DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 18-936/S-064

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 September 14, and received September 15, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prozac (fluoxetine hydrochloride) pulvules.

We additionally reference Agency action letters dated July 12, 2001, and March 19, 2002 as well as a conference call between representatives of the Agency and Lilly dated January 2, 2003.

We acknowledge receipt of your submission dated July 2, 2002. Your submission of July 2, 2002 constituted a complete response to our March 19, 2002 action letter.

We additionally acknowledge receipt of your correspondences dated July 23, August 22 and 28, September 5, October 4, and December 11 and 17, 2002.

This supplemental new drug application provides for the use of Prozac in the treatment of major depressive disorder (MDD) and obsessive compulsive disorder (OCD) in the pediatric population.

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 the agreed upon enclosed 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 agreed upon enclosed labeling (text for the package insert).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 18-936/S-064." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 postmarketing study commitments in your submissions dated July 2, and December 11, 2002 as well as those agreed upon in our conference call dated January 2, 2003. These commitments are listed below.

1. Juvenile Animal Toxicology Studies

   We acknowledge your agreement to conduct juvenile animal toxicology studies as a Phase 4 postmarketing commitment. We additionally acknowledge your commitment to submit these reports to the Agency within 2 years from the date of the approval action for this supplement.

   We note that, in your correspondence dated July 2, 2002, you submitted two draft juvenile animal toxicology protocols. We have the following comments in regard to these studies.

   The proposed dosing periods (postnatal days 21 through 65 or 84) should be justified in terms of their relationship to the age range of the pediatric patient population. Since the clinical population for this product may include very young children, it is suggested that treatment be initiated at an earlier age in rats (1-2 weeks postnatally) in order to ensure that the appropriate developmental events are covered. In order to better evaluate the potential for long-term changes and avoid potentially confounding acute pharmacological effects, it is recommended that neurobehavioral and reproductive testing be conducted after cessation of dosing (post-treatment). A more sensitive test of learning and memory, such as the Cincinnati (multiple-T) or Morris water maze, is recommended. A specific histopathological examination of the CNS that includes all major areas and cellular elements should be performed.

2. Clinical Pediatric Trial to Assess the Longer-Term Effects of Fluoxetine on Growth

   We note your Phase 4 postmarketing commitment to conduct a prospective longer-term trial to assess the effect of fluoxetine treatment on growth in pediatric patients. We additionally note your commitment to submit the protocol design to the Agency for review prior to implementing the study, and your commitment to submit the final study report within 5 years of the date of this letter.

3. Analysis of Pediatric ECG Readings Using Different Leads

   We note your Phase 4 postmarketing commitment, agreed upon in a conference call dated January 2, 2003, to conduct analyses of the study HCJE pediatric QTc intervals using additional ECG leads. These analyses would, at a minimum, include QTc interval measurements from leads AVF and V5. The types of analyses should be consistent with those included in your December 11, 2002 submission. We additionally note your commitment to submit this study report no later than 3 months from the date of this letter.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled “Postmarketing Study Protocol”, “Postmarketing Study Final Report”, or “Postmarketing Study Correspondence.”

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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, call Mr. Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

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

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
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