DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021520 S-038

SUPPLEMENT APPROVAL

Eli Lilly and Company
Attention: Ashraff Rampersaud, M.S. PMP
Manager, Global Regulatory Affairs, US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Mr. Rampersaund:

Please refer to your Supplemental New Drug Application (sNDA) dated and received July 25, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Symbyax (olanzapine and fluoxetine HCl) Capsules 3 mg/25 mg, 6 mg/25 mg, 12 mg/25 mg, 6 mg/50 mg, 12 mg/50 mg.

This "Changes Being Effected" supplemental new drug application provides for revisions to the Pregnancy (8.1) and Carcinogenesis (13.1) sections of labeling. The revisions, in red, follow –

8.1 Pregnancy

In a pre- and postnatal study conducted in rats, olanzapine and fluoxetine were orally administered during pregnancy and throughout lactation in combination ~~(low-~~, at dose~~:~~ levels up to 2 ~~and~~(olanzapine) plus 4 (fluoxetine) mg/kg/day ~~[~~(1 and 0.5 times the MRHD on a mg/m2 ~~basis], respectively, high-dose: 4 and 8 mg/kg/day [2 and 1 times the MRHD on a mg/m^2 basis], respectively, and alone: 4 and 8 mg/kg/day [2 and 1 times the MRHD on a mg/m^2 basis], respectively). Administration of the high-dose combination resulted in a marked elevation in offspring mortality and growth retardation in comparison to the same doses of olanzapine and fluoxetine administered alone. These effects were not observed with the low-dose combination; however, there were a few cases of testicular degeneration and atrophy, depletion of epididymal sperm and infertility in the male progeny. The effects of the high-dose combination on postnatal endpoints could not be assessed due to high progeny mortality.~~body surface area. An elevation of early postnatal mortality (survival through postnatal day 4 was 69% per litter) and reduced bodyweight (approximately 8% in females) occurred among offspring at the highest dose; the no-effect dose was 0.5 (olanzapine) plus 1 (fluoxetine) mg/kg/day (0.25 and 0.13 times the MRHD on a mg/m2 body surface area). Among the surviving progeny, there were no adverse effects on physical or neurobehavioral development and reproductive performance at any dose.

8.1 Pregnancy

Embryo fetal development studies were conducted in rats and rabbits with olanzapine and fluoxe-tine in low-dose and high-dose combinations. In rats, the doses were: 2 and 4 mg/kg/day (low-dose) [1 and 0.5 times the maximum recommended human dose (MRHD) ~~on a mg/m^2 basis~~for olanzapine (20mg) and fluoxetine (80mg), respectively, on a mg/m2 body surface area], and 4 and 8 mg/kg/day (high-dose) [2 and 1 times the MRHD on a mg/m2 ~~basis~~body surface area, respectively].

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity, mutagenicity, or fertility studies were conducted with SYMBYAX. The following data are based on findings in studies performed with the individual components, therefore all dose multiples (based on body sur-face area) reflect the maximum recommended human dose (MRHD) of 20 mg olanzapine or 80 mg fluoxetine, when each drug is administered separately.

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REPORTING REQUIREMENTS

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 Keith Kiedrow, PharmD, RAC, Regulatory Project Manager, at (301) 796-1924.

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(S):
Content of Labeling

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

/s/

THOMAS P LAUGHREN
08/08/2012