

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
204168Orig1s000

OTHER REVIEW(S)

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

N/A

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study will obtain data on the pharmacokinetic, efficacy and safety of levomilnacipran in the relevant adolescent population aged 12-17 (Study 1). This study must be a placebo-and active-controlled (escitalopram or fluoxetine), fixed-dose study.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial

- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

NDA/BLA #
Product Name:

NDA 204168 FETZIMA, levomilnacipran

PMR/PMC Description: PREA PMR – Study 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..

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

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>07/25/2016</u>
	Study/Trial Completion:	<u>07/25/2019</u>
	Final Report Submission:	<u>07/25/2020</u>
	Other: PK modeling data to inform dose/sampling	<u>04/25/2016</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

This is a pediatric study required under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c). With concurrence from PeRC, the division is deferring submission of the pediatric study for ages 7 to 17 years old in the treatment of major depressive disorder, because this product is ready for approval for use in adults and the pediatric studies have not been completed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

N/A

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study will obtain data on the efficacy and safety of levomilnacipran in the relevant pediatric population aged 7-17 (Study 2). This study must be a placebo-and active-controlled (fluoxetine), fixed-dose study.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials

- Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-

- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

NDA/BLA # NDA 204168 FETZIMA, levomilnacipran
Product Name: _____

PMR/PMC Description: PREA PMR – Study 3

To support the use of levomilnacipran in children less than 12 years of age, the sponsor 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. The sponsor should submit the protocol for Agency comments prior to initiating the study. You may conduct this study concurrently with the pediatric clinical trials

PMR/PMC Schedule Milestones: Final Protocol Submission: 07/25/2014
Study/Trial Completion: 07/25/2016
Final Report Submission: 07/25/2017
Other: _____ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

This is a prerequisite study for the pediatric study (Study 2, for children under 12 years of age) required under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c). PeRC concurred with this PMR.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

N/A

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– Which regulation?

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Juvenile rat study that will include evaluation of neurological/behavioral development and reproductive development.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

NDA/BLA # NDA 204168 FETZIMA, levomilnacipran
Product Name: _____

PMR/PMC Description: Section 506B – Study 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.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>03/25/2014</u>
	Study/Trial Completion:	<u>03/25/2018</u>
	Final Report Submission:	<u>03/25/2019</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

N/A

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

N/A

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials

- Immunogenicity as a marker of safety

- Other (provide explanation)

Efficacy study (clinical trial)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

APPEARS THIS WAY ON ORIGINAL

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

/s/

RENMEET GREWAL
07/25/2013

MITCHELL V Mathis
07/25/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	FETZIMA (levomilnacipran) extended-release capsules, for oral use
Applicant	Forest Pharmaceuticals, Incorporated
Application/Supplement Number	NDA 204168
Type of Application	Original
Indication(s)	Treatment of major depressive disorder
Established Pharmacologic Class ¹	Serotonin and norepinephrine reuptake inhibitor
Office/Division	ODEI/DPP
Division Project Manager	Renmeet Grewal
Date FDA Received Application	September 25, 2012
Goal Date	July 25, 2013
Date PI Received by SEALD	July 19, 2013
SEALD Review Date	July 23, 2013
SEALD Labeling Reviewer	Debra Beitzell
SEALD Division Director	Laurie Burke

PI = prescribing information

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO**: The PI **does not meet** the requirement for this item (**deficiency**).
- **YES**: The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *DPP to grant waiver of 1/2 page HL limit in approval letter.*

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- NO** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *Under I&U heading, insert cross reference after "Limitation of Use" statement [i.e., "(1)"].*

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI

Selected Requirements of Prescribing Information

• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment:

Product Title

- YES** 10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

- NO** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *Insert year of Initial U.S. Approval of milnacipran and since this product is an enantiomer of milnacipran, include "milnacipran" in parentheses after the year [i.e., "2009 (milnacipran)"]*

Boxed Warning

- YES** 12. All text must be **bolded**.

Comment:

- YES** 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and

Selected Requirements of Prescribing Information

other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- NO** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

YES **Comment:** Remove white space above statement referring to full prescribing information for complete boxed warning.

15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

Selected Requirements of Prescribing Information

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: *Insert revision date (i.e., "July 2013").*

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- YES** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

Selected Requirements of Prescribing Information

- YES** 32. All section headings must be **bolded** and in UPPER CASE.
Comment:
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY

Selected Requirements of Prescribing Information

12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see *Warnings and Precautions (5.2)*]”.

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- YES** 42. All text is **bolded**.

Comment:

- YES** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

Selected Requirements of Prescribing Information

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

N/A

47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

YES

48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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

/s/

DEBRA C BEITZELL
07/23/2013

LAURIE B BURKE
07/23/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Labels, Labeling and Packaging Review

Date: July 2, 2013

Reviewer: Loretta Holmes, BSN, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, PharmD, BCPS
Division of Medication Error Prevention and Analysis

Deputy Director: Scott Dallas, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Fetzima (Levomilnacipran) Extended-release Capsules
20 mg, 40 mg, 80 mg, and 120 mg

Application Type/Number: NDA 204168

Applicant: Forest Laboratories Inc.

OSE RCM #: 2012-2387

***** This document contains proprietary and confidential information that should not be released to the public.*****

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1 INTRODUCTION

This review evaluates the proposed labels, labeling, and packaging for Fetzima (Levomilnacipran) Extended-release Capsules, for areas of vulnerability that can lead to medication errors.

1.1 BACKGROUND

Fetzima (Levomilnacipran) is an isomer of milnacipran, which is an already marketed product available under the proprietary name Savella. If approved, this will be the first levomilnacipran product on the market.

The proprietary name, (b) (4) is used on the labels and labeling. This name was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) in OSE Review 2012-2846, dated February 14, 2013, and was found unacceptable (b) (4)

The Applicant subsequently submitted the proposed proprietary name, Fetzima, for review, which was found acceptable in OSE Review 2013-659 dated June 3, 2013. Therefore, all proposed labels and labeling will need to be revised to reflect this proprietary name.

1.2 PRODUCT INFORMATION

The following product information is provided in the September 25, 2012 and December 21, 2012 submissions.

- Active Ingredient: Levomilnacipran
- Indication of Use: Treatment of Major Depressive Disorder (MDD)
- Route of Administration: Oral
- Dosage Form: Extended-release Capsules
- Strengths: 20 mg, 40 mg, 80 mg, and 120 mg
- Dose and Frequency: Initiate at 20 mg once daily for 2 days and then increase to 40 mg once daily. Based on efficacy and tolerability, the dose may be increased in increments of 40 mg at intervals of 2 or more days. The maximum recommended dose is 120 mg once daily. For patients with mild renal impairment (creatinine clearance 60 to 89 mL/min), the maintenance dose should not exceed 80 mg once daily. For patients with severe renal impairment (creatinine clearance of 15 to 29 mL/min), the maintenance dose should not exceed 60 mg once daily. Swallow capsules whole. Do not open, chew or crush the capsule. Can be taken with or without food.
- How Supplied: See tables below for the proposed commercial and professional sample packaging configurations
- Storage: Store at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F)

- Container and Closure System: HDPE bottles (b) (4)
Titration Packs; (b) (4)

Table 1: Commercial Bottles and Hospital Unit Dose (HUD) Configurations

Capsule Strength	Commercial Package Configurations
20 mg	Bottle / 30 count
	Hospital Unit Dose (Blister) / 10 x 10
40 mg	Bottle / 30 count
	Bottle / 90 count
	Hospital Unit Dose (Blister) / 10 x 10
80 mg	Bottle / 30 count
	Bottle / 90 count
	Hospital Unit Dose (Blister) / 10 x 10
120 mg	Bottle / 30 count
	Bottle / 90 count
	Hospital Unit Dose (Blister) / 10 x 10

Table 2: Commercial Titration Pack (b) (4)

Capsule Strength	Package Configuration
2 x 20 mg	Titration Pack/Starter Kit
26 x 40 mg	

(b) (4)

(b) (4)

(b) (4)

2 METHODS AND MATERIALS REVIEWED

Using the principals of human factors and Failure Mode and Effects Analysis,² along with postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted on January 29, 2013 (Appendix A)
- Hospital Unit-Dose (HUD) Blisters and Carton Labeling submitted January 29, 2013 (Appendix B)
- Commercial Titration Packs submitted January 29, 2013 (Appendix C)
- [REDACTED] (b) (4)
- [REDACTED] (b) (4)
- Insert Labeling submitted September 25, 2012 (no image)
- Actual samples of the product packaging received in January 2013.

3 MEDICATION ERROR RISK ASSESSMENT

The following sections discuss our risk assessment of the Fetzima labels, labeling, and packaging.

3.1 RISK ANALYSIS OF MULTIPLE TITRATION PACKS

The Applicant initially proposed [REDACTED] (b) (4)

² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Commercial Titration Pack (b) (4)

Capsule Strength	Package Configuration
2x 20 mg	Titration Pack/Starter Kit
26x 40 mg	

(b) (4)

DMEPA was concerned that (b) (4)

(b) (4)

(b) (4)

According to the response from the Applicant, they would like to retain the commercial and professional sample 28-day titration packages that titrate patients up to the lowest therapeutic dose of 40 mg (2 x 20 mg and 26 x 40 mg) because this is consistent with the Dosage and

(b) (4)

Administration section of the proposed Prescribing Information (PI). (b) (4)

Although there is no standard titration schedule after the 40 mg dose is reached, a single titration pack that titrates patients up to the lowest therapeutic dose of 40 mg may be reasonable (b) (4)

Additionally, offering a single titration pack that reflects both the 20 mg and 40 mg strengths may increase convenience and facilitate patient adherence.

In the NDA Wrap-Up meeting held on May 20, 2013, DMEPA and DPP discussed the Applicant's proposal to retain the single 28-day titration pack configuration and determined that the proposal appears reasonable given the dosage and administration proposed for this product. DPP had no objections to an initial 28-day supply of medication being made available to the patient.

3.2 COMMERCIAL 28-DAY TITRATION PACK

(b) (4)

(b) (4)

(b) (4)

3.4 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

Our review of the labels and labeling determined they can be improved to increase the readability and prominence of important information as well as provide more clarity to promote the safe use of Fetzima.

(b) (4)

4 CONCLUSIONS AND RECOMMENDATIONS

Our review of the labels and labeling has determined they can be improved to increase the readability and prominence of important information as well as provide more clarity to promote the safe use of Fetzima.

(b) (4)

We provide recommendations below and we advise their implementation prior to approval of this NDA. If you have further questions or need clarifications, please contact OSE Project Manager, Louis Flowers, at 301-796-3158.

4.1 COMMENTS TO THE DIVISION

DMEPA provides the following comments for consideration by the review division prior to the approval of this NDA:

(b) (4)

We agree with the Applicants decision to retain the 28-day commercial and professional sample titration packs that titrate up

(b) (4)

to the 40 mg dose.

(b) (4)

[REDACTED]

[REDACTED]

(b) (4)

[REDACTED]

(b) (4)

4.2 COMMENTS TO THE APPLICANT

DMEPA advises the recommendations below be implemented prior to approval of this NDA:

A. General Comments for Container Labels and Carton Labeling (all strengths)

1. The proposed proprietary name [REDACTED] (b) (4) is used in the labels and labeling but the name was found unacceptable by DMEPA. Revise the labels and labeling accordingly to read “Fetzima”.
2. The logo immediately following the proprietary name is too prominent and in too close proximity to the proprietary name. Remove the logo, or minimize the size and move it away from the proprietary name.
3. The established name on the labels and labeling incorrectly states [REDACTED] (b) (4). According to the Office of New Drug Quality Assessment (ONDQA), the established name should read: “levomilnacipran extended-release capsules”. Revise the labels and labeling accordingly.
4. The dosage form statement has a smaller font size compared to the active ingredient statement. Ensure the entire established name (including the dosage form) utilizes the same font and is printed in letters that are at least ½ as large as the letters comprising the proprietary name and that the font has a prominence commensurate with the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2).
5. The “Rx Only” statement is too prominent. Debold the “Rx Only” statement to decrease its prominence.

6. The “swallow whole...” instructions are included in the Usual Dosage statement and may be overlooked. Revise the Usual Dosage statement to read: See full Prescribing Information. Additionally, relocate the “Swallow whole” and “Do not chew or crush” statements to appear on a separate line below the Usual Dosage statement.

B. General Comments (Titration Packaging (b) (4))



C. Container Labels

1. The net quantity statement is too prominent on the labels. Remove the color highlighting from the net quantity statement, slightly decrease its size, and relocate the statement to a less prominent area on the label that is not too close in proximity to the statement of strength (e.g., lower right or left corner).
2. Relocate the statement of strength so that it is positioned directly below the established name for customary placement and to improve readability of the labels.

D. Hospital Unit Dose Blister

1. The vertical alignment and location of the statement of strength on the HUD blister labels decreases its readability. Position the statement of strength so that it is horizontal to facilitate readability. Additionally, relocate the statement of strength to a position below the established name. Consider relocating the barcode in order to provide space for relocation of the statement of strength.
2. The statement of strength on the HUD blister labels lacks prominence. Increase the size of the statement of strength in order to improve readability.
3. The dosage form is not stated on the HUD blister labels. Add the dosage form “extended-release capsule” to the blister label.

E. Hospital Unit-Dose Carton Labeling

1. The net quantity statements located in the middle of each panel (i.e., 100 Capsules) are too prominent and are duplicative. Delete those statements and keep the net quantity statement that is located at the bottom of the principal display panel. However, revise this statement to read: 10 x 10-count blister cards.
2. Relocate the statement of strength so that it is positioned beneath the established name.

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page.

J. Commercial Titration Pack (2 x 20 mg and 26 x 40 mg capsules)

1. The instructions for opening the titration pack are inadequate. The top panel of the flap does not have any instructions that state the flap should first be lifted up. Place instructions on the top panel of the flap that inform patients to lift up the flap to find instructions for sliding out the tray.
2. The “glue” used to secure the flap in place is very sticky which makes the flap difficult to lift up. Reconsider the need to secure the flap.
3. The instructions for use under the heading “Dosage” on the titration pack is not optimally worded for clarity and safe use of the titration packs. For example, one

of the statements reads: [REDACTED] (b) (4)

[REDACTED] If not read thoroughly, patients might inadvertently take two 20 mg capsules as the initial dose. Consider revising the statement and the statements that follow to the following format: Take one 20 mg capsule once daily on days 1 and 2; Take one 40 mg capsule once daily on days 3 through 28. Additionally, remove the hyphens from all dosing instructions and replace them with “to” or “through” accordingly in order to avoid any misinterpretation or confusion with their use (see aforementioned example).

14 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

LORETTA HOLMES
07/02/2013

IRENE Z CHAN
07/03/2013

SCOTT M DALLAS
07/03/2013

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 204168

Application Type: New NDA

Name of Drug: levomilnacipran HCl Extended-Release Capsules
Proprietary Name: Fetzima (Name Granted June 6, 2013)

Applicant: Forest Laboratories, Inc.

Submission Date: September 24, 2012

Receipt Date: September 25, 2012

1.0 Regulatory History and Applicant's Main Proposals

Forest submitted a new NDA 204168 for levomilnacipran HCl sustained-release capsules 20mg, 40mg, 80mg, 120mg. It is an SNRI developed for the treatment of Major Depressive Disorder (MDD). It is the levo-enantiomer of Savella® (milnacipran HCl) tablets approved in 2009 for the treatment of fibromyalgia.

Pierre Fabre discovered levomilnacipran and sponsored initial Phase 1 and Phase 2 studies. Forest sponsored additional Phase 1 studies and all Phase 3 studies (under IND 104483) that have been conducted to date. The clinical development program for levomilnacipran consists of the following studies.

- 19 completed clinical pharmacology and biopharmaceutics studies
- 5 completed placebo-controlled studies in MDD
- 1 completed randomized withdrawal relapse prevention study in MDD
- 1 ongoing open-label extension study in patients with MDD
- [REDACTED] (b) (4)
- [REDACTED] (b) (4)

The following list represents formal meetings between Forest and the FDA.

- May 18, 2009: Type B End of Phase 2 Teleconference
- March 12, 2010: Type C Clinical Development of a New Indication
- January 25, 2012: Type B Pre-NDA CMC Meeting
- May 4, 2012: Type B Pre-NDA Meeting: Clinical/Non-Clinical Review of Levomilnacipran for the Treatment of MDD

Selected Requirements of Prescribing Information (SRPI)

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI and other labeling issues identified above were conveyed to the applicant in the 74-day letter/an advice letter sent to the sponsor on November 27, 2012. The applicant was asked to correct these deficiencies and resubmit the PI in Word format within 3 weeks of receipt of the letter. The resubmitted PI was used for further labeling review.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- NO** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select "YES" in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select "NO" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

Selected Requirements of Prescribing Information (SRPI)

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **“HIGHLIGHTS OF PRESCRIBING INFORMATION”**.

Comment:

Highlights Limitation Statement

Selected Requirements of Prescribing Information (SRPI)

- YES** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

- YES** 10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

- NO** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment: *Delete the month from the Initial U.S. Approval in Highlights.*

Boxed Warning

- YES** 12. All text must be **bolded**.

Comment:

- YES** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- YES** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year)

Selected Requirements of Prescribing Information (SRPI)

format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

N/A

20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES

21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

Dosage Forms and Strengths

N/A

22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES

23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

YES

24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES

25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

YES

26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Selected Requirements of Prescribing Information (SRPI)

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- YES** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YE** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

NO

Selected Requirements of Prescribing Information (SRPI)

38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: Subsection 9.2 Abuse and Dependence should be separated: 9.2 Abuse and 9.3 Dependence.

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Selected Requirements of Prescribing Information (SRPI)

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

YES 42. All text is **bolded**.

Comment:

YES 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

YES 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment: *The language in the Boxed Warning (except the title) should have a left margin.*

Contraindications

N/A 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment: *The sponsor’s proposed language (below) is not verbatim but is acceptable. This is what the sponsor proposes:*

 (b) (4)

N/A 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

YES

Selected Requirements of Prescribing Information (SRPI)

48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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/s/

JULIETTE T TOURE
06/27/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: June 20, 2013

To: Mitchell Mathis, M.D.
Acting Director
Division of Psychiatry Products (DPP)

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Associate Director, Patient Labeling Team
Division of Medical Policy Programs (DMPP)

Robin Duer, RN, BSN, MBA
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Twanda Scales, RN, MSN/Ed.
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Susannah K. O'Donnell, MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name: levomilnacipran

Dosage Form and Route: extended-release capsules

Application
Type/Number: NDA 204168

Applicant: Forest Laboratories, Inc.

