

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
204168Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 204168

SUPPL # 0

HFD # 130

Trade Name Fetzima

Generic Name levomilnacipran hydrochloride

Applicant Name Forest

Approval Date, If Known July 25, 2013

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Single enantiomers.

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, which deals with certain drugs containing single enantiomers?

YES NO

If "YES", complete Addendum 1

3. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 3 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # YES ! NO
! Explain:

Investigation #2 !
!

IND # YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES ! NO
Explain: ! Explain:

Investigation #2 !
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

ADDENDUM 1
Certain Drugs Containing Single Enantiomers

NOTE: Only complete this Addendum and attach it to the Exclusivity Summary if the applicant (a) elected 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) requested exclusivity pursuant to section 505(u) of the Act, which deals with certain drugs containing single enantiomers.

1. Is this a non-racemic drug containing as an active ingredient (including any ester or salt of the active ingredient) a single enantiomer that is contained in an already approved racemic drug? YES NO

If "NO", go to Part II, #2 of the Exclusivity Summary.

If "YES", identify the already approved racemic drug: Savella (milnacipran)

NDA# 022256

2. Did the application rely on any clinical investigations that are part of the application of the approved racemic drug? YES NO

If "YES", identify the investigations

(_____) and go to Part II, #2 of the Exclusivity Summary.

3. a) Does the application include full reports of new clinical investigations (other than bioavailability studies)? YES NO

If "NO", go to Part II, #2 of the Exclusivity Summary.

b) Were any such clinical investigations necessary for approval of the application? (see page 4 of the Exclusivity Summary for an explanation of this concept)

YES NO

If "NO", go to Part II, #2 of the Exclusivity Summary.

c) Were such necessary clinical investigations conducted or sponsored by the applicant?

YES NO

If "NO", go to Part II, #2 of the Exclusivity Summary.

4. a) Except in the approved racemic drug identified above, has the single enantiomer been previously approved? YES NO

If "YES", identify the previous approval (NDA# _____) and go to Part II, #3 of the Exclusivity Summary.

If "NO", using the list at the end of this Addendum, identify all therapeutic categories for which the racemic drug is approved:

Fibromyalgia (5030800) _____

b) Using the list at the end of this Addendum, identify all therapeutic categories for which any other enantiomer of the racemic drug has been approved:

None _____

c) Is any condition of use for which this application was submitted for approval in any of the therapeutic classes identified in either a) or b)?

YES NO

If "YES", identify the relevant condition of use
(_____) and therapeutic class
(_____) and go to Part II, #3 of the Exclusivity Summary.

=====

Name of person completing form: CDR Renmeet Grewal, Pharm.D.,RAC for CDR Juliette Toure, Pharm.D.

Title: Senior Regulatory Project Manager

Date: 7/25/2013

Name of Office/Division Director signing form: Mitchell Mathis, M.D.

Title: Acting Division Director/ Division of Psychiatry Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 204168 BLA #	NDA Supplement # 000 BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Fetzima Established/Proper Name: levomilnacipran Dosage Form: Extended-release capsules		Applicant: Forest Agent for Applicant (if applicable):
RPM: Juliette Touré, PharmD, RAC		Division: Division of Psychiatry Products
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A 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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>	
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>July 25, 2013</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDA: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p>REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<p><input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other</p>

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
DPP Comment: This NDA is a single enantiomer, whose racemate (Savella, NDA 022256) has been approved for fibromyalgia, which is considered a different therapeutic category from Major Depressive Disorder studied under this NDA (Levomilnacipran, 204168).	
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

<p><i>If "No," continue with question (5).</i></p> <p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	July 25, 2013
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	July 25, 2013
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	July 25, 2013
• Original applicant-proposed labeling	September 25, 2012
• Example of class labeling, if applicable	SNRI: Pristiq (desvenlafaxine) NDA 21992/S-033, approved Feb 14, 2013

