DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDAs 18-936/S-078, 21-235/S-008, & 20-101/S-036

Eli Lilly & Company
Attention: Lori de los Reyes, RN, MSN
Senior Regulatory Associate, US Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN46285

Dear Ms. Reyes:

We acknowledge receipt of your supplemental new drug applications dated January 8, 2007,and received January 9, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prozac (fluoxetine) Pulvules (18-936), Prozac Oral Suspension (20-101), & Prozac Weekly (21-235).

Reference is also made to an Agency letter dated April 10, 2006, as well as an electronic communication from Renmeet Grewal, Pharm.D., of this Agency, on July 13, 2006, requesting revisions to product labeling pertaining to Persistent Pulmonary Hypertension of the Newborn (PPHN).

Reference is also made to an Agency letter dated March 21, 2006, as well as an electronic communication from Renmeet Grewal, Pharm.D., on November 16, 2006, requesting revision to product labeling pertaining to the propafenone drug interaction.

These "Changes Being Effected" supplemental applications provide for the following revisions to product labeling (double underline font denotes additions to the labeling and strike through font denotes deletions):

PRECAUTIONS-PREGNANCY-NONTERATOGENIC EFFECTS

Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1-2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk.

When treating a pregnant woman with Prozac during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment (*see* DOSAGE AND ADMINISTRATION). Physicians should note that in a prospective longitudinal study of 201 women

with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

Precautions-Propafenone:

~~Drugs metabolized by CYP2D6 Approximately 7% of the normal population has a genetic defect that leads to reduced levels of activity of the cytochrome P450 isoenzyme 2D6. Such individuals have been referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and TCAs. Many drugs, such as most drugs effective in the treatment of major depressive disorder, including fluoxetine and other selective uptake inhibitors of serotonin, are metabolized by this isoenzyme; thus, both the pharmacokinetic properties and relative proportion of metabolites are altered in poor metabolizers. However, for fluoxetine and its metabolite, the sum of the plasma concentrations of the 4 active enantiomers is comparable between poor and extensive metabolizers (*see* Variability in metabolism *under* CLINICAL PHARMACOLOGY).~~

Drugs metabolized by CYP2D6 —Fluoxetine, ~~like other agents that are metabolized by CYP2D6,~~ inhibits the activity of ~~this isoenzyme~~CYP2D6, and thus may make individuals with normal ~~metabolizers~~CYP2D6 metabolic activity resemble a poor metabolizers. Coadministration of fluoxetine with other drugs that are metabolized by CYP2D6, including certain antidepressants (e.g., TCAs), antipsychotics (e.g., phenothiazines and most atypicals), and antiarrhythmics (e.g., propafenone, flecainide, and others) should be approached with caution.

Drugs with a narrow therapeutic index represent the greatest concern (e.g., flecainide, propafenone, vinblastine, and TCAs).

We have completed our review of these applications, and they are approved, effective on the date of this letter, for use as recommended in the enclosed labeling text.

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
Food and Drug Administration
WO 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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 Renmeet Grewal, Pharm.D., Regulatory Project Manager, at (301) 796-1080.

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

Enclosure

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
3/15/2007 03:45:03 PM