1 INTRODUCTION

On September 25, 2012, Forest Laboratories submitted for the Agency's review an original New Drug Application (NDA) for levomilnacipran extended-release capsules. Levomilnacipran is indicated for the treatment of Major Depressive Disorder (MDD).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry Products (DPP) on November 9, 2012 and November 8, 2012, respectively, for DMPP and OPDP to review the Applicant's proposed review the Applicant's proposed Medication Guide (MG) for levomilnacipran extended-release capsules.

2 MATERIAL REVIEWED

- Draft levomilnacipran extended-release capsules MG received on September 25, 2012, and received by DMPP on June 10, 2013
- Draft levomilnacipran extended-release capsules MG received on September 25, 2012, and received by OPDP on June 10, 2013
- Draft levomilnacipran extended-release capsules Prescribing Information (PI) received on September 25, 2012, revised by the Review Division throughout the review cycle, and received by DMPP June 10, 2013
- Draft levomilnacipran extended-release capsules Prescribing Information (PI) received on September 25, 2012, revised by the Review Division throughout the review cycle, and received by OPDP on June 13, 2013
- PRISTIQ (desvenlafaxine) Extended-Release Tablets comparator labeling approved February 14, 2013
- VIBRYD (vilazodone hydrochloride) Tablets comparator labeling approved December 21, 2012

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG are consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
06/20/2013

ROBIN E DUER
06/20/2013

LASHAWN M GRIFFITHS
06/20/2013

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Consumer Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 20, 2013

To: Juliette Touré, PharmD
Senior Regulatory Project Manager
Division of Psychiatry Products (DPP)

From: Susannah O'Donnell, MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Mathilda Fienkeng, PharmD
Team Leader, OPDP

Subject: **NDA #204168**
TRADENAME™ (levomilnacipran) Extended-Release Capsules

OPDP has reviewed the draft product labeling (PI) for TRADENAME™ (levomilnacipran) Extended-Release Capsules as requested in the consult from DPP dated November 8, 2012.

OPDP's comments on the draft PI for levomilnacipran are based on the version provided by email from Juliette Touré on June 13, 2013, and are provided directly on the draft PI below.

If you have any questions, please feel free to contact me by phone at 301-796-3245 or by email at Susannah.ODonnell@fda.hhs.gov.

OPDP appreciates the opportunity to provide comments on these materials. Thank you!

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/s/

SUSANNAH O'DONNELL
06/20/2013



Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Date: June 19, 2013

From: Amy M. Taylor, MD, MHS Medical Officer
Pediatric and Maternal Health Staff

Through: Hari Cheryl Sachs, MD Team Leader and Acting OND
Associate Director, Pediatric and Maternal Health Staff

NDA Number: 204-168

Sponsor: Forest Laboratories, Inc.

Product: levomilnacipran (Trade Name still under negotiation)

**Dosage form and
Route of administration:** Extended Release Capsules for oral use

Proposed use: Treatment of Major Depressive Disorder (adults)

Division Consult Request: The Division Psychiatric Products request assistance from PMHS with pediatric labeling for levomilnacipran.

Background

NDA 204-168 is under review for approval for the indication of Major Depressive Disorder (MDD). The product has not been studied in pediatric patients. The following waiver and post-marketing requirement under PREA are currently planned.

We are waiving the pediatric study requirement for ages 0 to 6 years because necessary studies are impossible or highly impracticable. This is because of the low prevalence of this disorder in this age range.

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

Draft labeling

There is a box warning for suicidal thoughts and behaviors at the beginning of the highlights section.

<p style="text-align: center;">WARNING: SUICIDAL THOUGHTS AND BEHAVIORS</p> <p><i>See full prescribing information for complete boxed warning.</i></p> <ul style="list-style-type: none">• Increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants (5.1).• Monitor for worsening and emergence of suicidal thoughts and behaviors (5.1).• TRADENAME is not approved for use in pediatric patients (8.4).
--

This box warning is accompanied by Warnings and Precautions section 5.1

5.1 Suicidal Thoughts and Behaviors in Adolescents and Young Adults

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a longstanding concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phase of treatment. Pooled analyses of short-term placebo-controlled studies of antidepressant drugs ([SSRIs] and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with MDD and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled studies in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term studies of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo controlled studies in adults with MDD or other psychiatric disorders included a total of 295 short-term studies (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency

toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in **Table 1**.

Table 1

<i>Age Range</i>	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric studies. There were suicides in the adult studies, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms: anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be

precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient’s presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms [see *Dosage and Administration* (b) (4) and *Warnings and Precautions* (b) (4)] for a description of the risks of discontinuation of TRADENAME].

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers.

Prescriptions for TRADENAME should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Screening patients for bipolar disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled studies) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that TRADENAME is not approved for use in treating bipolar depression.

The following language is in section 8.4 Pediatric Use.

8.4 Pediatric Use

Clinical studies on the use of TRADENAME in pediatric patients have not been conducted; therefore, the safety and effectiveness of TRADENAME in the pediatric population have not been established. TRADENAME is not approved for use in pediatric patients [see *Boxed Warning and Warnings and Precautions* (5.1)].

PMHS Recommendations:

The Pediatric Use statement is appropriate and consistent with the draft Guidance for Industry and Review Staff: Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling which recommends that “the following statement

(or a reasonable alternative) must be included (21 CFR 201.57(c)(9)(iv)(F)): ‘Safety and effectiveness in pediatric patients have not been established.’ The basis for this statement should be provided (e.g., stating that studies have not been conducted or providing an explanation of why the available evidence does not support a pediatric approval).

If a risk is associated with the use of the drug in a particular pediatric population (e.g., preterm or neonatal infants), the risk must be described in the Pediatric Use subsection or, if appropriate, described in the CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS section and referenced in the Pediatric Use subsection (21 CFR 201.57(c)(9)(iv)).

Conclusion

The draft labeling is appropriate for the pediatric population and consistent with the pediatric labeling draft guidance.

Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here.

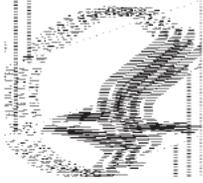
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/s/

AMY M TAYLOR
06/19/2013

HARI C SACHS
06/19/2013

I agree and am acting on behalf of Lynne P. Yao, Associate Director, PMHS



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pediatric and Maternal Health Staff Review

Date: June 14, 2013

From: Carrie Ceresa, Pharm D, MPH
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Melissa S Tassinari, PhD, DABT
Acting Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Lynne Yao, M.D., OND Associate Director,
Pediatric and Maternal Health Staff

To: Division of Psychiatry Products (DPP)

Drug: Fetzima (levomilnacipran) sustained release capsule/NDA 204-168

Subject: Labeling Revisions – Pregnancy, Nursing Mothers

Applicant: Forest Laboratories, Inc.

Materials Reviewed: levomilnacipran labeling, submitted December 18, 2012.

Consult Question: “We would like your input on all relevant sections of the label, e.g., use in specific populations (pregnancy, labor and delivery, nursing mothers, pediatric use), highlights, patient counseling, and med guide.”

INTRODUCTION

On September 25, 2012, Forest Laboratories., submitted an original New Drug Application for levomilnacipran sustained release capsules for the proposed indication of Major Depressive Disorder (MDD).

The Division of Psychiatry Products (DPP) consulted the Pediatric and Maternal Health Staff – Maternal Health Team (PMHS-MHT) to review and update the pregnancy and nursing mothers information in the levomilnacipran labeling. Pediatric Use labeling will be reviewed by the PMHS pediatrics group.

This review provides suggested revisions and re-ordering of existing information related to pregnancy and nursing mothers labeling for levomilnacipran in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements.

BACKGROUND

Levomilnacipran is the levo-enantiomer of the serotonin/norepinephrine (5-HT/NE) reuptake inhibitor (SNRI) milnacipran (Savella[®]).¹ Savella was approved January 14, 2009, for the “management of fibromyalgia.”

The proposed indication for levomilnacipran is Major Depressive Disorder (MDD). The exact mechanism of action of levomilnacipran for MDD is unknown. In clinical trials, levomilnacipran demonstrated high affinity for norepinephrine (NE) and serotonin (5-HT) transporters and inhibited NE and 5-HT reuptake *in vitro*.¹ Levomilnacipran demonstrated a 2-fold greater strength for norepinephrine compared to serotonin reuptake inhibition through *in vitro* studies.¹

Major Depressive Disorder (MDD)

MDD is a persistent and chronic illness which affects women more commonly than men.² MDD often causes cognitive impairment in individuals such as distractibility, poor concentration, slow thought process and the inability to process information. In addition, these patients often display a lack of interest to self-care and their surrounding environment.² MDD can also be accompanied by delusions or hallucinations, a loss of interest in activities that used to be pleasurable to the patient. Overall MDD can be a debilitating health problem to many patients and is often misdiagnosed.³

¹ Auclair, A.L., et al. “Levomilnacipran (F2695), a norepinephrine-preferring SNRI: Profile *in vitro* and in models of depression and anxiety.” *Neuropharmacology* 70 (2013): 338-347.

² Practice Guideline for the Treatment of Patients with Major Depressive Disorder. Third Edition. 2010. Available at www.psychiatryonline.com/pracGuide/pracGuideTopic_7.aspx. Accessed 3 May 2013.

³ Kupfer, D., et al. “Major depressive disorder: new clinical, neurobiological, and treatment perspectives.” *Lancet* 379 (2012): 1045-55.

According to the American Psychological Association (APA) clinical practice guidelines for MDD approximately 10% to 15% of pregnant patients will experience MDD.² In addition, 9 % to 16% of postpartum women will experience postpartum depression with a possible increase to 41% in subsequent pregnancies.⁴ The APA guidelines also stress the importance of evaluating the benefits and risks of antidepressants during pregnancy and breast-feeding.² In addition, many pregnancies, including those that are unplanned, are likely to occur in female patients actively treated for MDD as the condition is often recurring or chronic.²

DISCUSSION AND CONCLUSION

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in nursing mothers labeling, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

The PMHS-MHT discussed labeling recommendations with the review team during labeling meetings held on May 20, 2013 and June 3, 2013. The following PMHS- MHT recommendations reflect the discussions with the Division at those meetings.

PMHS LABELING RECOMMENDATIONS

PMHS-MHT labeling recommendations (label excerpts) appear below. The animal data section below in 8.1 is under review by the Pharm/Tox reviewer and may be further revised.

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----USE IN SPECIFIC POPULATIONS-----

(b) (4)

⁴ American Psychological Association. *Postpartum Depression*. Retrieved June 10, 2013, from www.apa.org/pi/women/programs/depression/postpartum.aspx.

FULL PRESCRIBING INFORMATION

2 DOSAGE AND ADMINISTRATION

(b) (4)

Reviewer comment: PMHS-MHT recommends deleting this language because there are no dosing recommendations specific for (b) (4). This language is found under the clinical considerations subsection of (b) (4).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy (b) (4)

Pregnancy Category C

(b) (4)

Risk Summary

There are no adequate and well-controlled studies of Fetzima in pregnant women. Neonates exposed to dual reuptake inhibitors of serotonin and norepinephrine (SNRIs) (such as Fetzima), or selective serotonin reuptake inhibitors (b) (4) late in the third trimester have developed complications (b) (4) that can arise immediately upon delivery. Levomilnacipran was not teratogenic in rats and rabbits when given during the period of organogenesis at doses up to 8 and 16 times the maximum recommended human daily dose (MRHD) of 120 mg on a mg/m² basis respectively. However, an increase in early postnatal rat pup mortality was seen at a dose equivalent to 5 times the MRHD (b) (4) given during pregnancy and lactation. Fetzima should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Neonates exposed to SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of these classes of drugs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [see *Warnings and Precautions (5.2)*].

A prospective longitudinal study of 201 women with history of major depression who were euthymic at the beginning of pregnancy, showed women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

Animal Data

No teratogenic effects were observed when levomilnacipran was administered to pregnant rats or rabbits during the period of organogenesis at doses up to 100 mg/kg/day. This dose is 8 and 16 times (in rats and rabbits, respectively) the maximum recommended human daily dose (MRHD) of 120 mg on a mg/m² basis. Fetal body weights were reduced in rats, and skeletal ossification was delayed in both rats and rabbits at this dose; these effects were not observed (b) (4) (b) (4), 2.4 times the MRHD in rats or (b) (4) 5 times the MRHD in rabbits.

When levomilnacipran was administered to pregnant rats at an oral dose of (b) (4) mg/kg/day, 5 times the MRHD, during organogenesis and throughout pregnancy and lactation, there was an increase in early postnatal pup mortality. Among the surviving pups, pre- and post-weaning pup weight gain was reduced up to 8 weeks of age; however, physical and functional development (b) (4) including reproductive performance of the progeny (b) (4) not affected. (b) (4)

Reviewer comment: The Animal Data section will be reviewed and edited by the pharm/tox reviewer. PMHS-MHT recommends adding the animal doses along with the recommended daily human doses in the data section as indicated in the above two paragraphs as (b) (4) mg/kg/day.

8.3 Nursing Mothers

(b) (4)

It is not known if Fetzima is present in human milk. Studies have shown that levomilnacipran is present in the milk of lactating rats. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Fetzima, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother.

Reviewer comment: The LactMed database had no listing for levomilnacipran. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breastmilk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.⁵

17 PATIENT COUNSELING INFORMATION

Pregnancy

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during therapy with Fetzima [see *Use in Specific Populations (8.1)*].

Nursing Mothers

Advise patients to notify their healthcare provider if they are breastfeeding an infant and would like to continue or start Fetzima [see *Use in Specific Populations (8.3)*].

Reviewer comment: PMHS-MHT agrees with the Pregnancy and Nursing Mothers language listed above which can be found in the Patient Counseling Information section of the package insert.

⁵ U.S. National Library of Medicine. National Institute of Health. *LactMed: A New NLM Database on Drugs and Lactation*. (2013). Retrieved June 10, 2013, from www.nlm.nih.gov/news/lactmed_announce_06.html.

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

/s/

CARRIE M CERESA
06/14/2013

MELISSA S TASSINARI
06/14/2013

LYNNE P YAO
06/16/2013

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: May 30, 2013

TO: Mitchell V. Mathis, M.D.
Director,
Division of Psychiatry Products

FROM: Arindam Dasgupta Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

THROUGH: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch,
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

and

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIRs Covering NDA 204-168, Levomilnacipran
sponsored by Forest Laboratories, USA.

At the request of the Division of Psychiatry Products (DPP), the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted inspections of the clinical and analytical portions of the following bioequivalence studies:

Study Number: LVM-PK-12
Study Title: "A Single-Center, Randomized, Open-Label, Crossover, Single Dose Study Evaluating the Bioequivalence of the Levomilnacipran To Be Marketed Formulation and the Clinical Formulation and the Effect of Food on Oral Bioavailability of the To-Be-Marketed Formulation in Healthy Subjects"

Study Number: LVM-PK-14
Study Title: "A Single-Center, Randomized, Open-Label, Crossover, Single Dose Study Evaluating the Bioequivalence of Elan To-Be-Marketed Levomilnacipran SR Capsule and Clinical Levomilnacipran SR Capsules in Healthy Subjects"

The clinical and analytical portions of the study were audited at PPD Phase 1 Clinic, Austin, TX (4/29-5/03/2013 by ORA Investigator Johann M. Fitch), QPS Bio-Kinetic, Springfield, MO (5/20-5/22/2013 by ORA Investigator Karen Montgomery), and Forest Research Institute Inc, Farmingdale, NY (1/11-1/17/2013 by ORA Investigator Iram Hassan and OSI/DBGLPC Scientist Arindam Dasgupta).

The audits included a thorough examination of facilities and equipment; examination of study records, including communications among PPD Phase 1, QPS Bio-Kinetic, and the sponsor; and interviews and discussions with PPD Phase 1, QPS Bio-Kinetic, and Forest Research Laboratories management and staff.

Following the inspections at the clinical sites (PPD Phase 1, and QPS Bio-Kinetic), no objectionable conditions were observed and Form FDA-483 was not issued at either site. Following inspection of the analytical site (Forest Research Institute Inc., Form FDA-483 was issued (**Attachment 1**). DBGLPC received a written response to the inspectional findings from Forest Research Institute on February 6, 2013. The Form FDA-483 observation, Forest Research Laboratories Response (**Attachment 2**) and my evaluation of the observations follow.

Analytical Site: Forest Research Laboratories Inc.

1. Failure to use freshly prepared calibration curves in long term frozen, bench top and freeze thaw (F/T) cycles stability studies for levomilnacipran and N-desethyl levomilnacipran. Examples include:
 - a. The calibration standards for levomilnacipran and N-desethyl levomilnacipran were prepared and then frozen [REDACTED] (b) (4)
 - b. The calibration standards used to evaluate 5 cycles F/T stability and bench top stability used in

validation run on August 30, 2010 were prepared and frozen on [REDACTED] (b) (4)

In their response, Forest acknowledged the observation and stated that their interpretation of "Fresh Sample" in Forest Standard Operating Procedure PRD-SOP-BDM-00014 allowed for [REDACTED] (b) (4)

[REDACTED] However, this comparison is not equivalent to using fresh calibrators to demonstrate that the method measures the actual concentrations achieved in the body. Since the inspection, Forest clarified their SOP (effective [REDACTED] (b) (4)

To address specific concerns raised in the FDA-483 observation, Forest re-evaluated long term frozen stability, bench top stability and freeze-thaw stability of levomilnacipran and N-desethyl levomilnacipran against freshly prepared and processed calibrators. Forest also stated that they would generate fresh stability data for Forest's other active projects for which frozen calibrators or references had been used to evaluate stabilities.

Assessment of Data Integrity: The long-term stability (882 days at -30°C and -70°C), bench top stability (25.75 hours) and freeze-thaw stability (3 freeze-thaws at -30°C and 5 freeze-thaws at -70°C) data provided by Forest in the response adequately covered the duration of storage of samples during study conduct. In my opinion, observations 1a and 1b were adequately addressed by the data in the new validation experiments. The above finding is not likely to impact outcome of the current studies.

2. Stock solution stabilities of levomilnacipran, N-desethyl levomilnacipran and deuterated internal standards were not evaluated against freshly prepared standard stock solutions.

Forest acknowledged the observation and stated that they have implemented corrective actions. Forest updated their SOP (effective 01/18/2013), [REDACTED] (b) (4)

[REDACTED] Forest provided additional data for stock solution stabilities for levomilnacipran, N-desethyl levomilnacipran and deuterated internal standard, evaluated against freshly prepared references. Forest also promised to generate fresh stability

data for other active projects where frozen solutions were used in the past.

Assessment of Data Integrity: The stock solution stability data provided by Forest indicate that stock solutions were stable for the times and conditions of the study testing. In my opinion, the above finding is not likely to impact outcome of the current studies.

