DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 18-936/S-071/S-073
NDA 20-101/S-032
NDA 20-974/S-005
NDA 21-235/S-003

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 applications dated September 2, 2004, and December 14, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prozac and Sarafem (fluoxetine hydrochloride) pulvules (NDA 18-936), Prozac solution (NDA 20-101), Prozac tablets (NDA 20-974), and Prozac Delayed-Release Capsules (NDA 21-235).

We acknowledge receipt of your submission dated May 31, 2005.

Your submission of May 31, 2005 constituted a complete response to our May 12, 2005 action letter.

Reference is also made to an e-mail from CAPT Paul A. David of this Agency to Dr. Barbara Arning, of Eli Lilly, dated August 31, 2005, requesting that you agree to revise the labeling.

We additionally refer to Dr. Arning's e-mail dated November 3, 2005, accepting the agreed upon labeling (as noted below).

These supplements, submitted as "Changes Being Effected" applications, provide for revisions to the labeling to incorporate the results of your juvenile animal toxicology studies under the **CARCINOGENESIS**, **MUTAGENESIS, IMPAIRMENT of FERTILITY**, **ANIMAL TOXICOLOGY**, and **Pediatric Use** sections as well as minor editorial changes.

We completed our review of these application, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

We note your agreement to add the following language at the end of the **PRECAUTIONS-Pediatric Use** section as follows:

PRECAUTIONS-Pediatric Use

Significant toxicity, including myotoxicity, long-term neurobehavioral and reproductive toxicity, and impaired bone development, has been observed following exposure of juvenile animals to fluoxetine. Some of these effects occurred at clinically relevant exposures.

In a study in which fluoxetine (3, 10, or 30 mg/kg) was orally administered to young rats from weaning (Postnatal Day 21) through adulthood (Day 90), male and female sexual development was delayed at all doses, and growth (body weight gain, femur length) was decreased during the dosing period in animals receiving the highest dose. At the end of the treatment period, serum levels of creatine kinase (marker of muscle damage) were increased at the intermediate and high doses, and abnormal muscle and reproductive organ histopathology (skeletal muscle degeneration and necrosis, testicular degeneration and necrosis, epididymal vacuolation and hypospermia) was observed at the high dose. When animals were evaluated after a recovery period (up to 11 weeks after cessation of dosing), neurobehavioral abnormalities (decreased reactivity at all doses and learning deficit at the high dose) and reproductive functional impairment (decreased mating at all doses and impaired fertility at the high dose) were seen; in addition, testicular and epididymal microscopic lesions and decreased sperm concentrations were found in the high dose group, indicating that the reproductive organ effects seen at the end of treatment were irreversible. The reversibility of fluoxetine-induced muscle damage was not assessed. Adverse effects similar to those observed in rats treated with fluoxetine during the juvenile period have not been reported after administration of fluoxetine to adult animals. Plasma exposures (AUC) to fluoxetine in juvenile rats receiving the low, intermediate, and high dose in this study were approximately 0.1 - 0.2, 1 - 2, and 5 - 10 times, respectively, the average exposure in pediatric patients receiving the maximum recommended dose (MRD) of 20 mg/day. Rat exposures to the major metabolite, norfluoxetine, were approximately 0.3 - 0.8, 1 - 8, and 3 - 20 times, respectively, pediatric exposure at the MRD.

A specific effect of fluoxetine on bone development has been reported in mice treated with fluoxetine during the juvenile period. When mice were treated with fluoxetine (5 or 20 mg/kg, intraperitoneal) for 4 weeks starting at 4 weeks of age, bone formation was reduced resulting in decreased bone mineral content and density. These doses did not affect overall growth (body weight gain or femoral length). The doses administered to juvenile mice in this study are approximately 0.5 and 2 times the MRD for pediatric patients on a body surface area (mg/m^2) basis.

In another mouse study, administration of fluoxetine (10 mg/kg intraperitoneal) during early postnatal development (Postnatal Days 4 to 21) produced abnormal emotional behaviors (decreased exploratory behavior in elevated plus-maze, increased shock avoidance latency) in adulthood (12 weeks of age). The dose used in this study is approximately equal to the pediatric MRD on a mg/m^2 basis. Because of the early dosing period in this study, the significance of these findings to the approved pediatric use in humans is uncertain.

Additionally, and as communicated in our May 12, 2005 letter, we concur with your proposed revisions to the **CARCINOGENESIS**, **MUTAGENESIS, IMPAIRMENT of FERTILITY** section.

The final printed labeling (FPL) must be identical to the labeling above.

Please submit an electronic version of the FPL 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 but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions "FPL for approved supplements 18-936/S-071/S-073, 20-101/S-032, 20-974/S-005, & 21-235/S-003". Approval of these submissions by FDA is not required before the labeling is used.

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, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Paul David, R.Ph., Chief Project Management Staff, at (301) 796-1058.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Thomas Laughren

12/1/2005 03:34:44 PM