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	July 25, 2013
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	September 25, 2012
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	SNRI: Pristiq (desvenlafaxine) NDA 21992/S-033, approved Feb 14, 2013
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	July 25, 2013 July 12, 2013 January 29, 2013 December 21, 2012 September 25, 2012
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	Letters: -Fetzima, Granted Jun 6, 2013 - (b)(4) Denied Feb 14, 2013 - (b)(4) Denied Oct 31, 2012 Reviews: - Fetzima, Review June 4, 2013 - (b)(4) Review Feb 14, 2013 - (b)(4) Review Oct 25, 2012
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM SRPI dated June 27, 2013 (done at filing in 25Nov 2012) <input checked="" type="checkbox"/> DMEPA 7/2/13, 6/3/13,2/14/13,10/25/12 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) June 20, 2013 <input checked="" type="checkbox"/> ODPD (DDMAC) June 20, 2013 <input checked="" type="checkbox"/> SEALD 7/24/13 <input type="checkbox"/> CSS N/A <input checked="" type="checkbox"/> Other reviews DRISK 7/24/13 MHT June 16, 2013 PMHS June 19, 2013 QT-IRT April 11, 2013
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	November 15, 2012
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input checked="" type="checkbox"/> Not a (b)(2) <input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP	<input type="checkbox"/> Yes <input type="checkbox"/> No
○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)	
○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	<input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>)	
• Date reviewed by PeRC <u>June 5, 2013</u>	
If PeRC review not necessary, explain: _____	
• Pediatric Page/Record	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	10/1/2012 Ack Ltr 11/6/2012 IR 11/27/2013 No Issues, Filing Ltr 11/28/2012 IR 2/20/2013 IR 4/26/2013 IR 4/29/2013 IR 6/25/2013 IR
❖ Internal memoranda, telecons, etc.	N/A
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg May 4, 2012 Pre-NDA CMC Mtg Jan 25, 2012
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg May 18, 2009
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	Type C Clinical Development of a New Indication – March 12, 2010
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/25/13
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/2/13
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 7/25/13 (3PMRs 4PMC)
Clinical Information⁶	

⁶ Filing reviews should be filed with the discipline reviews.

❖ Clinical Reviews		
• Clinical Team Leader Review(s) (indicate date for each review)		See CDTL memo above
• Clinical review(s) (indicate date for each review)		7/2/13
• Social scientist review(s) (if OTC drug) (indicate date for each review)		<input type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (indicate date of review/memo)		
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review)		<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)		<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and Supporting Statement (indicate date(s) of submission(s)) • REMS Memo(s) and letter(s) (indicate date(s)) • Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review) 		<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)		<input type="checkbox"/> None requested May 23, 2013
Clinical Microbiology		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)		<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)		<input type="checkbox"/> None
Biostatistics		<input type="checkbox"/> None
❖ Statistical Division Director Review(s) (indicate date for each review)		<input type="checkbox"/> None Signed primary review
Statistical Team Leader Review(s) (indicate date for each review)		<input type="checkbox"/> None Signed primary review
Statistical Review(s) (indicate date for each review)		<input type="checkbox"/> None July 24, 2013 June 14, 2013
Clinical Pharmacology		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)		<input type="checkbox"/> None Signed primary review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)		<input type="checkbox"/> None Signed primary review
Clinical Pharmacology review(s) (indicate date for each review)		<input type="checkbox"/> None May 20, 2013
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)		<input type="checkbox"/> None May 30, 2013

Nonclinical		<input type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None	Signed primary review
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None	Signed primary review
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None	June 17, 2013
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None	
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input type="checkbox"/> No carc	March 19, 2013
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None	March 28, 2013 Included in P/T review, page N/A
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested	
Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None	Signed primary review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None	Signed primary review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None	June 25, 2013
❖ Microbiology Reviews	<input checked="" type="checkbox"/> Not needed	
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None	Biopharmaceutics May 20, 2013
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		October 9, 2012
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i>	Date completed: June 24, 2013	<input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed:	<input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input checked="" type="checkbox"/> Completed (DMEPA 6/6/2013) <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per CMC review, for OPDRA, EA, and Microbiology)
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/s/

RENMEET GREWAL
07/26/2013



NDA 204168

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Forest Laboratories, Inc.
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, NJ 07311

ATTENTION: Ann Howell, PharmD, MS
Senior Manager, Regulatory Affairs

Dear Dr. Howell:

Please refer to your New Drug Application (NDA) dated and received September 25, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Levomilnacipran Extended-release Capsules, 20 mg, 40 mg, 80 mg, and 120 mg.

We also refer to:

- Your initial correspondence dated and received March 11, 2013, requesting review of your proposed proprietary name, Fetzima.
- Your amendment dated and received March 25, 2013, for the Fetzima external name study report.

We have completed our review of the proposed proprietary name, Fetzima, and have concluded that it is acceptable.