3. All aspects of study conduct were not documented.

For example:

- a. Failure to maintain documentation for individual calibrators and QC sets used during sample processing for levomilnacipran studies LVM-PK-12 and LVM-PK-14. QC samples were not tracked along with the study samples.**

Forest acknowledged the observation and stated that they will implement a new labeling procedure for future studies such that individual calibrators and QCs were uniquely identified and tracked along with study samples. The above finding is not likely to impact outcome of the current study.

- b. Failure to maintain contemporaneous records in freezer logbook inventories. Examples include:**
- i. Storage of QC samples in the [REDACTED] (b) (4)**
 - ii. Movement of samples associated with run ID numbers LVM-PK-12-3 and LVM-PK-12-29.**
 - iii. Movement of samples for LVM-PK-14 between [REDACTED] (b) (4)**

Forest acknowledged the documentation errors made during movement of samples [REDACTED] (b) (4)

[REDACTED] However, Forest maintained that sample movements were correctly tracked in Watson LIMS, the primary records.

The above observation is not likely to affect the outcomes of the study.

- c. Failure to document the Tomtec program used during processing of samples from studies LVM-PK-12 and LVM-PK-14.**

Forest acknowledged the observation and stated that for all new studies, the analyst would document the Tomtec ID and Tomtec program names used in each analytical run.

The above observation is not likely to affect the outcome of the current study.

Conclusions:

Following review and evaluation of the Form FDA-483 observations and response from the analytical site, in my opinion, the clinical and analytical data generated for study LVM-PK-12 and LVM-PK-14 were not affected by the cited deficiencies. I recommend that the data for clinical and analytical portions of studies LVM-PK-12 and LVM-PK-14 be accepted for further agency review.

Arindam Dasgupta Ph.D.
Bioequivalence Branch, DBGLPC, OSI

Final Classifications:

NAI: PPD Phase 1 Clinic, Austin, TX

NAI: QPS Bio-Kinetic, Springfield, MO

VAI Forest Research Institute, Farmingdale, NY

CC:

CDER OSI PM TRACK

OSI/DBGLPC/Taylor/Dejernett

DBGLPC/BEB/Haidar/Skelly/Dasgupta

OND/ODEI/DPP/Mathis/Toure

OCP/DCPI/Kumi

ORA/NE-FO/NYK-DO/NYK-DIB/Hassan

ORA/SW-FO/KAN-DO/STL-MO/Montgomery

ORA/SW-FO/DAL-DO/DAL-IB/SAN-TX/Fitch

Draft: AD 05/28/2013

Edit: MFS 5/28/13; SHH 5/29/2013

BE File # 6399; O:\BE\EIRCOVER\204168for.lev.doc

ECMS: Cabinets/CDER OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/Electronic Archive/BEB

FACTS: 1475822

Attachment 1

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER Ronald Pace, District Director 158-15 Liberty Avenue Jamaica, NY 11433 Industry Information: www.fda.gov/oc/industry	DATE(S) OF INSPECTION January 11-17, 2013
	FEI NUMBER 1000521508

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED
TO: Andreas Grill, Executive Director

FIRM NAME Forest Research Institute, Inc.	STREET ADDRESS 220 Sea Lane
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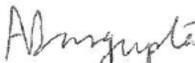
CITY, STATE AND ZIP CODE Farmingdale, NY 11735	TYPE OF ESTABLISHMENT INSPECTED Bioanalytical Laboratory
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THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS; AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

The following observations were made during an evaluation of studies LVM-PK-12, LVM-PK-14 and its associated method validation conducted in support of NDA 204-168:

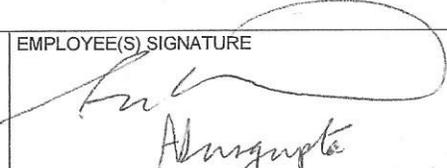
1. Failure to use freshly prepared calibration curves in long term frozen, bench top and freeze thaw (F/T) cycles stability studies for levomilnacipran and N-desethyl levomilnacipran. Examples include:
 - i. The calibration standards for levomilnacipran and N-desethyl levomilnacipran were prepared and then frozen (b) (4)
 - ii. The calibration standards used to evaluate 5 cycles F/T stability and bench top stability used in validation run on August 30, 2010 were prepared and frozen (b) (4)
2. Stock solution stabilities of levomilnacipran, N-desethyl levomilnacipran and deuterated internal standards were not evaluated against freshly prepared standard stock solutions.
3. All aspects of study conduct were not documented. For example:
 - a) Failure to maintain documentation for individual calibrators and QC sets used during sample processing for levomilnacipran studies LVM-PK-12 and LVM-PK-14. QC samples were not tracked along with the study samples.
 - b) Failure to maintain contemporaneous records in freezer logbook inventories. Examples include:
 - i. Storage of QC samples in the (b) (4)
 - ii. Movement of samples associated with run ID numbers LVM-PK-12-3 and LVM-PK-12-29.
 - iii. Movement of samples for LVM-PK-14 (b) (4)

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE 	EMPLOYEE(S) NAME AND TITLE (Print or Type) Iram R. Hassan, Ph.D., Investigator	DATE ISSUED 01/17/2013
		Arindam Dasgupta, Ph.D., Pharmacologist	

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER Ronald Pace, District Director 158-15 Liberty Avenue Jamaica, NY 11433 Industry Information: www.fda.gov/oc/industry		DATE(S) OF INSPECTION January 11-17, 2013
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED TO: Andreas Grill, Executive Director		FEI NUMBER 1000521508
FIRM NAME Forest Research Institute, Inc.	STREET ADDRESS 220 Sea Lane	
CITY, STATE AND ZIP CODE Farmingdale, NY 11735	TYPE OF ESTABLISHMENT INSPECTED Bioanalytical Laboratory	

c) Failure to document the Tomtec program used during processing of samples from studies LVM-PK-12 and LVM-PK-14.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE 	EMPLOYEE(S) NAME AND TITLE (<i>Print or Type</i>) Iram R. Hassan, Ph.D., Investigator Arindam Dasgupta, Ph.D., Pharmacologist	DATE ISSUED 01/17/2013
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Attachment 2

16 Page(s) have been Withheld in Full as
b4 (CCI/TS) immediately following this page

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

/s/

ARINDAM DASGUPTA
05/30/2013

SAM H HAIDAR
05/30/2013

WILLIAM H TAYLOR
05/30/2013

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: May 24, 2013

TO: Juliette Touré, Pharm.D., Regulatory Project Manager
Kavneet Kohli-Chhabra, M.D., Medical Officer
Ni Khin, M.D., Clinical Team Leader
Division of Psychiatry Products

FROM: John Lee M.D., Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D., Acting Team Leader
Susan Thompson, M.D., Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

APPLICATION: NDA 204-168

APPLICANT: Forest Research Institute, Inc.

DRUG: Levomilnacipran HCl Sustained-Release Capsules

NME: No

INDICATION: Treatment of major depressive disorder

THERAPEUTIC CLASSIFICATION: Standard

CONSULTATION REQUEST DATE: November 9, 2012

INSPECTION SUMMARY GOAL DATE: May 25, 2013

REGULATORY ACTION GOAL DATE: July 25, 2013

PDUFA DUE DATE: July 25, 2013

I. BACKGROUND

Major depressive disorder (**MDD**) affects 5% of the adult population in the United States (**US**) at any given time, and poses a lifetime risk of 15% worldwide. Available pharmacologic agents for managing MDD include tricyclic antidepressants (**TCA**), selective serotonin reuptake inhibitors (**SSRI**), and serotonin-norepinephrine reuptake inhibitors (**SNRI**). TCAs are effective but often have unacceptable histaminic or cholinergic adverse effects. SSRIs and SNRIs have fewer adverse effects, and SNRIs appear more effective. Despite the availability of SNRIs, pharmacologic monotherapy remains inadequate in up to two-thirds of patients with MDD, and multiple agents are typically used to manage MDD.

Milnacipran is a potent SNRI approved for MDD outside the US and for fibromyalgia in the US (Savella[®]). The more active enantiomer levomilnacipran has been touted to be more potent than other SNRIs (including racemic milnacipran) in ameliorating MDD symptoms attributed to deficits in neurotransmission via serotonin (mood, anxiety, obsessive-compulsive behavior) and via norepinephrine (pain, energy, attention). The sponsor of this NDA (Forest Research Institute, Inc.) has developed a sustained-release formulation of levomilnacipran (F2695) for once-daily dosing to treat MDD, and seeks marketing approval based on three similar double-blind placebo-controlled studies: fixed-dose Studies LVM-MD-01 and LVM-MD-10 and flexible-dose Study LVM-MD-03.

Study LVM-MD-01

A Double-blind, Placebo-Controlled, Fixed-Dose Study of F2695 SR in Adult Patients with Major Depressive Disorder

This randomized, double-blind, fixed-dose, eight-week study was conducted at 38 US sites (724 subjects) over 20 months (September 2009 to May 2011). The primary study objective was to evaluate the efficacy, safety, and tolerability of fixed doses of levomilnacipran compared with placebo in treating adult MDD.

Treatment Groups and Regimen

- Subjects were randomized in equal ratio to four treatment groups: levomilnacipran 40, 80, and 120 mg, and placebo (once-daily oral administration)
- One-week single-blind placebo run-in period was followed by eight weeks of double-blind treatment and two weeks of double-blind down-taper

Inclusion Criteria

- Outpatient men and women (18 to 65 years of age) who meet *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)* criteria for MDD
- Current major depressive episode for at least eight weeks with minimum total scores on the Montgomery-Asberg Depression Rating Scale (**MADRS**) of:
 - 30 on clinician-rated MADRS (**MADRS-CR**) at Visits 1 and 2 (screening and baseline)
 - 26 on self-rated MADRS (**MADRS-SR**) at Visit 2 (baseline)
- Normal physical examination (**PE**), laboratory tests, and electrocardiogram (**ECG**); negative pregnancy testing in women; body mass index (**BMI**) ≥ 14 and ≤ 40

Exclusion Criteria

- Per DSM-IV-TR criteria, any Axis I disorder within six months or any of the following: schizophrenia, schizoaffective, or other psychotic disorder; depression unresponsive to adequate use (≥ 8 weeks per package insert) of two or more antidepressants; treatment (or plan for treatment) within three months for depression; history of manic or hypomanic episode, or depressive episode with psychotic features; obsessive-compulsive disorder, bulimia, or anorexia nervosa; borderline or antisocial personality disorder; mental retardation, dementia, amnesia, or other cognitive disorders; substance abuse or dependence (except nicotine and caffeine) within six months

- Electroconvulsive therapy (**ECT**) for current MDD; history of inadequate response to ECT; treatment (or need for treatment) with any prohibited agent with psychotropic activity within (longer of) two weeks or five drug half-lives except eszopiclone, zolpidem, or zaleplon (sleep aids)
- At screening and at baseline, suicide risk as evidenced by suicide attempt within past year, score ≥ 5 on MADRS-CR Item 10, or investigator judgment
- Vagus nerve stimulation or any experimental treatment for central nervous system (**CNS**) disorders within six months; history of seizure or seizure predisposition (stroke, head injury, CNS tumor), narrow angle glaucoma, or syndrome of inappropriate antidiuretic hormone (**SIADH**)
- Hypothyroidism or hyperthyroidism (unless stable on medication without dose change within two months); previous participation in any investigational study of levomilnacipran
- Any significant cardiovascular disease, including history of QTc prolongation (QTc ≥ 450 or 470 msec for men and women, respectively); second degree Mobitz II or third degree atrioventricular (**AV**) block; heart rate (**HR**) ≤ 50 or ≥ 120 , or any symptomatic HR; new myocardial infarction (**MI**) within 12 months or ischemic heart disease (**IHD**) within six months; symptomatic or complex premature ventricular contractions (**PVC**); atrial fibrillation or flutter with onset within 12 months or unknown, uncontrolled, symptomatic, or requiring anticoagulation
- At screening and at baseline, supine (≥ 6 minutes) systolic blood pressure (**BP**) > 140 mm Hg or < 90 mm Hg, diastolic BP > 90 mm Hg or < 50 mm Hg, or any significant BP per investigator judgment
- History of serotonin syndrome or neuroleptic malignant syndrome; HIV or hepatitis B/C infections; liver transaminases over 1.5 times upper limit of normal; gastric bypass or any condition that affects drug absorption; men with urinary retention
- Women who are (or planning to be) pregnant or breastfeeding through 30 days after end of study or not using acceptable contraception
- Treatment with an investigational drug within (longer of) three months or five drug half-lives; history of intolerance or hypersensitivity to levomilnacipran or other chemically related agents; any condition that interferes with study conduct, confounds results, or affects subject safety or welfare

Major Endpoints

- **Efficacy:** changes in total score, baseline to Week 8
 - Primary: MADRS-CR
 - Secondary: Sheehan Disability Scale (**SDS**), Clinical Global Impressions-Improvement (**CGI-I**)
- **Safety Endpoints**
 - Efficacy-related: Columbia–Suicide Severity Rating Scale (**C-SSRS**) scores
 - General: adverse events (**AE**), laboratory measures, ECGs, and PEs
- **Pharmacokinetic Endpoints:** levomilnacipran plasma concentrations
 - Selected sites: eight serial blood samples over 24 hours
 - All other sites: single blood samples at four consecutive visits

Major Study Results: relative to placebo

- Efficacy: statistically significant improvement (baseline to Week 8) in MADRS-CR (all levomilnacipran groups) and SDS (levomilnacipran 80 mg and 120 mg groups)
- Safety: increased liver transaminases and HR (with orthostasis and weight loss), ECG changes (increased QTcB and decreased PR intervals)

Study LVM-MD-03

A Double-blind, Placebo-Controlled, Flexible-Dose Study of F2695 SR in Patients with Major Depressive Disorder

This randomized, double-blind, flexible-dose, eight-week study was conducted at 23 US sites (442 subjects) over two years (December 2009 to December 2011). The primary study objective was to evaluate the efficacy, safety, and tolerability of fixed doses of levomilnacipran compared with placebo in treating MDD.

Treatment Groups and Regimen

- Subjects were randomized in equal ratio to two treatment groups, levomilnacipran or placebo (once-daily oral administration):
 - Milnacipran dosed initially at 20 mg (Days 1-2), increased to 40 mg (Day 3 and thereafter)
 - Further dose increase per clinical response: 40 to 80 mg (Visits 3-5) or 80 to 120 mg (Visit 5)
- One-week, single-blind placebo run-in period was followed by eight weeks of double-blind treatment and two weeks of double-blind taper

Inclusion Criteria

- Outpatient men and women (18 to 80 years of age) meeting DSM-IV-TR criteria for MDD, confirmed with Mini International Neuropsychiatric Interview (**MINI**)
- Current major depressive episode for at least four weeks with minimum total scores of 30 on MADRS-CR (Visits 1 and 2) and 26 on MADRS-SR (Visit 2)
- Normal PE, laboratory tests, and ECG; negative pregnancy test in women; BMI ≥ 14 and ≤ 40

Exclusion Criteria

- Per DSM-IV-TR criteria: any axis I disorder within six months or any of the following: schizophrenia, schizoaffective, or other psychotic disorder; depression unresponsive to adequate use (≥ 8 weeks per package insert) of two or more antidepressants; treatment (or plan for treatment) within three months for depression; history of manic or hypomanic episode, or depressive episode with psychotic features; obsessive-compulsive disorder, bulimia, or anorexia nervosa; borderline or antisocial personality disorder; mental retardation, dementia, amnesia, or other cognitive disorders; substance abuse or dependence (except nicotine and caffeine) within six months
- ECT for current MDD; history of inadequate response to ECT; treatment (or need for treatment) with any prohibited agent with psychotropic activity within (longer of) two weeks or five drug half-lives except eszopiclone, zolpidem, or zaleplon; at screening and at baseline, suicide risk as evidenced by suicide attempt within past year, score ≥ 5 on MADRS-CR Item 10, or investigator judgment
- History of seizure or seizure predisposition (stroke, head injury, CNS tumor), narrow angle glaucoma, or SIADH; hypothyroidism or hyperthyroidism (unless stable on medication without dose change within two months); vagus nerve stimulation or any experimental treatment for CNS disorders within six months; previous participation in any investigational study of levomilnacipran
- Any significant cardiovascular disease, including history of QTc prolongation (QTc ≥ 450 or 470 msec for men or women, respectively); second degree Mobitz II or third degree AV block; HR ≤ 50 or ≥ 120 , or any symptomatic HR; new MI within 12 months or IHD within six months; symptomatic or complex PVCs; atrial fibrillation or flutter of onset within 12 months or unknown onset, uncontrolled, symptomatic, or requiring anticoagulation; at screening and at baseline, supine (≥ 6 minutes) systolic BP > 140 mm Hg or < 90 mm Hg, diastolic BP > 90 mm Hg or < 50 mm Hg, or any significant BP per investigator judgment

- History of serotonin syndrome or neuroleptic malignant syndrome; HIV or hepatitis B/C infections; liver transaminases over 1.5 times upper limit of normal; gastric bypass or any condition that affects drug absorption; men with urinary retention; women who are (or planning to be) pregnant or breastfeeding through 30 days after end of study or not using acceptable contraception; treatment with an investigational drug within (longer of) three months or five drug half-lives; history of intolerance or hypersensitivity to levomilnacipran or other chemically related agents; any condition that interferes with study conduct, confounds results, or affects subject safety or welfare

Major Endpoints

- **Efficacy:** changes in total score, baseline to Week 8
 - MADRS-CR (primary) and SDS (secondary) total scores
 - MADRS-CR response and remission rate, CGI-I total score and response rate
 - 17-Item Hamilton Rating Scale for Depression (**HAMD-17**) total and subscale scores
 - HAMD-17 response and remission rates, SDS item scores
 - Motivation and Energy Inventory–Short Form (**MEI-SF**) total and subscale scores
- **Safety Endpoints**
 - Efficacy-related: C-SSRS scores
 - General: AEs, laboratory measures, ECGs, and PEs

Major Study Results: levomilnacipran relative to placebo, baseline to Week 8

- Efficacy: statistically significant improvement in MADRS-CR, SDS, HAMD-17, CGI-S ($p \leq 0.008$), and MEI-SF ($p = 0.04$) and in MADRS-CR response rate (42% vs 29%, $p = 0.008$)
- Safety: increased AEs (82% vs 62% of subjects), HR (9 bpm), BP (4 mm Hg), incidence of orthostasis, and ventricular beats (14 vs 2 bpm); C-SSRS not significantly different

Study LVM-MD-10

A Double-blind, Placebo-Controlled, Fixed-Dose Study of Levomilnacipran SR in Patients with Major Depressive Disorder

This randomized, double-blind, fixed-dose, eight-week study was conducted at 51 sites, 47 in US and four in Canada (568 subjects) over 14 months (January 2011 to March 2012). The primary study objective was to evaluate the efficacy, safety, and tolerability of fixed doses of levomilnacipran compared with placebo in treating MDD.

