



NDA 022256/S-014, S-015

**SUPPLEMENT APPROVAL**

Cypress Bioscience, Inc.  
c/o Forest Laboratories, Inc.  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

Attention: Debleena Sengupta, PhD, RAC  
Senior Manager, Regulatory Affairs

Dear Dr. Sengupta:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received May 31, 2012 (S-014), and February 20, 2013 (S-015), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Savella (milnacipran HCl) Tablets.

We acknowledge receipt of your amendments dated December 13, 2012 and January 18 and October 23, 2013 (S-014), and July 25, 2013 (S-014 and S-015).

Supplement S-014 proposes revisions to the **HIGHLIGHTS, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS**, and **DRUG INTERACTIONS** sections of the Package Insert, and the Medication Guide.

Supplement S-015 is submitted in response to the Agency's March 5, 2012, Supplement Request letter, and multiple email communications regarding the proposed revisions to the Package Insert, including an email dated February 8, 2013, in which an agreement was reached regarding revisions to the **HIGHLIGHTS, WARNINGS AND PRECAUTIONS**, and **PATIENT COUNSELING INFORMATION** sections of the Package Insert.

**APPROVAL & LABELING**

We have completed our review of these supplemental applications, as amended. They are 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 and 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 that includes labeling changes 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).

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

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).

If you have any questions, call Diana L. Walker, Ph.D., Sr. Regulatory Health Project Manager, at (301) 796-4029.

Sincerely,

*{See appended electronic signature page}*

Judith A. Racoosin, M.D., M.P.H.  
Deputy Director for Safety  
Division of Anesthesia, Analgesia, and  
Addiction Products  
Office of Drug Evaluation II  
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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JUDITH A RACOOSIN  
10/30/2013