CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

204168Orig1s000

Trade Name:	Fetzima Extended-Release Capsules (20 mg, 40 mg, 80 mg, and 120 mg)
Generic Name:	Levomilnacipran
Sponsor:	Forest Laboratories, Inc.
Approval Date:	07/25/2013
Indications:	Treatment of Major Depressive Disorder.

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204168

NDA APPROVAL

Forest Laboratories, Inc.
Attention: Ann Howell, PharmD, MS
Senior Manager, Regulatory Affairs
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, NJ 07311

Dear Dr. Howell:

Please refer to your New Drug Application (NDA) dated and received September 25, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for FETZIMA (levomilnacipran) extended-release 20 mg, 40 mg, 80 mg and 120 mg capsules.

We acknowledge receipt of your amendments dated:

October 3, 2012	January 29, 2013	July 3, 2013
November 9, 2012	February 19, 2013	July 5, 2013
November 12, 2012	February 29, 2013	July 12, 2013
November 20, 2012	March 6, 2013	July 15, 2013
December 14, 2012	March 6, 2013	July 18, 2013
December 17, 2012	March 11, 2013	July 20, 2013
December 18, 2012	March 25, 2013	July 24, 2013
December 21, 2012	April 1, 2013	July 25, 2013
December 21, 2012	May 3, 2013	
January 16, 2013	May 23, 2013	

This NDA provides for the use of FETZIMA (levomilnacipran) extended-release capsules for Major Depressive Disorder (MDD).

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

WAIVER OF HIGHLIGHTS SECTION

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.

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). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and immediate-container labels that are identical to the July 25, 2013, submitted carton and immediate-container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 204168**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

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 to 6 years in the treatment of major depressive disorder because necessary studies are impossible or highly impractical. This is because of the low prevalence of major depressive disorder in this age range.

We are deferring submission of your pediatric studies for ages 7 to 17 years for this application because the product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under section 505B(a) of the FDCA are postmarketing requirement studies (PMR). The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

1943-1 A deferred pediatric study under PREA for the treatment of major depressive disorder in pediatric patients ages 12 to 17 years. Conduct a study to obtain data on the pharmacokinetics (PK), efficacy and safety of levomilnacipran in the relevant adolescent population (ages 12 to 17 years). This study must be a placebo-and active-controlled (escitalopram or fluoxetine) fixed-dose study.

You should submit data from population PK modeling in adults to justify dose selection and PK sampling schedule for this adolescent study, at least 3 months prior to submitting the protocol. When the appropriate number of PK samples becomes available from this adolescent study (PMR#1943-1), an interim population PK analysis should be conducted to determine the dosing and regimen for the second efficacy and safety study in children and adolescents (ages 7-17 years).

PK modeling data to inform dose sampling:	April 25, 2014
Final Protocol Submission Date:	July 25, 2014
Study Completion Date:	July 25, 2017
Final Report Submission:	July 25, 2018

1943-2 A deferred pediatric study under PREA for the treatment of major depressive disorder in pediatric patients ages 7 to 17 years. Conduct a study to obtain data on the efficacy and safety of levomilnacipran in the relevant pediatric population (ages 7-17 years). This study must be a placebo-and active-controlled (fluoxetine) study. This study may be a fixed-dose study.

You should submit data from population PK model using data from adults and adolescents (PMR# 1943-1) to justify the dose(s) and the schedule for sparse PK sampling, at least 3 months prior to submitting the protocol.

PK modeling data to inform dose sampling:	April 25, 2016
Final Protocol Submission Date:	July 25, 2016
Study Completion Date:	July 25, 2019
Final Report Submission:	July 25, 2020

1943-3 To support the use of levomilnacipran in children less than 12 years of age, you must conduct a study to assess the safety of levomilnacipran in juvenile rats. This study must include evaluation of neurological/behavioral development and reproductive development. You should submit the protocol for our comments prior to initiating the study. You may conduct this study concurrently with the pediatric clinical trials.

Final Protocol Submission Date:	July 25, 2014
Study Completion Date:	July 25, 2016
Final Report Submission:	July 25, 2017

Submit the protocol(s) to your IND 104483 with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS"** in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment agreed upon in your email communication dated July 20, 2013. This commitment is listed below.

1943-4 A controlled trial to evaluate the longer-term (i.e., maintenance) efficacy of levomilnacipran in the treatment of adults with major depressive disorder. This trial must be placebo-controlled, utilize a randomized withdrawal design, and include an adequate period of stabilization with open-label treatment of levomilnacipran prior to double-blind randomization.

Final Protocol Submission:	March 25, 2014
Trial Completion:	March 25, 2018
Final Report Submission:	March 25, 2019

Submit clinical protocols to your IND 104483 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

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 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
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, 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 Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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, email Juliette Touré, PharmD, Senior Regulatory Project Manager, at Juliette.Toure@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
CAPT, USPHS
Director (acting)
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures:
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/

MITCHELL V Mathis
07/25/2013