Treatment Groups and Regimen

- Subjects were randomized in equal ratio to three treatment groups: levomilnacipran 40 mg, levomilnacipran 80 mg, or placebo (once-daily oral administration)
- One-week single-blind placebo run-in period was followed by eight weeks of double-blind treatment and one week of double-blind taper

Inclusion Criteria

- Outpatient men and women (18 to 75 years of age) meeting DSM-IV-TR criteria for MDD, confirmed with MINI
- Current major depressive episode ≥ 6 weeks and ≤ 12 months, ≤ 5 major depressive episodes within five years, with minimum total scores ≥ 26 on MADRS and ≥ 4 on CGI-S (Visits 1 and 2)
- Normal PE, laboratory tests, and ECG; negative urine drug screen, negative pregnancy testing in women; BMI ≥ 14 and ≤ 40

Exclusion Criteria

- Per DSM-IV-TR criteria: any Axis I disorder within six months or any of the following: schizophrenia, schizoaffective, or other psychotic disorder; depression unresponsive to adequate use (≥ 8 weeks per package insert) of two or more antidepressants; treatment (or plan for treatment) within three months for depression; history of manic or hypomanic episode, or depressive episode with psychotic features; obsessive-compulsive disorder, bulimia, or anorexia nervosa; borderline or antisocial personality disorder; mental retardation, dementia, amnesia, or other cognitive disorders; substance abuse or dependence (except nicotine and caffeine) within six months
- ECT within 10 years; history of inadequate response to ECT; treatment (or need for treatment) with any prohibited agent with psychotropic activity within (longer of) two weeks or five drug half-lives except eszopiclone, zolpidem, or zaleplon; at screening and at baseline, suicide risk as evidenced by suicide attempt within past year, score ≥ 5 on MADRS-CR Item 10, score > 3 on HAMD-17 Item 3, or investigator judgment
- History of seizure (except simple childhood febrile seizure before age five) or seizure predisposition (stroke, head injury, CNS tumor), narrow angle glaucoma, or SIADH; hypothyroidism or hyperthyroidism (unless stable on medication without dose change within two months); vagus nerve stimulation or any experimental treatment for CNS disorders within six months; previous participation in any investigational study of levomilnacipran at any time
- Any significant cardiovascular disease, including history of QTc prolongation (QTc ≥ 450 or 470 msec for men or women, respectively); second degree Mobitz II or third degree AV block; HR ≤ 45 or ≥ 100 , or any symptomatic HR; new MI within 12 months or IHD within six months; symptomatic or complex PVCs; atrial fibrillation or flutter with onset within 12 months or unknown onset, uncontrolled, symptomatic, or requiring anticoagulation; at screening and at baseline, supine (≥ 6 minutes) systolic BP > 140 mm Hg or < 90 mm Hg, diastolic BP > 90 mm Hg or < 50 mm Hg, or any significant BP per investigator judgment
- History of serotonin syndrome or neuroleptic malignant syndrome; HIV or hepatitis B/C infections; liver transaminases over 1.5 times upper limit of normal; gastric bypass or any condition that affects drug absorption; men with urinary retention; women who are (or planning to be) pregnant or breastfeeding through 30 days after end of study or not using acceptable contraception; treatment with an investigational drug within (longer of) three months or five drug half-lives; history of intolerance or hypersensitivity to levomilnacipran or other chemically related agents; any condition that interferes with study conduct, confounds results, or affects subject safety or welfare

Major Endpoints

- **Efficacy:** change in total score, baseline to Week 8
 - MADRS-CR (primary) and SDS (secondary) total scores
 - Rates of MADRS-CR response ($\geq 50\%$ score reduction) and remission (score ≤ 10)
 - CGI-I, HAMD-17, and SDS scores
- **Safety Endpoints**
 - Efficacy-related: C-SSRS scores
 - General: AEs, laboratory measures, ECGs, and PEs

Major Study Results: levomilnacipran relative to placebo, baseline to Week 8

- Efficacy: statistically significant improvement in MADRS ($p = 0.003$) and SDS ($p = 0.05$) total scores and MADRS responder and remission rates; extent of improvement similar for both dose groups and evident at four weeks

- Safety: subject discontinuations more common for levomilnacipran 40 mg (6%) and 80 mg (10%) than for placebo (2%) commonly due to AEs (nausea, tachycardia, rash, headache, dizziness, hyperhidrosis, urinary hesitation, testicular pain); liver transaminases slightly higher for levomilnacipran 80 mg than for 40 mg or placebo; increases in BP (4 mm Hg) and HR (6 bpm), overall incidence of orthostasis similar for all groups

II. INSPECTIONS

For this NDA (new clinical indication for an approved agent), three pivotal studies (described above) were audited at four clinical study sites (shown below). The sites were selected for inspection based on: (1) multiple studies at same site, (2) relatively large subject enrollment with significant contribution to overall product efficacy, and (3) number of CDER INDs and prior FDA inspection history (not inspected within two years or significant findings at last inspection).

	Inspected Entity	Studies, Sites, and Subject Enrollment	Inspection Outcome
1	Nick G. Vatakis, MD Social Psychiatry Research Institute Brooklyn, NY	LVM-MD-01 Site 32, 19 subjects	December 19 - 21, 2012 NAI
2	Zinoviy Benzar, MD, PhD Brooklyn Medical Institute Brooklyn, NY	LVM-MD-03 Site 51, 28 subjects LVM-MD-10 Site 04, 12 subjects	December 4 -13, 2012 NAI
3	Alexander Horwitz, MD Oregon Center for Clinical Investigations Salem, OR	LVM-MD-03 Site 58, 31 subjects LVM-MD-10 Site 17, 24 subjects	December 3 - 14, 2012 VAI
4	Arifulla Khan, MD Northwest Clinical Research Center Bellevue, WA	LVM-MD-10 Site 22, 33 subjects	March 12 - April 10, 2013 Pending (preliminary VAI)

NAI = no action indicated (no significant GCP deviations); VAI = voluntary action indicated (significant GCP deviations); OAI = official action indicated (serious GCP deviations and/or data unreliable)

Pending: Preliminary classification is based on information on Form FDA 483 and preliminary communication with the field investigator. The final establishment inspection report has not been received from the field office and OSI's complete review of the EIR remains pending as of this clinical inspection summary.

1. Nick G. Vatakis, M.D.

Site 32 of Study LVM-MD-01: 21 subjects were screened, 19 were enrolled (~3% of total study enrollment), and 13 completed the study.

a. What was inspected:

- Evaluating regulatory compliance with the study protocol, good clinical practice regulations, and applicable standard operating procedures
- Data verification: subject eligibility, informed consent, subject randomization, major efficacy endpoints, adverse event reporting, protocol deviations, subject discontinuations, and concomitant medication use
- Records review for sponsor and IRB monitoring, financial disclosures, test article accountability, and case records for selected subjects and study evaluation
- Subject case records review: Case records were reviewed completely for seven randomly selected subjects completing the study. For all remaining enrolled subjects, case records were reviewed in detail to include informed consent, major endpoints (Montgomery-Asberg Depression Rating Scale and Sheehan Disability Scale), and adverse event reporting.

b. General observations and comments:

- No significant deficiencies were observed and a Form FDA 483 was not issued. IRB oversight and study monitoring appeared to be adequate. All subjects signed the informed consent document. Source records were well-maintained. Drug accountability records were adequate.
- Deficiencies verbally discussed (not cited on Form FDA 483, inspector discretion): For three subjects, minor data discrepancies were observed between source records (correct) and the corresponding case report forms (CRFs) and NDA data listings (data entry error).

Subject	Endpoint Assessment	Source	CRF
103	SDS, Question 3, Visit 2	8	7
112	MADRS, Visit 4, Reported Sadness	3	2
112	MADRS, Visit 4, Apparent Sadness	2	3
117	SDS, Question 1, Visit 7	10	9

Reviewer Comments: Visit 2 (baseline) and Visit 7 (end of blinded treatment) are important to endpoint data. However, the discrepancies in the affected data (SDS assessment, Subjects 103 and 117) were negligibly small and apparently isolated, and the errors are not expected to have importantly affected the study outcome at this site. All audited study data otherwise matched among source records, CRFs, and NDA data listings.

c. Assessment of data integrity: Data from this study site appear reliable as reported in the NDA.

2. Zinoviý Benzar, M.D., Ph.D.

Site 51 of Study LVM-MD-03: 33 subjects were screened, 28 were enrolled (~6% of total study enrollment), and 27 completed the study.

Site 04 of Study LVM-MD-10: 15 subjects were screened, 12 were enrolled (~2% of total study enrollment), and 12 completed the study.

- a. What was inspected:
- Evaluating regulatory compliance with the study protocol, good clinical practice regulations, and applicable standard operating procedures
 - Data verification: subject eligibility, informed consent, subject randomization, major efficacy endpoints, adverse event reporting, protocol deviations, subject discontinuations, and concomitant medication use
 - Records review for sponsor and IRB monitoring, financial disclosures, test article accountability, and case records for selected subjects and study evaluation
 - Subject case records review for Study LVM-MD-03: Case records were reviewed completely for eight randomly selected subjects completing the study. For all remaining subjects completing the study (19 subjects), case records were reviewed in detail to include informed consent, major endpoints (Montgomery-Asberg Depression Rating Scale and Sheehan Disability Scale), and adverse event reporting.
 - Subject case records review for Study LVM-MD-10: Case records were reviewed completely for five randomly selected subjects completing the study. For all remaining subjects completing the study (seven subjects), case records were reviewed in detail to include informed consent, major endpoints (Montgomery-Asberg Depression Rating Scale and Sheehan Disability Scale), and adverse event reporting.
- b. General observations and comments:
- No significant deficiencies were observed and a Form FDA 483 was not issued. IRB oversight and study monitoring appeared to be adequate. All subjects signed the informed consent document.
 - Source records were complete and well-maintained. Drug accountability records were adequate. The audited endpoint data matched among source records, case report forms, and NDA data listings.
- c. Assessment of data integrity: Data from this study site appear reliable as reported in the NDA.

3. Alexander E. Horwitz, M.D.

Site 58 of Study LVM-MD-03: 38 subjects were screened, 31 were enrolled (~7% of total study enrollment), and 26 completed the study.

Site 17 of Study LVM-MD-10: 30 subjects were screened, 24 were enrolled (~4% of total study enrollment), and 18 completed the study.

- a. What was inspected:
- Evaluating regulatory compliance with the study protocol, good clinical practice regulations, and applicable standard operating procedures
 - Data verification: subject eligibility, informed consent, subject randomization, major efficacy endpoints, adverse event reporting, protocol deviations, subject discontinuations, and concomitant medication use
 - Records review for sponsor and IRB monitoring, financial disclosures, test article accountability, and case records for selected subjects and study evaluation
 - Subject case records review: For each study, records were reviewed in detail for 10 enrolled subjects (selected at random) to include informed consent, major endpoints (Montgomery-Asberg Depression Rating Scale and Sheehan Disability Scale), and adverse event reporting.

b. General observations and comments:

- A Form FDA 483 was issued for the following deficiencies in failing to adhere to the protocol for Study LVM-MD-03:
 - For 17 blood samples from seven subjects (for study medication pharmacokinetic assay), the duration of the frozen storage between -20 and -70 °C exceeded the protocol-specified limit of one week (typically one to two weeks, up to one month)
 - For all 31 enrolled subjects, adherence to the protocol-specified parameters for preparing the pharmacokinetic samples prior to extended storage (e.g., centrifugation duration, temperature, and force) were not documented
 - Subject 323: The dose of the study medication was inappropriately increased at Visit 5. The clinical response (as measured by MADRS-CR) was adequate.
- Other deficiencies verbally discussed (not cited on Form FDA 483, inspector discretion):
 - No documentation of periodic calibration of temperature monitoring devices
 - Minor transcription errors on CRFs (e.g., doxycycline dose, subject ethnicity)
- Other than as noted above, no significant deficiencies were observed. IRB oversight and study monitoring appeared to be adequate. All subjects signed the informed consent document. Source records were well-maintained. Drug accountability records were adequate. The audited endpoint data matched among source records, case report forms, and NDA data listings.

c. Assessment of data integrity:

All observed deficiencies (cited and not cited on Form FDA 483) appear to be minor, isolated, and unlikely to importantly affect the study outcome at this study site. For both audited studies, data from this study site appear reliable as reported in the NDA.

4. Arifulla Khan, M.D.

Site 22 of Study LVM-MD-10: 44 subjects were screened, 33 were enrolled (~6% of total study enrollment), and 22 completed the study.

a. What was inspected:

- Evaluating regulatory compliance with the study protocol, good clinical practice regulations, and applicable standard operating procedures
- Data verification: subject eligibility, informed consent, subject randomization, major efficacy endpoints, adverse event reporting, protocol deviations, subject discontinuations, and concomitant medication use
- Records review for sponsor and IRB monitoring, financial disclosure, test article accountability, subject enrollment in multiple studies, and subject case history.
- Subject case records review: For each study, records were reviewed in detail for all enrolled subjects to include informed consent, major endpoints (Montgomery-Asberg Depression Rating Scale and Sheehan Disability Scale), and adverse event reporting.

b. General observations and comments:

- A Form FDA 483 was issued for failing to: (1) conduct Study LVM-MD-10 in accordance with the study protocol, (2) maintain adequate subject case histories, and (3) use an adequate informed consent form. Specifically:

- The protocol specifies that "reasonable efforts" must be made to recruit qualified subjects. However, the records request sent to outside patient-care centers was limited to *Authorization to Use or Disclose My Health Care Information* and did not include a request for medical records.
- The informed consent form did not contain a description of the risks of discontinuing the study medication (or substituting the study medication with another agent) abruptly without an adequate down-taper.
- There was no documentation of evaluation: (1) for all subjects, exclusion criterion 7 (prior vagus nerve stimulation or any experimental procedure for central nervous system disorders), and (2) for 13 subjects, exclusion criterion 10 (use of psychotropic drugs).
- For the following 10 subjects, the MINI assessment did not include ruling out non-psychiatric causes for all disorders: Subjects 0221002 - 0221006, 0221008, 0221010, 0221011, 0221022, and 0221032.
- For the following six subjects, some study data were inconsistent between source records and CRFs. The data discrepancies do not appear to be important to the study outcome at this site.

Subject	Data Discrepancy	Source	CRF
0221001	study treatment, AE management	one dose held	no action
0221003	Visit 7, SDS date	9/11/2011	9/1/2011
0221005	Visit 1, non-suicidal self-injurious behavior	"yes"	"no"
0221008	dosing time, AE management	AM to PM	no change
0221021	Visit 6, SDS value for family responsibilities	6	5
0221029	Visit 2, SDS value for family responsibilities	8	9

- Subjects 0221003 and 0221005: The study medication was dispensed without confirming negative urine drug screen (inclusion criterion 12). This protocol violation was reported to the sponsor (with receipt of prior sponsor approval) but not to the institutional review board (IRB). Visit 2 progress notes indicated meeting all eligibility criteria despite missing urine drug screen results for propoxyphene. Negative urine drug screen was later confirmed.
- Subject 0221004: Source records for suicidal assessment using C-SSRS at Visit 4 lacked documentation of suicidal ideation intensity.
- Subject 0221010: For this subject discontinued from the study, no attempt was made to schedule an early termination assessment and recover the unused study medication.
- Subject 0221016: This subject agreed to use a method of contraception specifically noted in the protocol as unacceptable (condom and spermicide). This protocol violation was not reported to the sponsor or the IRB.
- Subject 0221018: In a previous study conducted at this study site (CVD-PT-10203), this subject was noted to have post-traumatic stress disorder and panic disorder, two disorders for which the subject should have been excluded from the current study.

- Other deficiencies verbally discussed (not cited on Form FDA 483, inspector discretion):
 - For the following eight subjects, some isolated AEs of mild severity (< twice upper limit of reference range) were not reported on CRFs. The isolated underreporting of mild AEs appears unlikely to importantly affect the safety data obtained from this study site.

Subject	Visit	AE
0221009	1	increased gamma glutamyl transferase (GGT)
0221019	1, 5, 6, 7, 8	increased alanine aminotransferase (ALT) and GGT
0221024	5	increased ALT
0221026	5, 7	increased ALT and aspartate aminotransferase (AST)
0221004	5, 8	increased blood pressure
0221011	7	decreased heart rate (moderate, 39 beats per minute)
0221015	5, 7	symptoms consistent with urinary tract infection
0221042	1	headache

- Drug Accountability: The recorded number of study kits received from the sponsor did not match the number returned at the end of the study (three more returned than received). This discrepancy appeared to be an isolated deficiency in otherwise adequate drug accountability.
- Other than as noted above, no significant deficiencies were observed. IRB oversight and study monitoring appeared to be adequate. All subjects signed the informed consent document. Source records were complete and adequately maintained. There was no evidence of unblinding, and all subjects received the study medication as intended (randomized). The major endpoint data matched among source records, case report forms, and NDA data listings.

Reviewer Comments:

- *The most recent inspection of this clinical investigator site was performed in January 2012. At that inspection, the major concern was the observation that the primary study diagnosis for the same subject differed in different studies (e.g., MDD, bipolar disorder, and schizophrenia) for all five subjects with multiple available study records. The field office had recommended an OAI outcome classification. CDER's classification has not been finalized (as of this clinical inspection summary), pending completion of other investigations currently on-going for this clinical investigator site.*
- *Given the inspectional history and concern about potentially inaccurate primary study diagnosis, an unusually detailed and rigorous audit of Study LVM-MD-10 was performed during the current inspection. Every attempt was made to detect inaccurate or inconsistent assessment of subject eligibility, particularly inaccurate diagnosis of MDD. There was no evidence that the study diagnosis of MDD was incorrect for any subject.*
- *The study protocol specifies the demonstration of "reasonable efforts to obtain qualified patients for the study" without mentioning medical records review. In Study LVM-MD-10 as conducted at this site, subject eligibility was assessed by on-study evaluation (history and MINI) typically without medical records review (consistent with study protocol). This clinical investigator has extensive experience in conducting clinical trials of investigational psychiatric medications (133 CDER INDs). For the current inspection, the significance of the clinical investigator's extensive clinical trial experience is unclear.*

c. Assessment of data integrity:

The relatively large number of deficiencies observed reflects an unusually detailed and rigorous audit of Study LVM-MD-10 as conducted at this study site. All observed deficiencies (cited and not cited on Form FDA 483) appear to be relatively minor, isolated, and unlikely to importantly affect the study outcome. Data from this study site appear reliable as reported in the NDA.

Note: The final EIR has not been received from the field office and the final inspection outcome classification remains pending. The observations noted above are based on preliminary communications with the field investigator.

