CENTER FOR DRUG EVALUATION AND RESEARCH

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

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

NDA 18-936/S-060

MAY - 2 2000

Eli Lilly and Company
Attention: Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285-2643

Dear Dr. Brophy:

Please refer to your supplemental new drug application dated July 6, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prozac (fluoxetine hydrochloride) pulvules.

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

We have completed our review of your supplemental application, and it is approvable. However, before this application may be approved, it will be necessary for you to provide further justification for distinguishing the two entities, i.e., neuroleptic malignant syndrome and serotonin syndrome, and to make the revisions as listed below.

Specifically, we concur that neuroleptic malignant syndrome and serotonin syndrome can resemble each other. However, we do not believe that your proposed revisions to the **CONTRAINDICATIONS** section are justified based upon the data submitted in your supplemental application. Therefore, we request that Lilly retrieve the reports involving an MAOI combined with fluoxetine, and then review these cases to see how they can be described; i.e., as cases of neuroleptic malignant syndrome, serotonin syndrome, or something else.

We concur with your proposed footnote addition to the **ADVERSE REACTIONS-Other Events Observed in US Clinical Trials** section.

With respect to your proposed revisions to the **ADVERSE REACTIONS-Postintroduction Reports** section, we believe that simply adding "serotonin syndrome" and retaining "neuroleptic malignant syndrome like events" is sufficient. As noted in your supplemental application, neuroleptic malignant syndrome and serotonin syndrome can sometimes be distinguished, so we do not agree with [redacted] in this section.

Please submit draft labeling incorporating the above changes to labeling. Additionally, as noted above, you will need to submit additional information to support your proposed revision to the **CONTRAINDICATIONS** section of labeling.

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 application, 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 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.

Should you have any questions concerning this request, please contact Mr. Paul A. David, Regulatory Project Manager, at (301) 594-5530.

Sincerely yours,

3/2/00

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

cc:
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