



NDA 021520 S-033

## SUPPLEMENT APPROVAL

Eli Lilly and Company  
Attention: Roland W. Usher, MS  
Director, Global Regulatory Affairs, US  
Lilly Corporate Center  
Indianapolis, IN 46285

Dear Mr. Usher:

Please refer to your Supplemental New Drug Application (sNDA) dated and received August 18, 2011, 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 an addition to section 6.1, Clinical Trials Experience, which is part of section 6, Adverse Reactions. The addition, in red, follows -

### Section 6.1

#### Additional Findings Observed in Clinical Studies

*Sexual Dysfunction* — In the pool of controlled SYMBYAX studies in patients with bipolar depression, there were higher rates of the treatment-emergent adverse reactions decreased libido, anorgasmia, erectile dysfunction and abnormal ejaculation in the SYMBYAX group than in the placebo group. One case of decreased libido led to discontinuation in the SYMBYAX group. In the controlled studies that contained a fluoxetine arm, the rates of decreased libido and abnormal ejaculation in the SYMBYAX group were less than the rates in the fluoxetine group. None of the differences were statistically significant.

Sexual dysfunction, including priapism, has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

**There are no adequate and well-controlled studies examining sexual dysfunction with SYMBYAX or fluoxetine treatment. Symptoms of sexual dysfunction occasionally persist after discontinuation of fluoxetine treatment.**

We have completed our review of this supplemental application, as amended. 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 Effectuated” (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).

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

### **REPORTING REQUIREMENTS**

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

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If you have any questions, contact Keith Kiedrow, Pharm.D., Senior 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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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THOMAS P LAUGHREN  
10/04/2011