III. OVERALL ASSESSMENT AND RECOMMENDATIONS

The sponsor (Forest Research Institute, Inc.) seeks marketing approval for levomilnacipran for the treatment of MDD. Three pivotal studies were identified for GCP audit at four clinical study sites with large subject enrollment. At all four inspections, no significant deficiencies were observed (Form FDA 483 not issued at two sites) and the clinical efficacy and safety data from all inspected sites appear reliable as reported in the NDA. The major observations for each inspected site are summarized below.

- Site 32, Study LVM-MD-01 (Vatakis, 3% of enrollment): At data verification audit, minor discrepancies were observed between source records (correct) and CRFs (incorrect, data entry error) in SDS data for Subjects 103 and 117, and in non-primary endpoint MADRS data for Subject 112. The discrepancies were negligibly small and apparently isolated and appear unlikely to be significant.
- Site 51, Study LVM-MD-03 (Benzar, 6% of enrollment); and Site 04, Study LVM-MD-10 (Benzar, 2% of enrollment): No significant deficiencies were observed.
- Site 58, Study LVM-MD-03 (Horwitz, 7% of enrollment); and Site 17, Study LVM-MD-10 (Horwitz, 4% of enrollment): The observed deficiencies were limited to Study LVM-MD-03.
 - For 17 blood samples from seven subjects intended for the determination of study medication pharmacokinetics (PK), the duration of the frozen storage between -20 and -70 °C exceeded the protocol-specified limit of one week (typically one to two weeks, up to one month).
 - For all enrolled subjects, details of PK sample preparation (e.g., centrifugation duration, temperature, and force) were not documented.
 - For Subject 323, the dose of the study medication was increased at Visit 5 to the next dose level despite adequate clinical response as assessed using MADRS according to the study protocol.
- Site 22, Study LVM-MD-10 (Khan, 6% of enrollment): Deficiencies were observed in protocol adherence, subject records maintenance, and informed consent.
 - No documentation of evaluation: (1) for all subjects, exclusion criterion 7 (prior vagus nerve stimulation or any experimental procedure for central nervous system disorders), and (2) for 13 subjects, exclusion criterion 10 (use of psychotropic drugs).
 - For 10 subjects, the MINI assessment did not include ruling out non-psychiatric causes for all disorders: Subjects 0221002 - 0221006, 0221008, 0221010, 0221011, 0221022, and 0221032.
 - For six subjects, some study data were inconsistent between source records and CRFs. The data discrepancies do not appear to be important to the study outcome at this site.
 - Subject 0221018: In a previous study conducted at this study site (CVD-PT-10203), this subject was noted to have post-traumatic stress disorder and panic disorder, two disorders for which the subject should have been excluded from the current study.
 - Eight mild AEs in as many subjects were not reported on CRFs. The underreporting of mild AEs appears to be isolated events and unlikely to be significant.

- The recorded number of study kits received from the sponsor did not match the number returned at the end of the study. This discrepancy appeared to be an isolated deficiency in otherwise adequate recordkeeping for drug accountability.

In brief, deficiencies were observed at three of four inspections (including one NAI site). The relatively large number of deficiencies observed at Site 22 of Study LVM-MD-10 (Khan) is consistent with an unusually rigorous audit. All deficiency observations (whether or not cited on Form FDA 483) appear to be minor, isolated, and unlikely to affect study outcome. All audited study data appear reliable as reported in the NDA. The inspectional observations are nonetheless summarized to facilitate the on-going NDA review, should they prove significant as the review progresses.

Note: For Site 22 of Study LVM-MD-10 (Khan), the final EIR has not been received from the field office and the final inspection outcome classification remains pending. The observations noted above are based on preliminary communications with the field investigator. An addendum to this clinical inspection summary will be forwarded to the review division if the final classification changes from the pending classification, or if additional observations of clinical or regulatory significance are discovered after completing the EIR review.

{See appended electronic signature page}

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/s/

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05/23/2013

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05/23/2013

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05/23/2013

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

NDA	204168
Brand Name	N/A
Generic Name	Levomilnacipran HCl
Sponsor	Forest Laboratories, Inc.
Indication	Major Depressive Disorder (MDD)
Dosage Form	Capsule
Drug Class	NE and serotonin uptake inhibitor
Therapeutic Dosing Regimen	120 mg/day
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	300 mg/day
Submission Number and Date	SDN 001, 15 Nov 2012
Review Division	DPP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

Levomilnacipran HCl prolongs QTc interval. The QT effect following the administration of levomilnacipran HCl was evaluated in a thorough QT study (Study LVM-PK-07). Significant QTc prolongation effect of 120 mg and 300 mg levomilnacipran HCl was detected in Study LVM-PK-07. The largest upper bounds of the 2-sided 90% CI for the mean difference between levomilnacipran 120 mg and placebo, and between levomilnacipran 300 mg and placebo were 10.8 and 10.5 ms observed at 8 and 16 hours post-dose, respectively.

In this randomized, blinded, parallel-crossover study, 170 healthy subjects received levomilnacipran HCl, placebo, and a single oral dose of moxifloxacin 400 mg. The overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Levomilnacipran HCl and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta QTcI$ (ms)	90% CI (ms)
Levomilnacipran 120 mg	8	7.3	(3.9, 10.8)
Levomilnacipran 300 mg	16	7.5	(4.5, 10.5)
Moxifloxacin 400 mg*	3	9.5	(7.4, 11.6)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 6.6 ms.

The hERG results are consistent with there being the kind of modest QT prolongation observed in this study. The lack of dose-response or (see Figure 6) exposure-response, however, is, at least, inconsistent with hERG blockade being the *only* effect. Possibilities include some defect in the hERG data, some problem with QT correction by heart rate, or a small effect of levomilnacipran on an inward current. Given the modest effect seen, it is not critical to have the sponsor do additional studies to resolve among these possibilities.

1.2 QT INTERDISCIPLINARY REVIEW TEAM’S COMMENTS

- A modest increase in QTc (~ 7 ms) was detected in this thorough QT study. The increase was not dose- or concentration-dependent. The suprathreshold dose in this study (300 mg) provides exposure (C_{max} and AUC) that are 2.8-fold those values at the maximum therapeutic dose and covers a worst-case exposure scenario in patients. The increase in QTc in this study is similar to the increase reported in the label for milnacipram (8 ms).
- An increase in heart rate (~ 20 bpm) was also detected in this study at both doses. The effect was not dose- or concentration dependent.
- We also note that an increase in blood pressure was observed in this study. The placebo-adjusted change from baseline in systolic and diastolic blood pressure was approximately 7 mm Hg and 12 mm Hg, respectively.

2 PROPOSED LABEL

2.1 SPONSOR’S PROPOSED LABEL



Reviewer's Comment: We recommend striking the sentence,

(b) (4)

(b) (4)

12.2 Pharmacodynamics

(b) (4)

2.2 QT-IRT'S PROPOSED LABEL

QT-IRT recommendations for labeling are suggestions only. We defer final labeling decisions to the Division.

12.6 Cardiac Electrophysiology

The effect of levomilnacipran at 120 mg daily (maximum therapeutic dose) and 300 mg daily (supratherapeutic dose) on the QTc interval was evaluated in a randomized, placebo-, and active-controlled (moxifloxacin 400 mg), parallel-group, thorough QT study in 170 healthy subjects. The maximum mean (95% upper confidence bound) difference in QTc from placebo after baseline-correction was 7.3 (10.8) ms and 7.5 (10.5) ms after dosing of levomilnacipran 120 mg and 300 mg daily, respectively.

An increase in heart rate was also observed. The maximum mean (95% upper confidence bound) difference in heart rate from placebo after baseline-correction was 20.3 (22.3) beats/min and 21.7 (23.8) beats/min seen 6 hours after dosing of levomilnacipran 120 mg and 300 mg daily, respectively.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Levomilnacipram is a "selective" inhibitor of norepinephrine uptake and serotonin uptake. It is being developed as an antidepressant.

3.2 MARKET APPROVAL STATUS

Levomilnacipran HCl is not approved for marketing in any country. The racemate milnacipram (Savella) is approved to treat fibromyalgia.

3.3 PRECLINICAL INFORMATION

Levomilnacipram inhibits hERG with an IC50 that is 12% of the human peak exposure. Corresponding changes are seen in the action potential duration. QT prolongation was demonstrated in dogs but not cynomolgus monkeys.

3.4 PREVIOUS CLINICAL EXPERIENCE

Over 2500 subjects have been exposure in clinical trials for a total of about 900 patient-years. Tachycardia (mean 7-9 bpm) and pressor effects (mean 3-4 mmHg) are seen. ECG and other cardiovascular adverse events of note were uncommon.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of levomilnacipran's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 104483. The sponsor submitted the study report LVM-PK-07 for levomilnacipran, including electronic datasets and waveforms and a thorough QT study to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

“Evaluation of the Effects of Sequential Multiple-Dose Regimens of Levomilnacipran on Cardiac Repolarization in Healthy Subjects”

4.2.2 Protocol Number

LVM-PK-07

4.2.3 Study Dates

February 7, 2011 - June 3, 2011

4.2.4 Objectives

The objective of this study was to assess the effects of the investigated maximum therapeutic dose (120 mg/d) and a suprathreshold dose (300 mg/d) of levomilnacipran on cardiac repolarization as determined by manual measurement of QTc on repeated digitally recorded 12-lead ECGs.

Source: Sponsor's study report, page 30.

4.2.5 Study Description

4.2.5.1 Design

This was a Phase 1, multicenter, randomized (stratified by sex), double-blind, placebo and positive-controlled, parallel-group, escalating multiple-dose study in 170 healthy male and female subjects aged 18 through 45 years.

Source: Sponsor's study report, page 31.

4.2.5.2 Controls

The sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

All treatment arms were administered blinded using a double dummy approach.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Subjects were randomized to receive 1 of the following 3 treatment regimens under fed conditions:

Group 1: Placebo on Day -2 and Day -1; escalating once-daily doses of levomilnacipran on Day 1 to Day 24, as follows: 20 mg on Day 1; 40 mg once a day for 3 days (Days 2-4); 80 mg once a day for 3 days (Days 5-7); 120 mg once a day for 4 days (Days 8-11); 160 mg once a day for 3 days (Days 12-14); 200 mg once a day for 3 days (Days 15-17); 260 mg once a day for 3 days (Days 18-20); 300 mg once a day for 4 days (Days 21-24); and placebo on Day 25.

Group 2: Placebo on Day -2 and Day -1; moxifloxacin 400 mg on Day 1; placebo on Day 2 to Day 24; placebo on Day 25.

Group 3: Placebo on Day -2 and Day -1; placebo on Day 1 to Day 24; moxifloxacin 400 mg on Day 25.

Source: Sponsor's study report, page 36.

4.2.6.2 Sponsor's Justification for Doses

The recommended dose range for levomilnacipran is 40 mg to 120 mg. A supratherapeutic dose of 300 mg/d was previously found to be safe and tolerable in healthy subjects and is 2.5 times greater than the investigated therapeutic dose of 120 mg/d. Approximately 50% of levomilnacipran was found to be excreted unchanged in urine (Study F02695 GE 1 01, 2005). Furthermore, in vitro studies have shown low potential for interaction with drugs that are substrates of CYP isoenzymes due to induction or inhibition of these enzymes.

Source: Sponsor's study report, page 38.

Reviewer's Comment: The dose selection in this study appears to be acceptable. The maximal therapeutical dose is 120 mg q.d. This study included 120 mg daily as the therapeutic dose and 300 mg q.d. as the supratherapeutic dose. As shown in clinical pharmacology highlights (Appendix 6.1), the intrinsic and extrinsic factors that have been studied seem to have a small magnitude of effect on PK of levomilnacipran, except for renal impairment. But the proper dose adjustment is proposed in patients with moderate and severe renal impairment. Thus, the 300-mg q.d. dose delivering 2.8 fold the exposure of the maximal therapeutic dose, is expected to cover the worst-case scenario, when patients may experience a higher exposure to levomilnacipran.

4.2.6.3 Instructions with Regard to Meals

Standardized, low-fat (< 20 g) meals were provided to all subjects while institutionalized.
Source: Sponsor's study report, page 36.

Reviewer's Comment: The instructions for food are acceptable. The PK of levomilnacipran is not affected by food.

4.2.6.4 ECG and PK Assessments

Blood samples were obtained at 0 hour (predose) and 1, 2, 3, 4, 6, 8, 12, 16, 20, 23, and 24 hours postdose on Days 1, 11, and 24. On Day 25, blood samples were obtained at 1, 2, 3, 4, 6, 8, 12, 16, 20, 23, and 24 hours postdose. Forty-seven PK samples were to be obtained for each subject in the study. Plasma samples were analyzed for levomilnacipran, F17400, and moxifloxacin levels using validated LC-MS/MS methods with good accuracy, linearity, reproducibility, and precision.

Serial time-matched triplicate ECGs of QT/QTc intervals were extracted from Holter for 24 hours after dosing on Days -2, 1, 11, 24, and 25. Additionally, Holter ECGs were recorded on Day -1 under conditions of increased heart rate by running on a treadmill, starting about 10 minutes before initiation of the exercise and continuing for a total of 2 hours.

Source: Sponsor's study report, page 5.

Reviewer's Comment: The timing of ECGs and PK appears to be acceptable.

4.2.6.5 Baseline

The sponsor used a pre-dose baseline for moxifloxacin.

4.2.7 ECG Collection

Twelve-lead Holter monitoring was used to obtain digital ECGs.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 170 subjects, age 18 to 45 years, 48% female, were enrolled and 149 completed study.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary PD outcome was $\Delta \Delta QTcNi$, the largest time-matched mean difference between levomilnacipran and placebo in $\Delta QTcNi$ (change from time-matched baseline measurement on Day -2 in individually corrected QT interval) with QT/RR adjustment for Days 11 and 24 derived from the exercise QT/RR data on Day -1 for Group 1.

A linear mixed-effects model was used to evaluate treatment effect of levomilnacipran (in Group 1) versus placebo (in Groups 2 and 3) on $QTcNi$ interval change from time matched baseline measurement on Day -2. This model included treatment group, sex, time, and treatment-by-time interaction as the fixed effects; subject, subject-by-treatment,

and subject-by-time as random effects; and time-matched baseline value and time matched baseline-by-time interaction as covariates. The least squares mean (LSM) estimate of treatment effect was calculated, as well as the corresponding two-sided 90% confidence intervals (CI) (equivalent to one-sided 95% CI), for each postbaseline time point. For the comparison between levomilnacipran 120 mg/d and placebo on Day 11, and between levomilnacipran 300 mg/d and placebo on Day 24, the upper limit of the two-sided 90% CI for the largest time-matched $\Delta \Delta$ QTcNi for postbaseline time points was compared with the upper boundary threshold of 10 msec. The same analysis was repeated for QT and QTcF intervals.

The QTcNi was calculated in 2 steps: First, for each subject, baseline QT/RR data on Day -2 (supine) was fitted to a linear regression model $QT = ai' + bi' \times RR + error$, where ai' is the intercept and bi' is the slope, and exercise QT/RR data on Day -1 (with exercise) was fitted to another linear regression model $QT = ai'' + bi'' \times RR + error$.

Second, for subjects in Group 1, the individually corrected QT (QTcNi) on Day -2 was computed as: $QTcNi = QT + bi' (1 - RR)$, and the postbaseline QTcNi (on Day 11 and Day 24) was computed as $QTcNi = QT + bi'' \times (1 - RR)$; for subjects in Groups 2 and 3, all QTcNi were computed as: $QTcNi = QT + bi' \times (1 - RR)$.

Source: Sponsor's study report, pages 55-56.

The sponsors found that both the therapeutic and suprathreshold dosages of levomilnacipran slightly prolonged the QT interval. See Table 2.

Table 2: Sponsor’s Least Squares Mean Results for Levomilnacipran 120 mg and 300 mg

Hours After Dose (h)	LSM Differences of Levomilnacipran (Group 1) (N=92) vs. Placebo (Groups 2 and 3) (N=76) ($\Delta\Delta$ QTcNi)			
	Levomilnacipran 120 mg/d ^a (n=92)		Levomilnacipran 300 mg/d ^b (n=80)	
	Difference in LSM	Two-Sided 90% CI	Difference in LSM	Two-Sided 90% CI
0	4.49	(0.58, 8.41)	2.62	(-1.33, 6.57)
1	5.23	(1.31, 9.15)	3.21	(-0.74, 7.15)
2	6.30	(2.38, 10.21)	4.41	(0.46, 8.36)
3	6.47	(2.56, 10.38)	5.28	(1.34, 9.23)
4	5.13	(1.22, 9.05)	4.26	(0.31, 8.21)
6	2.90	(-1.02, 6.82)	1.16	(-2.79, 5.11)
8	6.46	(2.54, 10.38)	4.42	(0.48, 8.37)
12	4.72	(0.81, 8.63)	3.16	(-0.79, 7.11)
16	6.40	(2.47, 10.32)	7.00	(3.04, 10.96)
20	3.11	(-0.81, 7.03)	4.84	(0.89, 8.79)
23	4.47	(0.54, 8.39)	3.64	(-0.31, 7.60)

^aLevomilnacipran 120 mg/d (Day 11) = escalating once-daily doses of levomilnacipran on Day 1 to Day 11, as follows: 20 mg on Day 1; 40 mg once a day for 3 days; 80 mg once a day for 3 days; 120 mg once a day for 4 days;

^bLevomilnacipran 300 mg/d (Day 24) = escalating once-daily doses of levomilnacipran on Day 1 to Day 24, as follows: 20 mg on Day 1; 40 mg once a day for 3 days; 80 mg once a day for 3 days; 120 mg once a day for 4 days; 160 mg once a day for 3 days; 200 mg once a day for 3 days; 260 mg once a day for 3 days; 300 mg once a day for 4 days.

Source: Sponsor’s study report, Table 1.3.2.1-1.

The FDA analysis is similar to the sponsor’s results, showing that the QT interval was elongated. See section 5.2.

4.2.8.2.2 Assay Sensitivity

The assay sensitivity was to evaluate treatment effect of moxifloxacin (in Groups 2 and 3) versus placebo (in Groups 2 and 3) in QTcNi interval change from time-matched baseline measurement with QT/RR adjustment for Days 1 and 25 derived from the QT/RR data on Day 24 and Day -2 for Group 2 and Group 3, respectively.

For Group 2, Δ QTcNi for moxifloxacin on Day 1 was compared with that for placebo on Day 24. Day 25 served as the baseline for Day 1 moxifloxacin, and Day -2 served as the baseline for Day 24 placebo. Similarly for Group 3, Δ QTcNi for moxifloxacin on Day 25 was compared with that for placebo on Day -2, and the baselines were the evaluations on Days 1 and 24, respectively.

