DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-256

NDA APPROVAL

Cypress Bioscience, Inc.
c/o Forest Laboratories, Inc.
Harborside Financial Center
Plaza III, Suite 602
Jersey City, NJ 07311

Attention: Michael K. Olchaskey, PharmD
Director, Regulatory Affairs

Dear Dr. Olchaskey:

Please refer to your new drug application (NDA) dated and received December 18, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Savella (milnacipran HCl) 12.5 mg, 25 mg, 50 mg, and 100 mg Tablets.

We acknowledge receipt of your submissions dated January 18 and 30, February 8, 11, 13, 15, and 28, March 17 and 31, April 10, 17, 22, 28, and 30, May 30, June 2, 9, 10, 11, and 26, July 3, 15, 28, and 30, August 6, 7, 8, 11, 12, 13, 19, 20, 25, 26, and 27, September 2, 5, 16, 17, and 23, and October 8, 9, 10, 14, 15, 16, 17, and 24, 2008, and January 2 and 8, 2009.

This new drug application provides for the use of Savella (milnacipran HCl) Tablets for the management of fibromyalgia.

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

Your application was not referred to an advisory committee because, although Savella is a new molecular entity, it is not the first drug in the class of norepinephrine-serotonin reuptake inhibitors (NSRIs) indicated for the management of fibromyalgia, the clinical study design was acceptable, and the product did not pose unique concerns beyond those applicable to other members of this class.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the

product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 through 12 years for this application because necessary studies are impossible or highly impracticable. The population of pediatric fibromyalgia patients 12 years of age and younger is extremely small.

We are deferring submission of your pediatric study for ages 13 through 17 years for this application until October 2014 because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required under section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. This required study is listed below.

1. Deferred pediatric study under PREA for the management of fibromyalgia in pediatric patients ages 13 through 17

   You will conduct this trial according to the following timetable:

Protocol Submission:	July 2009
Study Start Date:	January 2010
Final Report Submission:	October 2014

Submit the protocol to your IND 63,736 with a cross-reference letter to your NDA 22-256. Submit the final report to your NDA 22-256. Prominently identify the submissions with the following wording in bold, capital letters at the top of the first page of the submission:

REQUIRED PEDIATRIC ASSESSMENT

RISK EVALUATION AND MITIGATION STRATEGIES (REMS) REQUIREMENTS

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Savella (milnacipran HCl) to ensure that the benefits of the drug outweighs the risks. Savella (milnacipran HCl) is a norepinephrine and serotonin reuptake inhibitor. The known serious risks associated with drugs of this class are serious psychiatric symptoms, including suicidal ideation, particularly in patients with depression. Mood disorders, such as major depression, bipolar disorder, major mood disorder, and anxiety disorders, commonly co-occur in patients with fibromyalgia. The REMS, once approved, will create enforceable obligations.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Savella (milnacipran HCl) poses a serious and significant public health concern requiring distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Savella (milnacipran HCl). FDA has determined that Savella (milnacipran HCl) is a product that has serious risks of which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use, or continue to use Savella (milnacipran HCl). In addition, patient labeling could help prevent serious adverse effects related to the use of the product. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Savella (milnacipran HCl).

Your proposed REMS, submitted on October 9, 2008, and appended to this letter, is approved. The REMS consists of the Medication Guide included with this letter and the timetable for submission of assessments of the REMS included in your October 9, 2008, submission.

Your assessment of the REMS should include an evaluation of:

a. Patients' understanding of the serious risks of Savella (milnacipran HCl)
b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

If you do not submit electronically, please send five copies of your REMS assessment or proposed REMS modification to your NDA. Prominently identify the amendment containing the REMS assessment or proposed REMS with the following wording in bold, capital letters at the top of the first page of the submission:

NDA 22-256 REMS ASSESSMENT
NDA 22-256 PROPOSED REMS MODIFICATION

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of FDAAA also amends the FDCA to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that it is necessary to assess for a signal of a serious risk among pregnant female patients and neonates exposed to Savella (milnacipran HCL). We have become aware of adverse pregnancy outcomes in neonates of women taking drugs in the same class as Savella (milnacipran HCL) during pregnancy. Now, with the approval of the fibromyalgia indication, the population of patients taking Savella (milnacipran HCL) will be overwhelmingly females of childbearing potential, and a study is necessary to assess for a signal of serious risk. We have

also determined that it is necessary to identify an unexpected serious risk to the nursing infants of women who are treated with Savella (milnacipran HCl).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of a serious risk of adverse reactions in fetuses exposed to Savella (milnacipran HCl) or to identify an unexpected serious risk to the nursing infants of women who are treated with Savella (milnacipran HCl).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) has not yet been established and is therefore not sufficient to assess the signal of a serious risk or identify an unexpected serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following postmarketing study.

2. Develop and maintain a prospective, observational pregnancy exposure registry study conducted in the United States that compares the pregnancy and fetal outcomes of women exposed to Savella (milnacipran HCl) during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, and any serious adverse pregnancy outcomes. These events will be assessed among the enrolled women throughout the pregnancy. The events will also be assessed among infants through at least the first year of life. Annual interim reports will be submitted until FDA has acknowledged that sufficient data have been collected.

   You will conduct this study according to the following timetable:

Protocol Submission:	July 2009
Study Start Date:	January 2010
Final Report Submission:	Within six months of FDA notification that sufficient data have been collected.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk to the nursing infants of women who are treated with Savella (milnacipran HCl).

Based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following clinical trial.

3. A single-dose, pharmacokinetic, open-label, clinical trial in healthy, lactating women. Concentrations of Savella (Milnacipran HCl) will be assessed in maternal plasma and breast mild so as to estimate potential infant exposure.

Protocol Submission:	August 2009
Trial Start Date:	August 2010

Final Report Submission: February 2012

Submit the protocols to your IND 63,736 with a cross-reference letter to your NDA 22-256. Submit the final reports to your NDA 22-256.

Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing study requirements as appropriate:

Required Postmarketing Protocol under 505(o)
Required Postmarketing Final Report under 505(o)
Required Postmarketing Correspondence under 505(o)

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii), requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii), provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your October 16, 2008, submission containing final draft carton and container labels.

CONTENT OF LABELING

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert, text for the Medication Guide) dated January 8, 2009. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, “SPL for approved NDA 22-256.”

Marketing the product(s) with final printed labeling that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROMOTIONAL MATERIALS

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

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

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

Sincerely,

{See appended electronic signature page}

Curt Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures: REMS dated October 9, 2008
Package insert dated January 8, 2009
Medication Guide dated January 8, 2009
Carton and Immediate Container Labels dated October 16, 2008

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

/s/

Curtis Rosebraugh

1/14/2009 02:46:03 PM