phrase "as with other SSRIs" concerning hyponatremia.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

Additionally, the labeling submitted on August 11, 1999 supersedes the FPL submitted to the supplemental applications, NDAs 18-936/S-054/S-059 and 20-101/S-026, since it incorporates the labeling changes made to these supplemental applications. Therefore, we will not review your July 21, 1999 submission but it will be retained in our files.

If you have any questions, contact Paul David, R.Ph., Regulatory Project Manager, at (301) 594-5530.

Sincerely,

/S/

Russell Katz, M.D.
Acting Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Archival NDAs 18-936 & 20-101
HFD-120/Div. Files
HFD-120/PDavid
HFD-120/RKatz/TLaughren/AMosholder
HFD-120/RSeevers/DKlein
HF-2/MedWatch (with labeling)
HFD-95/DDMS (with labeling)
HFD-100/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/OPDRA (with labeling)
DISTRICT OFFICE

final:10/05/99pd
filename:C:\PROZAC\GERIATRIC SUPPLEMENT APPROVAL LETTER.DOC

NDAs 18-936/S-052 & 20-101/S-024 APPROVED (AP)
NDAs 18-936/S-054/S-059 & 20-101/S-026 ACKNOWLEDGE AND RETAIN (AR) [7-21-99 Labeling]

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18-936/S-052
20-101/S-024

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

AUG 11 1999

NDA 18-936/S-052
NDA 20-101/S-024

Lilly Research Laboratories
Attention: Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, Indiana 46285

Dear Dr. Brophy:

Please refer to your May 11, 1998, supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prozac (fluoxetine hydrochloride) pulvules (NDA 18-936) and solution (NDA 20-101).

We have completed the review of these applications and they are approvable.

These supplements propose the following changes in labeling: The revision of the **Clinical Pharmacology-Age, Clinical Pharmacology-Clinical Trials, Indications And Usage, Precautions-Geriatric Use,** and **Dosage And Administration** sections. We note that this supplement was submitted to comply with the final rule published in the Federal Register on August 27, 1997 to establish a "Geriatric Use" subsection in labeling.

Additionally, we note that the supplement provides for [redacted] ng.

Therefore, before these applications may be approved, it will be necessary for you to submit final printed labeling incorporating the changes listed below.

1. We believe that it would be more appropriate for you to include the standard language from the geriatric final rule published on August 27, 1997 for the Geriatric Use section. We request that it reads 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 or 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. Fluoxetine has been associated with cases of clinically significant hyponatremia in elderly patients (see **Hyponatremia** under **Precautions**).

2. As stated above, we believe that th [redacted] is potentially confusing in the labeling. Therefore, we request that the changes you have proposed regarding the [redacted] be omitted in this application.

All of your remaining proposed revisions are acceptable.

Once you have implemented these labeling revisions, we will consider the Prozac labeling to be in compliance with the aforementioned Federal Register notice regarding geriatric labeling.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 copies of the final printed labeling (to each application) ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with this change prior to approval of these supplemental applications.

If you have any questions, contact Paul David, R.Ph., Regulatory Management Officer, at (301) 594-2850.

Sincerely,

/S/

Russell Katz, M.D.
Acting Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Archival NDAs 18-936/20-101
HFD-120/Div. Files
HFD-120/PDavid
HFD-120/RKatz/TLaughren/AMosholder
HFD-95/DDMS
HFD-810/DNDC Division Director
DISTRICT OFFICE

rd:03/10/99pd
rev:05/10/99am; 08/09/99am
ft:08/09/99pd
filename: S-52-AE.LTR

APPROVABLE (AE)