A linear mixed effects model was used to evaluate the treatment effect of moxifloxacin versus placebo in QTcNi interval change from time-matched baseline measurement. This model included treatment group, sex, time, and treatment-by-time interaction as the fixed effects; subject, subject-by-treatment, and subject-by-time as random effects; time-matched baseline value and time-matched baseline-by-time interaction as covariates. The LSM estimate of treatment effect was also calculated as corresponding two-sided 90% CI for each postdose time points. The larger lower limit of the two-sided 90% CI for 3-hour and 4-hour time points was compared with lower boundary threshold of 5 msec. The Hochberg

procedure was used to control the multiplicity of comparison at multiple time points. Specifically, let p_1 and p_2 denote the ranked nominal p-values in decreasing order of the tests of mean Δ QTcNi of moxifloxacin are 5 msec. or less than that of placebo for 3 hour and for 4-hour time points.

Step 1: if p_1 is less than or equal to .10, then claim assay sensitivity obtained at both 3-hour and 4-hour and stop here.

Step 2: if p_2 is less than or equal to .05, then claim assay sensitivity obtained at the time point corresponds to, stop here.

Source: Sponsor's study report, page 57.

The sponsor found that assay sensitivity was established.

Table 3: Sponsor's Least Squares Mean Results for Moxifloxacin 400 mg

Hours After Dose (h)	Moxifloxacin ^a (N=76) vs. Placebo (N=76) ($\Delta\Delta$ QTcNi) Groups 2 ^b and 3 ^c	
	Difference in LSM	Two-Sided 90% CI
0	-1.40	(-3.61, 0.82)
1	-0.54	(-2.77, 1.68)
2	8.16	(5.95, 10.37)
3	8.60	(6.39, 10.81)
4	8.52	(6.32, 10.72)
6	3.90	(1.69, 6.11)
8	5.27	(3.08, 7.46)
12	4.27	(2.08, 6.47)
16	5.82	(3.61, 8.02)
20	6.29	(4.09, 8.49)
23	2.38	(0.18, 4.59)

^aMoxifloxacin = 2 days of placebo + a single 400 mg moxifloxacin dose (Day 1) + 24 days of placebo, or 26 days of placebo + a single 400 mg moxifloxacin dose (Day 25);

^bGroup 2: moxifloxacin on Day 1 was compared with placebo on Day 24. Day 25 served as the baseline for Day 1, and Day -2 served as the baseline for Day 24;

^cGroup 3: moxifloxacin on Day 25 was compared with placebo on Day -2, and the baselines were the evaluations on Days 1 and 24, respectively.

Source: sponsor's study report, Table 11.3.1.1-1.

The FDA analysis does not agree with the sponsor's conclusions. See section 5.2.

4.2.8.2.3 Categorical Analysis

The number and percentage of subjects with extreme values for QTcNi interval were presented by treatment group for each postdose time point. Extreme values were defined as QTcNi interval greater than 450, 480, or 500 msec; or QTcNi interval change from time-matched baseline on Day -2 of greater than 30 or 60 msec. The number and percentage of subjects with an ECG diagnostic abnormality (QRS complex, ST segment, T wave, or U wave morphologies) were presented by treatment group for each time point at which Holter ECG are collected.

Source: Sponsor's study report, page 57.

4.2.8.3 Safety Analysis

There were no deaths or serious adverse events. The safety profile was similar to the overall database.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 4. C_{max} and AUC values following administration of the 300-mg suprathreshold dose were 2.8-fold values seen with the 120 mg dose, the maximal clinical dose.

Table 4: Pharmacokinetic Parameters (Mean \pm SD) for levomilnacipran and moxifloxacin

<i>PK Parameter</i>	<i>Levomilnacipran 120 mg/d Mean \pm SD (n = 90)</i>	<i>Levomilnacipran 300 mg/d Mean \pm SD (n = 80)</i>
$C_{max,ss}$, ng/mL	305 \pm 59.0	864 \pm 159.2
T_{max}^a , h	6.00 (3.00 - 8.00)	6.00 (3.00 - 8.00)
$AUC_{0-t,ss}$, ng•h/mL	5067 \pm 996.9	13995 \pm 2753.1
$C_{min,ss}$, ng/mL	141 \pm 34.6	379 \pm 108.4

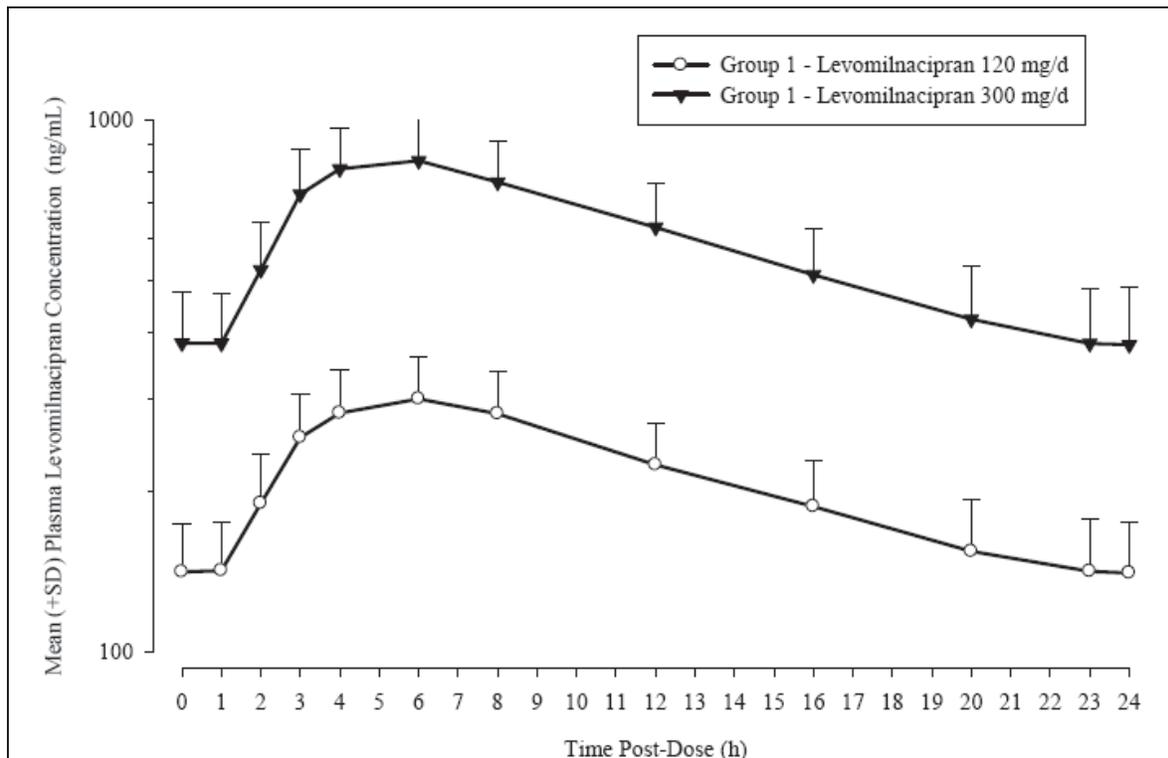
<i>PK Parameter</i>	<i>Moxifloxacin 400 mg Mean \pm SD (N = 72)</i>
C_{max} , ng/mL	2013 \pm 535
T_{max}^a , h	2.00 (1.00 - 6.00)
AUC_{0-t} , ng•h/mL	21538 \pm 4948
$AUC_{0-\infty}$, ng•h/mL	27823 \pm 6396
$T_{1/2}$, h	11.3 \pm 2.10

^a Median (Min - Max)

Source: Sponsor's study report, page 69 and 74.

The time-course concentration profiles of levomilnacipran are provided Figure 1.

Figure 1: Mean (+ SD) Levomilnacipran Plasma Concentrations (ng/mL) Versus Time (h) –Days 11 and 24 - Semi-Log Plot – PK Analysis Population

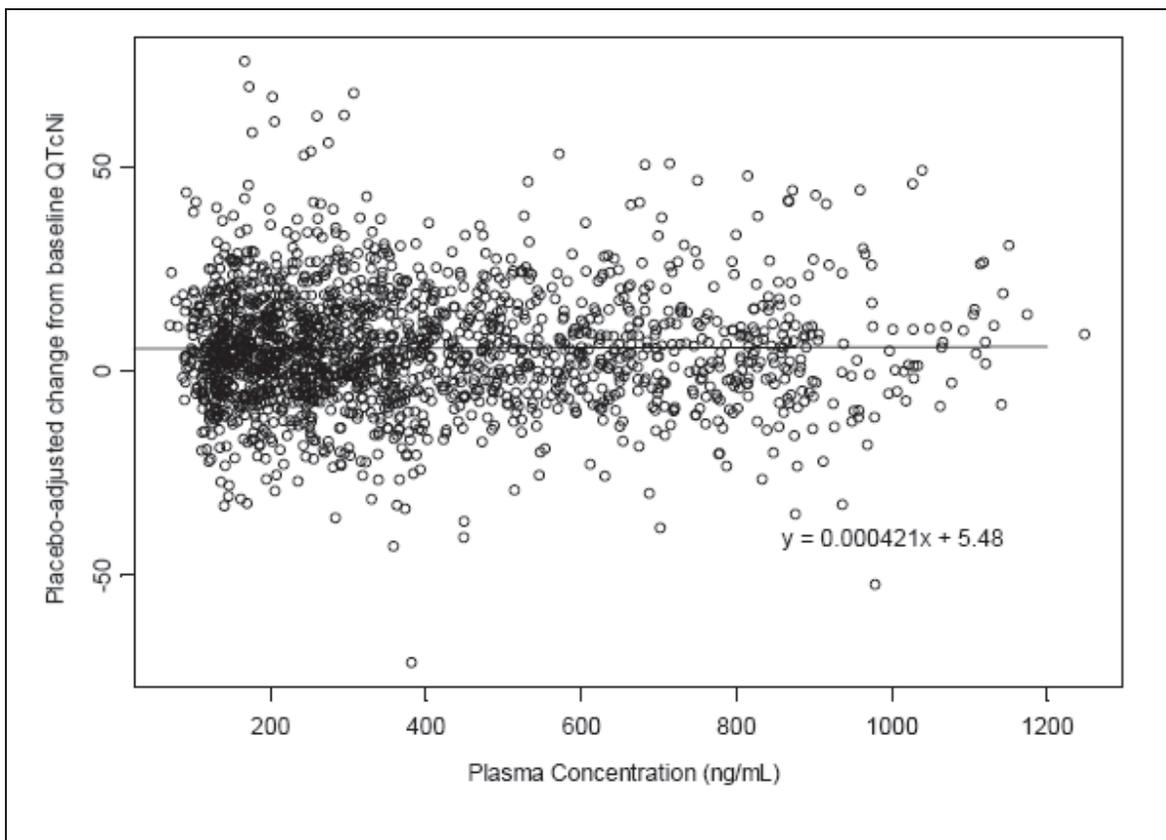


Source: Sponsor’s study report, page 69.

4.2.8.4.2 Exposure-Response Analysis

Sponsor conducted exposure-response analysis based on PD measures with different correction methods, including the primary QTcNi method (Figure 2), the QTcNi sensitivity method, and QTcF. Results all showed non-statistically significant slopes, suggesting there is no association between levomilnacipran concentration and QT prolongation.

Figure 2: C-QTcNi Linear Mixed-Effects Model Results for $\Delta\Delta\text{QTcNi}$ Based on QT/RR Data on Day -1 (With Exercise) and Plasma Concentrations of Levomilnacipran on Days 11 and Day 24 (Group 1)



Source: Sponsor's study report, page 92.

Reviewer's Analysis: The reviewer conducted independent exposure-response analysis using $\Delta\Delta\text{QTcI}$. A plot of $\Delta\Delta\text{QTcI}$ vs. concentrations (Figure 6) confirmed that there is no evident relationship between levomilnacipran concentration and QT prolongation.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcI). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

We used a mixed model of the pooled post-dose data of QTcF and QTcI distinguished by an indicator of correction method to evaluate the linear relationships between different correction methods and RR. The model included RR, correction type (QTcF or QTcI), and the interaction term of RR and correction type. The slopes of QTcF and QTcI versus RR are compared in magnitude as well as statistical significance in difference. As shown in Table 5, it appears that QTcI had smaller absolute slopes than QTcF. Therefore, QTcI is a better correction method for the study data.

Table 5: Comparison of QTcF and QTcI Using the Mixed Model

Treatment Groups	Slope of QTcF	Slope of QTcI	P-value
Levomilnacipran 120 mg	0.0349	-0.0064	0.0000
Placebo	0.0171	-0.0050	0.0000
Treatment Groups	Slope of QTcF	Slope of QTcI	P-value
Levomilnacipran 300 mg	0.0364	0.0141	0.0000
Placebo	0.0152	-0.0074	0.0000
Treatment Groups	Slope of QTcF	Slope of QTcI	P-value
Moxifloxacin	0.0307	0.0116	0.0000
Placebo	0.0201	-0.0000	0.0000

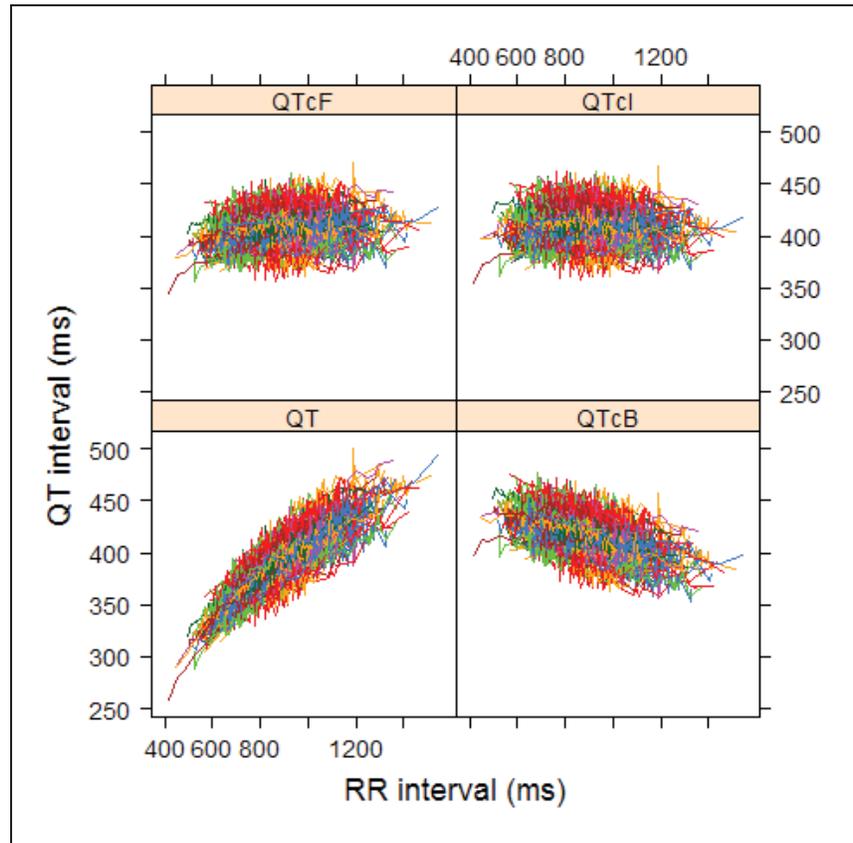
We also confirmed this conclusion by using the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 6, it also appears that QTcI is the best correction method. Therefore, this statistical reviewer used QTcI for the primary statistical analysis. This is consistent with the sponsor's choice of QTcI for their primary analysis.

Table 6: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	QTcF		QTcI	
	N	MSSS	N	MSSS
Levomilnacipran 120 mg	89	0.0031	86	0.0034
Placebo	74	0.0014	74	0.0020
Treatment Group	QTcF		QTcI	
Levomilnacipran 300 mg	80	0.0037	78	0.0033
Placebo	72	0.0012	72	0.0016
Treatment Group	QTcF		QTcI	
Moxifloxacin	72	0.0023	72	0.0022
Placebo	74	0.0018	74	0.0018

The relationship between different correction methods and RR is presented in Figure 3.

Figure 3: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Levomilnacipran

The statistical reviewer used a mixed model to analyze the Δ QTcI effect. The therapeutic and suprathreshold treatments were analyzed using a model for a parallel study, including treatment and sex as fixed effects and subject as a random effect. The positive control was analyzed using a model for a crossover study, including treatment as a fixed effect and subject as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in Table 7 and Table 8.

**Table 7: Analysis Results of Δ QTcI and $\Delta\Delta$ QTcI for Treatment Group A:
Levomilnacipran 120 mg x 11 days**

Time	Δ QTc: Levomilnacipran			Δ QTc: Placebo			$\Delta\Delta$ QTc		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0	83	1.3	1.4	73	-3.6	1.5	73	4.9	(1.6, 8.3)
1	84	2.8	1.4	73	-3.5	1.5	73	6.3	(3.0, 9.6)
2	86	3.0	1.2	72	-4.4	1.4	72	7.4	(4.3, 10.4)
3	86	2.8	1.3	74	-4.2	1.4	74	7.0	(3.8, 10.3)
4	84	2.9	1.3	73	-3.2	1.4	73	6.0	(2.8, 9.2)
6	83	2.5	1.6	73	-1.5	1.7	73	4.0	(0.1, 7.8)
8	82	2.3	1.4	72	-5.1	1.5	72	7.3	(3.9, 10.8)
12	86	2.4	1.4	74	-3.4	1.5	74	5.8	(2.5, 9.1)
16	85	3.5	1.3	70	-3.8	1.5	70	7.3	(4.0, 10.6)
20	84	1.9	1.4	70	-2.0	1.5	70	3.9	(0.5, 7.3)
23	83	3.3	1.3	71	-1.2	1.4	71	4.5	(1.3, 7.8)

**Table 8: Analysis Results of Δ QTcI and $\Delta\Delta$ QTcI for Treatment Group B:
Levomilnacipran 300 mg x 24 days**

Time	Δ QTc: Levomilnacipran			Δ QTc: Placebo			$\Delta\Delta$ QTc		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0	76	-0.2	1.4	70	-1.9	1.4	70	1.7	(-1.6, 4.9)
1	78	1.1	1.3	72	-1.9	1.4	72	3.0	(-0.1, 6.2)
2	78	1.3	1.2	70	-3.1	1.2	70	4.4	(1.6, 7.3)
3	77	2.9	1.4	72	-2.5	1.4	72	5.4	(2.1, 8.7)
4	77	2.4	1.3	71	-1.2	1.4	71	3.6	(0.4, 6.7)
6	77	1.1	1.4	70	-0.0	1.5	70	1.1	(-2.3, 4.4)
8	78	2.7	1.3	71	-2.1	1.4	71	4.8	(1.6, 7.9)
12	77	1.0	1.3	71	-2.7	1.4	71	3.7	(0.6, 6.8)
16	77	3.7	1.2	68	-3.8	1.3	68	7.5	(4.5, 10.5)
20	77	2.1	1.4	70	-3.1	1.4	70	5.2	(1.9, 8.4)
23	76	0.5	1.4	69	-2.3	1.5	69	2.7	(-0.6, 6.1)

The largest upper bounds of the 2-sided 90% CI for the mean difference between levomilnacipran 120 mg and placebo, and between levomilnacipran 300 mg and placebo were 10.8 ms and 10.5 ms, respectively.

