

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 18-936/S-054

APPROVAL LETTER



Food and Drug Administration
Rockville MD 20857

NDA 18-936/S-054

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

JUN 15 1999

Dear Dr. Brophy:

Please refer to your supplemental New Drug Application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prozac (fluoxetine hydrochloride) 10 mg and 20 mg pulvules.

Reference is also made to an Agency letter dated December 16, 1998, informing you that the application was not approvable under section 505(d) of the Act and 21 CFR 314.125(b).

We acknowledge receipt of your resubmission dated February 17, and received February 18, 1999, providing for additional information.

We additionally acknowledge receipt of your amendments dated March 12, March 16, and April 5, 1999.

This supplemental application provides for the addition of two new capsule strengths, 40 mg and 60 mg capsules.

We have completed the review of this supplemental application, 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 your labeling text. Accordingly, this supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the revisions proposed in your draft labeling submitted in your supplemental application (text for the package insert, immediate container and carton labels).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 18-936/S-054." Approval of this submission by FDA is not required before the labeling is used.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely,



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

17-99

cc:

Archival NDA 18-936

HFD-120/RKatz/TL^(S)Loaghren/AMosholder ^(S) 12/29

HFD-120/RSeevers/PDavid ^(S)

HFD-860/CSahajwalla/RY^(S)wanf ^(S) 12/29

HFD-120/Div. Files

HF-2/MedWatch (with labeling)

HFD-002/ORM (with labeling)

HFD-101/ADRA (with labeling)

HFD-40/DDMAC (with labeling)

HFD-613/OGD (with labeling)

HFD-95/DDMS (with labeling)

HFD-810/DNDC Division Director

DISTRICT OFFICE

05/03/99pd

filename: PZS4060.AP1

APPROVAL (AP)

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 18-936/S-054

NOT APPROVABLE LETTER



Food and Drug Administration
Rockville MD 20857

NDA 18-936/S-054

DEC 16 1998

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 supplemental New Drug Application dated June 17, 1998, for Prozac (fluoxetine hydrochloride) 10 mg and 20 mg pulvules.

We acknowledge receipt of your amendments dated October 20, and November 13, 1998.

This supplement application provides for the addition of two new capsule strengths, 40 mg and 60 mg.

We have completed our review and find the information presented is inadequate, and the supplemental application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

Biopharmaceutics

The request for a waiver of *in vivo* bioequivalence for the proposed higher strengths of Prozac capsule at 40 mg and 60 mg is denied, because the proposed formulations are not compositionally proportional to the approved formulation. You are requested to conduct a bioequivalency study using the highest proposed strength (60 mg). However, you may request a waiver of an *in vivo* bioequivalence for the lower strength (40 mg) and provide the following information along with the waiver request:

- (1) Compositional proportionality between 40 and 60 mg capsules;
- (2) Comparable dissolution profiles based on 12 units in 3 different pH media (0.1N HCl, water and phosphate buffer). F2 values should be calculated for each medium to demonstrate the comparability of dissolution profiles between the 40 mg and 60 mg capsules.

In addition, although these are not reasons for the not approvable action, the following deficiencies have been identified in the supplemental application:

Chemistry, Manufacturing and Controls

(1)

(2)

(3)

(4)

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. 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.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

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

✓ /S/

Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:

Archival NDA 18-936

HFD-120/Div. Files

HFD-120/PLEber/TLaughren/AMosholder

HFD-120/RSeevers/PDavid

HFD-860/CSahajwalla/RYuan

HFD-95/DDMS

HFD-810/DNDC Division Director

DISTRICT OFFICE

Drafted by: pd/db/December 9/15, 1998

Initialed by:

final:

filename: PZS4060.NA1

NOT APPROVABLE (NA)