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 9. The largest unadjusted 90% lower confidence interval is 7.4 ms. When considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 6.6 ms, which indicates that an at least 5 ms QTcI effect due to moxifloxacin can be detected from the study.

Table 9: Analysis Results of Δ QTcI and $\Delta\Delta$ QTcI for Moxifloxacin

Time	Δ QTc: Moxifloxacin			Δ QTc: Placebo			$\Delta\Delta$ QTc				
	N	Mean	SD	N	Mean	SD	N	Mean	SD	Unadjusted 90% CI	Adjusted* 90% CI
0	70	-2.0	1.0	72	-1.4	1.0	70	-0.7	1.1	(-2.4, 1.1)	(-3.1, 1.7)
1	68	-1.8	1.1	70	-2.2	1.1	68	0.4	1.3	(-1.8, 2.6)	(-2.6, 3.4)
2	70	5.6	1.0	72	-2.7	1.0	70	8.3	1.1	(6.6, 10.1)	(5.9, 10.8)
3	68	6.6	1.1	72	-2.9	1.0	68	9.5	1.3	(7.4, 11.6)	(6.6, 12.4)
4	70	7.7	1.1	72	-0.9	1.1	70	8.6	1.3	(6.5, 10.7)	(5.7, 11.5)
6	71	3.5	0.9	71	-0.7	0.9	71	4.1	1.2	(2.2, 6.1)	(1.5, 6.8)
8	72	3.6	0.9	73	-3.6	0.9	72	7.2	1.0	(5.6, 8.8)	(5.0, 9.4)
12	71	1.7	1.0	73	-3.3	1.0	71	5.0	1.2	(3.0, 7.1)	(2.2, 7.8)
16	71	3.8	1.1	74	-2.3	1.1	71	6.1	1.3	(3.9, 8.3)	(3.1, 9.1)
20	71	3.5	1.1	73	-2.4	1.1	71	6.0	1.2	(4.0, 8.0)	(3.2, 8.8)
23	71	1.6	1.2	73	-4.0	1.2	71	5.6	1.4	(3.2, 8.0)	(2.3, 8.9)

* Bonferroni correction was applied for multiple endpoint adjustment for 4 time points.

5.2.1.3 Graph of $\Delta\Delta$ QTcI Over Time

The following figures display the time profile of $\Delta\Delta$ QTcI for different treatment groups.

Figure 4: Mean and 90% CI $\Delta\Delta\text{QTcI}$ Timecourse: Levomilnacipran

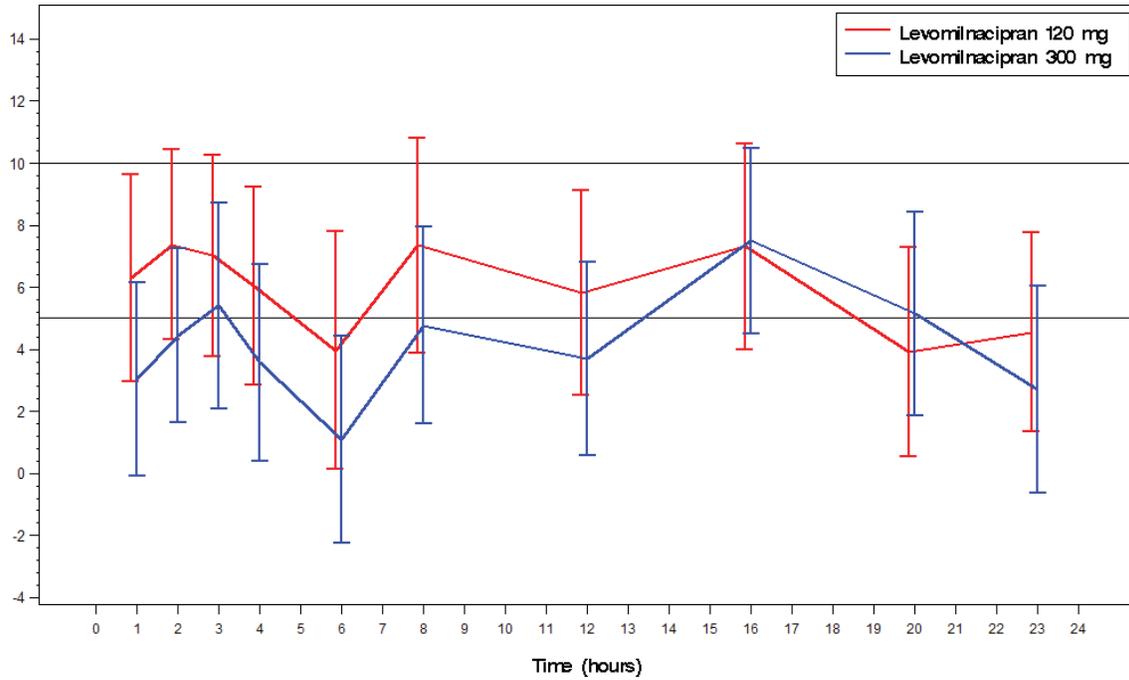
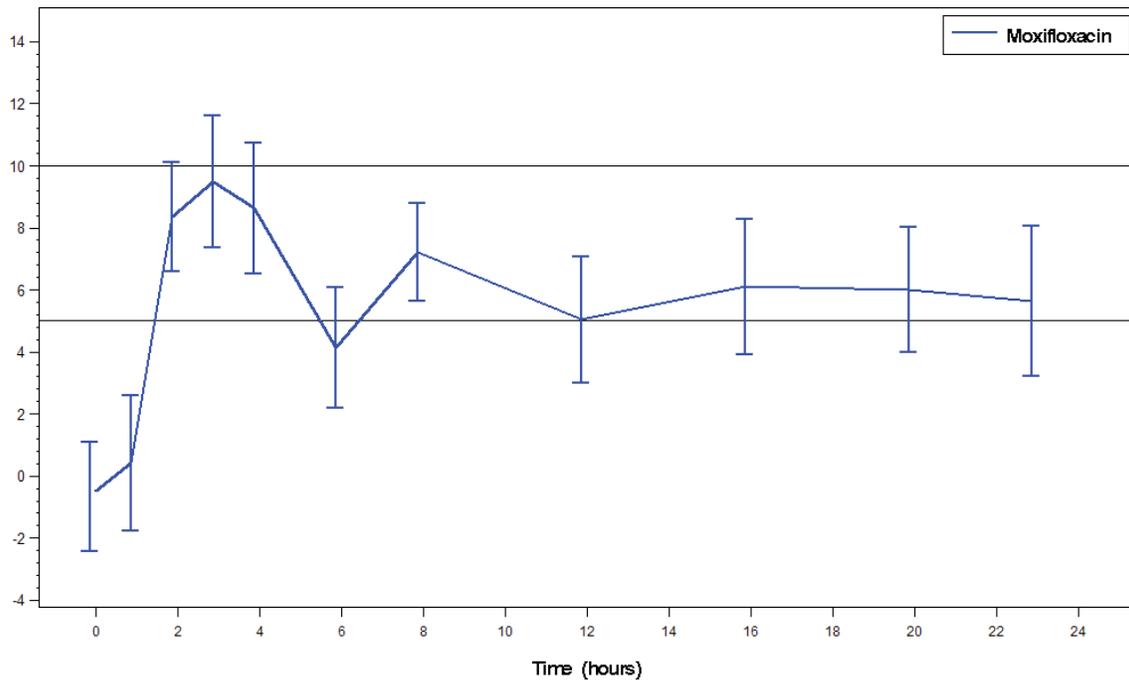


Figure 5: Mean and 90% CI $\Delta\Delta\text{QTcI}$ Timecourse: Moxifloxacin



All CIs are unadjusted, including moxifloxacin.

5.2.1.4 Categorical Analysis

Table 10 lists the number of subjects as well as the number of observations whose QTcI values are ≤ 450 ms or between 450 ms and 480 ms. No subject's QTcI was above 480 ms.

Table 10: Categorical Analysis for QTcI

	N	Value ≤ 450 ms	450 ms < Value ≤ 480 ms
Treatment Group			
Levomilnacipran 120 mg	86	80 (93.0%)	6 (7.0%)
Placebo	74	70 (94.6%)	4 (5.4%)
Treatment Group			
Levomilnacipran 300 mg	78	72 (92.3%)	6 (7.7%)
Placebo	72	69 (95.8%)	3 (4.2%)
Treatment Group			
Moxifloxacin 400 mg	72	63 (87.5%)	9 (12.5%)
Placebo	74	69 (93.2%)	5 (6.8%)

Table 11 lists the categorical analysis results for Δ QTcI. There is 1 (1.2%) subject who experienced QTcI greater than 60 ms in levomilnacipran 120 mg.

Table 11: Categorical Analysis of Δ QTcI

	N	Value ≤ 30 ms	30 ms < Value ≤ 60 ms	Value > 60 ms
Treatment Group				
Levomilnacipran 120 mg	86	79 (91.9%)	6 (7.0%)	1 (1.2%)
Placebo	74	72 (97.3%)	2 (2.7%)	0 (0.0%)
Treatment Group				
Levomilnacipran 300 mg	78	72 (92.3%)	6 (7.7%)	0 (0.0%)
Placebo	72	72 (100%)	0 (0.0%)	0 (0.0%)
Treatment Group				
Moxifloxacin 400 mg	72	71 (98.6%)	1 (1.4%)	0 (0.0%)
Placebo	74	73 (98.6%)	1 (1.4%)	0 (0.0%)

5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 12 and Table 13. The largest upper limits of 90% CI for the HR mean differences between levomilnacipran 120 mg and placebo and levomilnacipran 300 mg and placebo are 22.2 bpm and 23.8 bpm, respectively.

**Table 12: Analysis Results of Δ HR and $\Delta\Delta$ HR for Treatment Group A:
Levomilnacipran 120 mg x 11 days**

Time	Δ HR: Levomilnacipran			Δ HR: Placebo			$\Delta\Delta$ HR		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0	86	14.9	0.8	73	-0.7	0.9	73	15.5	(13.6, 17.5)
1	87	11.8	0.8	73	-3.4	0.9	73	15.1	(13.2, 17.1)
2	89	12.0	0.8	72	-3.5	0.9	72	15.4	(13.4, 17.5)
3	89	13.0	0.7	74	-3.8	0.8	74	16.8	(14.9, 18.6)
4	87	12.3	0.8	73	-4.3	0.9	73	16.5	(14.5, 18.6)
6	86	18.6	0.8	73	-1.6	0.9	73	20.2	(18.3, 22.2)
8	85	16.3	0.8	72	-1.8	0.9	72	18.1	(16.0, 20.2)
12	89	15.7	0.8	74	-1.5	0.9	74	17.2	(15.2, 19.2)
16	88	14.3	0.8	70	-1.8	0.8	70	16.1	(14.2, 18.0)
20	87	14.4	0.8	70	-1.1	0.8	70	15.4	(13.6, 17.3)
23	86	13.2	0.9	71	-1.8	1.0	71	15.0	(12.8, 17.1)

**Table 13: Analysis Results of Δ HR and $\Delta\Delta$ HR for Treatment Group B:
Levomilnacipran 300 mg x 24 days**

Time	Δ HR: Levomilnacipran			Δ HR: Placebo			$\Delta\Delta$ HR		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0	78	19.9	0.9	70	-0.5	1.0	70	20.3	(18.1, 22.5)
1	80	17.2	0.9	72	-2.3	1.0	72	19.5	(17.2, 21.8)
2	80	15.8	1.0	70	-2.2	1.1	70	18.1	(15.6, 20.6)
3	79	16.8	0.9	72	-3.7	1.0	72	20.5	(18.3, 22.7)
4	79	15.2	0.9	71	-5.3	0.9	71	20.6	(18.5, 22.6)
6	79	21.3	0.9	70	-0.4	0.9	70	21.7	(19.6, 23.8)
8	80	18.8	0.9	71	-1.4	0.9	71	20.2	(18.0, 22.3)
12	79	18.8	0.8	71	-1.5	0.9	71	20.3	(18.2, 22.3)
16	79	18.2	0.9	68	-0.8	0.9	68	19.0	(16.9, 21.1)
20	79	18.5	0.9	70	-1.3	1.0	70	19.7	(17.5, 21.9)
23	78	15.8	1.0	69	-3.0	1.0	69	18.8	(16.4, 21.2)

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 14 and Table 15. The largest upper limits of 90% CI for the PR mean differences between levomilnacipran 120 mg and placebo and levomilnacipran 300 mg and placebo are -1.8 ms and -2.0 ms, respectively.

There are 5 (5.6%) and 5 (6.3%) subjects who experienced PR interval greater than 200 ms in levomilnacipran 120 mg and levomilnacipran 300 mg, respectively.

The outlier analysis results for PR are presented in Table 16.

**Table 14: Analysis Results of Δ PR and $\Delta\Delta$ PR for Treatment Group A:
Levomilnacipran 120 mg x 11 days**

Time	Δ PR: Levomilnacipran			Δ PR: Placebo			$\Delta\Delta$ PR		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0	86	-7.2	1.1	73	0.4	1.2	73	-7.6	(-10.3, -5.0)
1	87	-5.8	1.1	73	0.8	1.2	73	-6.7	(-9.5, -3.9)
2	89	-4.0	1.3	72	2.0	1.4	72	-6.0	(-9.2, -2.8)
3	89	-6.3	0.9	74	2.0	1.0	74	-8.3	(-10.6, -6.0)
4	87	-5.5	0.9	73	1.3	1.0	73	-6.9	(-9.1, -4.6)
6	86	-5.6	0.8	73	3.5	0.9	73	-9.0	(-11.1, -7.0)
8	85	-3.2	1.4	72	1.9	1.5	72	-5.1	(-8.5, -1.8)
12	89	-8.1	1.5	74	0.1	1.6	74	-8.3	(-12.0, -4.6)
16	88	-5.5	1.5	70	1.1	1.7	70	-6.7	(-10.4, -2.9)
20	87	-5.6	1.1	70	4.3	1.2	70	-9.9	(-12.5, -7.3)
23	86	-4.8	0.9	71	4.1	0.9	71	-8.9	(-11.0, -6.8)

**Table 15: Analysis Results of Δ PR and $\Delta\Delta$ PR for Treatment Group B:
Levomilnacipran 300 mg x 24 days**

Time	Δ PR: Levomilnacipran			Δ PR: Placebo			$\Delta\Delta$ PR		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0	78	-7.2	1.2	70	2.8	1.2	70	-10.0	(-12.8, -7.2)
1	80	-5.3	1.2	72	3.3	1.3	72	-8.6	(-11.6, -5.6)
2	80	-3.9	1.4	70	3.4	1.4	70	-7.3	(-10.6, -4.0)
3	79	-4.9	1.1	72	3.3	1.1	72	-8.2	(-10.8, -5.5)
4	79	-4.7	1.1	71	4.0	1.2	71	-8.7	(-11.4, -6.0)
6	79	-6.6	1.0	70	2.8	1.0	70	-9.3	(-11.7, -7.0)
8	80	-2.9	1.5	71	2.6	1.6	71	-5.5	(-9.1, -2.0)
12	79	-7.0	1.1	71	2.4	1.1	71	-9.4	(-12.0, -6.8)
16	79	-4.9	1.0	68	3.9	1.1	68	-8.9	(-11.4, -6.4)
20	79	-6.6	1.1	70	6.7	1.1	70	-13.3	(-15.9, -10.7)
23	78	-3.3	1.1	69	4.4	1.1	69	-7.7	(-10.2, -5.1)

Table 16: Categorical Analysis for PR

Treatment Group	N	PR < 200 ms	PR >=200 ms
Levomilnacipran 120 mg	89	84 (94.4%)	5 (5.6%)
Placebo	74	67 (90.5%)	7 (9.5%)
Treatment Group	N	PR < 200 ms	PR >=200 ms
Levomilnacipran 300 mg	80	75 (93.8%)	5 (6.3%)
Placebo	72	64 (88.9%)	8 (11.1%)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 17 and Table 18.

The largest upper limits of 90% CI for the QRS mean differences between levomilnacipran 120 mg and placebo and levomilnacipran 300 mg and placebo are 0.8 ms and 0.9 ms, respectively. There are 4 (4.5%) and 4 (5.0%) subjects who experienced QRS interval greater than 110 ms in levomilnacipran 120 mg and levomilnacipran 300 mg, respectively.

The outlier analysis results for QRS are presented in Table 19.

Table 17: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Treatment Group A: Levomilnacipran 120 mg x 11 days

Time	Δ QRS: Levomilnacipran			Δ QRS: Placebo			$\Delta\Delta$ QRS		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0	86	-1.4	0.4	73	-0.3	0.4	73	-1.1	(-2.1, -0.2)
1	87	-0.9	0.4	73	0.2	0.4	73	-1.1	(-2.0, -0.2)
2	89	-0.2	0.4	72	0.9	0.5	72	-1.1	(-2.1, -0.1)
3	89	0.3	0.4	74	0.9	0.4	74	-0.6	(-1.6, 0.4)
4	87	0.1	0.4	73	0.9	0.4	73	-0.8	(-1.8, 0.2)
6	86	-0.4	0.4	73	1.0	0.5	73	-1.4	(-2.5, -0.4)
8	85	0.2	0.4	72	0.5	0.5	72	-0.3	(-1.3, 0.8)
12	89	-0.8	0.4	74	-0.3	0.5	74	-0.5	(-1.5, 0.5)
16	88	-0.5	0.4	70	-0.3	0.5	70	-0.3	(-1.3, 0.8)
20	87	-1.4	0.4	70	0.6	0.4	70	-2.1	(-3.0, -1.1)
23	86	-0.7	0.4	71	0.5	0.4	71	-1.2	(-2.1, -0.3)

**Table 18: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Treatment Group B:
Levomilnacipran 300 mg x 24 days**

Time	Δ QRS: Levomilnacipran			Δ QRS: Placebo			$\Delta\Delta$ QRS		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0	78	-1.9	0.5	70	0.2	0.5	70	-2.1	(-3.2, -1.0)
1	80	-1.2	0.5	72	0.8	0.5	72	-2.0	(-3.2, -0.9)
2	80	-0.2	0.5	70	1.3	0.5	70	-1.5	(-2.7, -0.3)
3	79	0.7	0.5	72	1.4	0.5	72	-0.8	(-2.0, 0.4)
4	79	0.9	0.5	71	1.2	0.5	71	-0.3	(-1.6, 0.9)
6	79	-0.7	0.5	70	0.6	0.6	70	-1.3	(-2.6, -0.0)
8	80	-0.0	0.5	71	0.6	0.6	71	-0.6	(-1.9, 0.6)
12	79	-0.7	0.5	71	0.2	0.5	71	-0.9	(-2.1, 0.2)
16	79	-1.0	0.5	68	0.4	0.5	68	-1.4	(-2.6, -0.1)
20	79	-2.0	0.5	70	0.1	0.5	70	-2.2	(-3.3, -1.1)
23	78	-0.8	0.5	69	0.7	0.5	69	-1.5	(-2.6, -0.3)

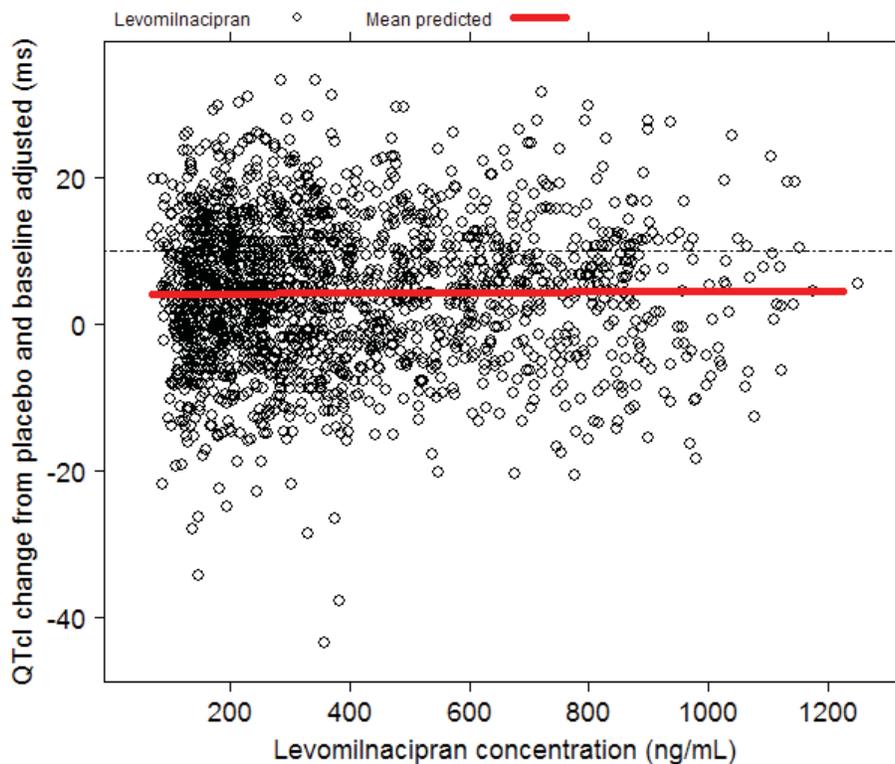
Table 19: Categorical Analysis for QRS

Treatment Group	N	QRS < 110 ms	QRS \geq 110 ms
Levomilnacipran 120 mg	89	85 (95.5%)	4 (4.5%)
Placebo	74	73 (98.6%)	1 (1.4%)
Treatment Group	N	QRS < 110 ms	QRS \geq 110 ms
Levomilnacipran 300 mg	80	76 (95.0%)	4 (5.0%)
Placebo	72	72 (100%)	0 (0.0%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between $\Delta\Delta$ QTcI and levomilnacipran concentrations is visualized in Figure 6 with no evident exposure-response relationship. This is consistent with sponsor's results using PD measures (QTc) with different correction methods.

Figure 6: $\Delta\Delta$ QTcI vs. Levomilnacipran concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

PR and QRS intervals were affected to no clinically relevant extent.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Note based on Sponsor's label

1. In mild (creatinine clearance of 50 - 79 ml/min), moderate (creatinine clearance of 30 - 49 ml/min), or severe (creatinine clearance <30 ml/min) renal impairment, AUC increased by 23%, 93%, or 180%, respectively, and terminal elimination half-life prolonged by 28%, 43%, or 105%, respectively, relative to healthy subjects with normal renal function. The effect of hepatic impairment on PK is small.
2. In vitro studies have shown low potential for interaction with drugs that are substrates of CYP isoenzymes due to induction or inhibition of these enzymes.
3. Gender has no significant effect on PK.

Intrinsic Factors	Age	Under investigation
	Sex	Under investigation
	Race	To be investigated by population PK approach
	Hepatic & Renal Impairment	About 50% of F2695 is excreted as unchanged in urine (LVM-PK-01). Hepatic elimination could contribute maximally to the other half of 50%. Studies evaluating the effect of varying degrees of renal or hepatic impairment on F2695 concentration are ongoing, but the magnitude of the effect is expected to be an approximately 2 fold.
Extrinsic Factors	Drug interactions	Since about 50% of F2695 is excreted as unchanged in urine (LVM-PK-01), CYP enzymes could maximally metabolize the remaining 50%. Studies evaluating potential interaction of F2695 with drugs that are inhibitors or inducers of CYP enzymes are ongoing, but the magnitude of interaction is not expected to be more than 100%.
	Food Effects	No significant food effect when 40-mg F2695 SR was administered under high-fat fed conditions vs fasted conditions For C _{max} : Ratio of geometric means =110.5% (90% CI=100.6-121.4%) For AUC _{0-∞} : Ratio of geometric means =98.4% (90% CI=89.3-108.4%)
Expected High Clinical Exposure Scenario	Around 50% of F2695 was found to be excreted as unchanged in urine. Assuming the remaining 50% of F2695 undergoes metabolism, an approximately 2-fold elevation of F2695 concentration would be anticipated in the presence of renal impairment, hepatic impairment, or drug-drug interactions based on the information known to-date on the PK properties of F2695. Ongoing Phase III trials are evaluating the efficacy and safety of F2695 SR doses of 40, 80, and 120 mg. Therefore, the dose of 300 mg F2695 SR will provide at least a 2.5 multiple of the highest potential therapeutic dose.	

a: dose reached in LVM-PK-01

b: geometric mean and geometric CV%

Highlights of Clinical Pharmacology

Anticipated therapeutic dose range	40-120 mg F2695 SR once daily	
Maximum tolerated dose	300 mg F2695 SR once daily ^a	
Principal adverse events	Most common adverse events reported have been: abdominal pain, blood pressure increased, constipation, diarrhea, dizziness, dry mouth, dysuria, hot flush, headache, hyperhidrosis, hypertension, insomnia, mydriasis, nausea, orthostatic hypotension, palpitations, somnolence, tachycardia, testicular pain, vomiting.	
Maximum dose tested	Single Dose	100 mg F2695 SR
	Multiple Dose	300 mg F2695 SR once daily with an up-titration schedule for 36 days
Exposures Achieved at Maximum Tested Dose	Single Dose (100mg)	C_{max} =208.1 ng/mL (CV=17.8%) $AUC_{0-\infty}$ =4034.0 h*ng/mL (CV=14.3%)
	Multiple Dose (300mg)	C_{max} =872.8 ng/mL (CV=13.6%) AUC_{0-t} =12829.3 h*ng/mL (CV=9.7%)
Range of linear PK	25-100 mg F2695 SR (single dose); 25-300 mg F2695 SR once daily (multiple doses)	
Accumulation at steady state	1.3 (CV=8.7%); at 300 mg F2695 SR once daily	
Metabolites	Quantifiable metabolite: F17400 (desethylated F2695), inactive. Full metabolite profile is not yet available	
Absorption	Absolute Bioavailability ^b	100% (CV=11%)
	T _{max}	5 hours (4-6 hours) at 300 mg SR once daily
Distribution	V _d ^b	426 L (CV=17%)
	% bound	21.7% (CV=15.8%)
Elimination	Route	<ul style="list-style-type: none"> • Urine 43-56% (immediate-release capsule at a dose range of 12.5-75 mg) 40-48% (sustained-release capsule at a dose range of 25-100 mg) • Other routes - under investigation
	Terminal t _{1/2}	11.1 hours (CV=19%)
	CL ^b	33.6 L/h (CV=16%)

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

/s/

JANICE B BRODSKY
04/10/2013

QIANYU DANG
04/10/2013

JINGYU YU
04/10/2013

KEVIN M KRUDYS
04/11/2013

JOHN E KOERNER
04/11/2013

NORMAN L STOCKBRIDGE
04/11/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 204168 BLA#	NDA Supplement #:S- 000 BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) (1 st Choice), (b) (4) (2 nd Choice) – (b) (4) was denied on 10/31/2012. Established/Proper Name: levomilnacipran HCl Dosage Form: Sustained-Release Capsules Strengths: 20 mg, 40 mg, 80 mg and 120 mg		
Applicant: Forest Laboratories Agent for Applicant (if applicable):		
Date of Application: September 24, 2012 Date of Receipt: September 25, 2012 Date clock started after UN:		
PDUFA Goal Date: July 25, 2013	Action Goal Date (if different):	
Filing Date: November 24, 2012	Date of Filing Meeting: November 5, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 5, 505(b)(1)		
Proposed indication(s)/Proposed change(s): Major Depressive Disorder		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): IND 104483				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes, explain in comment column.			X	
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			X																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			X																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>			X																	
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															X	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>			X																	

If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 5 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	X			
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>	X			

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)	YES	NO	NA	Comment
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			X	The NDA was submitted before Oct 1, 2012 and therefore not part of “the Program”.
<ul style="list-style-type: none"> If yes, were all of them submitted on time? 			X	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			X	
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			X	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			

<p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	X			
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	NDA 204168 is provided in electronic format, therefore a field copy is not provided.
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	Nonclinical filing review indicates that abuse is unlikely b/c levomilnacipran is a SNRI.

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?			X	Sponsor is requesting partial waiver for 0-6 y.o and partial deferral for 7-17 y.o.
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>		X		The pediatric plan was not submitted. Will request in the 74-day letter.
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>		X		Certifications required by FDCA Sections 505B(a)(3) and (4) are not included. Request will be included in 74-day letter
<u>BPCA (NDAs/NDA efficacy supplements only):</u> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
<u>Proprietary Name</u>	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			OSE asked sponsor to resubmit b/c it was included in the NDA submission. It was submitted on 10/1/12 as a separate submission.
<u>REMS</u>	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		X		
<u>Prescription Labeling</u>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	X			QT Consult Request – November 15, 2012.
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): May 18, 2009 <i>If yes, distribute minutes before filing meeting</i>	X			Included in sponsor NDA submission.
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): January 25, 2012 (Chemistry Manufacturing and Controls) and May 4, 2012 <i>If yes, distribute minutes before filing meeting</i>	X			Included in sponsor NDA submission.
Any Special Protocol Assessments (SPAs)? Date(s): March 19, 2009 (Rat carcinogenicity) July 2, 2010 (Transgenic (Tg) Mouse Carcinogenicity Protocol) August 12, 2010 (Final CAC Report) <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			Located in Division Eroom.

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 5, 2012

BLA/NDA/Supp #: NDA 204168

PROPRIETARY NAME: (b) (4) (1st Choice), (b) (4) (2nd Choice). (b) (4) was denied on 10/31/2012.

ESTABLISHED/PROPER NAME: levomilnacipran HCl

DOSAGE FORM/STRENGTH: 20mg, 40mg, 80mg, 120mg sustained-release capsules

APPLICANT: Forest Laboratories, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Major Depressive Disorder (MDD)

BACKGROUND:

Pierre Fabre discovered levomilnacipran and sponsored initial Phase 1 and Phase 2 studies. Forest sponsored additional Phase 1 studies and all Phase 3 studies that have been conducted to date. The clinical development program for levomilnacipran consists of the following studies.

- 19 completed clinical pharmacology and biopharmaceutics studies
- 5 completed placebo-controlled studies in MDD
- 1 completed randomized withdrawal relapse prevention study in MDD
- 1 ongoing open-label extension study in patients with MDD
- (b) (4)
- (b) (4)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Juliette Touré, PharmD	Y
	CPMS/TL:	Paul David, RPh (CPMS) Renmeet Grewal, PharmD (TL)	N
Cross-Discipline Team Leader (CDTL)	Ni Khin, MD		Y
Clinical	Reviewer:	Kavneet "Ripi" Kohli-Chhabra, MD	Y
	TL:	Ni Khin, MD	Y
Social Scientist Review (for OTC products)	Reviewer:	N/A	

	TL:	N/A	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Pharmacology	Reviewer:	Kofi Kumi, PhD	Y
	TL:	Hao Zhu, PhD	Y
Biostatistics	Reviewer:	Thomas Birkner, PhD	Y
	TL:	Peiling Yang, PhD	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Arippa Ravindran, PhD	Y
	TL:	Linda Fossom, PhD	N
Statistics (carcinogenicity)	Reviewer:	Atiar Mohammed Rahman, PhD	N
	TL:	Karl Lin, PhD	N
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Pei-I Chu, PhD Akm Khairuzzaman, PhD (Biopharmaceutics)	N
	TL:	Tele Chhagan, PhD Angela Dorantes, PhD (Biopharmaceutics)	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	N/A	
	TL:	N/A	
CMC Labeling Review	Reviewer:	Pei-I Chu, PhD	N
	TL:	Tele Chhagan, PhD	Y
Facility Review/Inspection	Reviewer:	Derek Smith	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Loretta Holmes, BSN, PharmD	N

	TL:	Irene Chan, PharmD, BCPS	Y
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:	N/A	
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:	N/A	
Bioresearch Monitoring (OSI)	Reviewer:	John Lee, MD	N
	TL:	Susan Leibenhaut, MD	Y
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers			
Other attendees	Hongshan Li, Bioequivalence Clinical Pharmacology Jeffrey Kraft, Pharmacogenomics Ethan Hausman, Pharmacovigilance Laurelle Cascio, Pharmacovigilance Jasminder Kumar, DRISK Jason Bunting, DRISK Reema Mehta, DRISK (TL) Josh Barton, Panorama technician		

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<p>Comments: Will request literature review.</p>	<input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: This drug is not the first in its class. This drug is also not an NME, as the racemic drug, Savella (milnacipran), has been approved for the treatment of fibromyalgia.
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments: Biopharmaceutics comments:</p> <ol style="list-style-type: none"> Because of the anticipated exposure with the 120 mg SR formulation in an alcohol dose dumping 	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter (Biopharmaceutics reviewers)

<p>situation may be even higher based on your simulation, we recommend that the increased GI adverse events with alcohol be appropriately labeled in product labeling.</p> <p>2. We have not found any details of the IVIVC report. Note that any biowaiver at post approval stage (if the NDA is recommended for approval) for a future Level 3 site change or other significant manufacturing/formulation change will not be granted if the validity of the IVIVC model cannot be confirmed.</p>	
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

Comments:																															
<u>Quality Microbiology (for sterile products)</u> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO																														
<u>Facility Inspection</u> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO																														
<u>Facility/Microbiology Review (BLAs only)</u> Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter																														
<u>CMC Labeling Review</u> Comments:	<input type="checkbox"/> Review issues for 74-day letter																														
REGULATORY PROJECT MANAGEMENT																															
Signatory Authority: Thomas P. Laughren, MD, Director, Division of Psychiatry Products or Mitchell Mathis, MD, Deputy Director, Division of Psychiatry Products Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): N/A 21st Century Review Milestones (see attached) (listing review milestones in this document is optional):																															
<table border="1"> <thead> <tr> <th>MILESTONES</th> <th>MILESTONE DEADLINES</th> <th>MEETINGS</th> </tr> </thead> <tbody> <tr> <td>Receipt Date</td> <td>Sep. 25, 2012 [Tue.]</td> <td></td> </tr> <tr> <td>Day 45</td> <td>Nov. 9, 2012 [Fri.]</td> <td>Nov. 5, 2012 [Mon.] Filing/Planning Meeting</td> </tr> <tr> <td>Day 60 (Filing Date)</td> <td>Nov. 24, 2012 [Sat.]</td> <td></td> </tr> <tr> <td>Day 74 Letter Due</td> <td>Dec. 8, 2012 [Sat.]</td> <td></td> </tr> <tr> <td>Month 5</td> <td>Feb. 25, 2013 [Tue.]</td> <td>Feb. 11, 2013 [Mon.] Midcycle Meeting</td> </tr> <tr> <td>Labeling Meetings</td> <td></td> <td>March 4, 2013 [Mon.] Label Planning Meeting</td> </tr> <tr> <td></td> <td></td> <td>Apr. 8, 2013 [Mon.]</td> </tr> <tr> <td></td> <td></td> <td>Apr. 22, 2013 [Mon.]</td> </tr> <tr> <td></td> <td></td> <td>May 6, 2013 [Mon.]</td> </tr> </tbody> </table>		MILESTONES	MILESTONE DEADLINES	MEETINGS	Receipt Date	Sep. 25, 2012 [Tue.]		Day 45	Nov. 9, 2012 [Fri.]	Nov. 5, 2012 [Mon.] Filing/Planning Meeting	Day 60 (Filing Date)	Nov. 24, 2012 [Sat.]		Day 74 Letter Due	Dec. 8, 2012 [Sat.]		Month 5	Feb. 25, 2013 [Tue.]	Feb. 11, 2013 [Mon.] Midcycle Meeting	Labeling Meetings		March 4, 2013 [Mon.] Label Planning Meeting			Apr. 8, 2013 [Mon.]			Apr. 22, 2013 [Mon.]			May 6, 2013 [Mon.]
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PeRC		~May 8, 2013 [Wed.]
Month 8	May 25, 2013 [Sat.]	May 20, 2013 [Mon.] Wrap-up Meeting
Send label & PMR/PMC to Sponsor	Jun. 27, 2013 [Thu.]	
Labeling Negotiation Meetings		Jun. 17, 2013 [Mon.]
		Jun. 24, 2013 [Mon.]
		Jul. 8, 2013 [Mon.]
		Jul. 15, 2013 [Mon.]
		Jul. 22, 2013 [Mon.]
Primary Review due to TL	Jun. 20, 2013 [Thu.]	
Secondary Review due to CDTL	Jun. 27, 2013 [Thu.]	
CDTL Review due to DD	Jul. 4, 2013 [Thu.]	
Month 10 Goal Date Assuming Standard, DD Sign-off	Jul. 25, 2013 [Thu.]	

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p>Please see Filing Letter for review issues (Clinical and Biopharmaceutics Information Requests).</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>

ACTIONS ITEMS

<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter

<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74 – will be sent before Dec. 8, 2012.
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

JULIETTE T TOURE
11/15/2012