The proposed proprietary name, Fetzima, will be re-reviewed 90 days prior to approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. Additionally, if **any** of the proposed product characteristics as stated in your March 11, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Louis Flowers, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3158. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Juliette Toure at (301)796-5419.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
06/06/2013

Executive CAC

Date of Meeting: March 26, 2013

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Paul Brown, Ph.D., OND IO, Member
Al DeFelice, Ph.D., DCRP, Alternate Member
Linda Fossom, Ph.D., DPP, Supervisor
Arippa Ravindran, Ph.D., DPP, Presenting Reviewer

Author of Draft: Arrippa Ravindran

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA 204-168

Drug Name: Levomilnacipran HCl (F2695)

Sponsor: Forest Laboratories, Inc.

Background: Levomilnacipran (F2695), a serotonin-norepinephrine reuptake inhibitor (SNRI), is the more active (levorotatory) enantiomer of milnacipran, which is approved for the treatment of fibromyalgia. This NDA is for the use of levomilnacipran for the treatment of major depressive disorder (MDD).

Levomilnacipran was not mutagenic in the *in vitro* bacterial mutagenicity (Ames assay) and mouse lymphoma assays, in the presence and absence of S9 metabolic activation. In addition, levomilnacipran was not clastogenic in the *in vivo* mouse micronucleus assay.

Protocols for the 2-year rat and 6-month Tg.rasH2 mouse carcinogenicity studies were presented to Executive-CAC on April 21, 2009 and August 10, 2010, respectively. The doses used in both studies were approved by the E-CAC, based on MTD.

Rat Carcinogenicity Study:

Male and female Sprague-Dawley rats were administered oral gavage doses of levomilnacipran at 0, 0 (2 identical vehicle control groups), 10, 30, and 90 mg/kg/d in distilled water for 104 weeks. The high dose in males was lowered (from 90 to 70 mg/kg/d) beginning in Week 45 due to significant decrease in mean body weight in that group. Beginning in Week 87 (Day 605), dosing was discontinued in HD female group due to increased mortality in that group. The exposure to levomilnacipran during the study period was verified in TK groups of rats; the exposure (AUC₀₋₂₄) at the high dose was 12x (males) and 14x (females) of the human exposure at the maximum recommended human dose (MRHD) of 120 mg/d. Microscopic examination was performed on all protocol-designated sections of organs and tissues from all main study rats of all dose groups.

The overall survival in males of all treatment groups was comparable to control groups; however, the overall survival was statistically significantly decreased for females at 30

and 90 mg/kg/d, compared to control groups. There were no biologically relevant, treatment-related increases in any of the observed tumor types in either sex. Pair-wise comparisons did not show a statistically significant increase in the incidence of any tumor type in any of the treated groups, when compared to the combined control groups.

Tg.rasH2 Mouse Carcinogenicity Study:

Male and female Tg.rasH2 mice were administered oral gavage doses of levomilnacipran at 0, 15, 50, and 150 mg/kg/d in distilled water for 26 weeks [a positive control group (urethane, 1000 mg/kg/d; i. p.) was used for study validation]. The exposure to levomilnacipran during the study period was verified in TK groups (CByB6H1 wild type littermate) mice; the exposure (AUC₀₋₂₄) at the high dose was 9x (males) and 12x (females) of the human exposure at the maximum recommended human dose (MRHD) of 120 mg/d. Microscopic examination was performed on all protocol-designated sections of organs and tissues from all main study animals of all dose groups and selected tissues from positive control animals (lungs and spleen).

A statistically significant increase in the incidence of splenic hemangiosarcomas was observed in males in the high dose group only, when compared to vehicle control group. However, the numerical increase in the incidence of hemangiosarcomas was only slightly higher than the historical control value (5 in the HDM versus 0-4 in the historical control) and therefore, the biological significance of this finding is unclear.

Executive CAC Recommendations and Conclusions:

Rat:

- The Committee concurred that the study was adequate.
- The Committee concurred that the study was negative for drug related neoplasms.

Tg.rasH2 Mouse:

- The Committee concurred that the study was adequate.
- The Committee concurred that the study was negative for drug related neoplasms.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\n
/Division File, DPP
/Linda Fossom, Supervisor, DPP
/Arippa Ravindran, Reviewer, DPP
/Juliette Toure, CSO/PM, DPP
/Adele Seifried, OND-IO

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/s/

ADELE S SEIFRIED
03/28/2013

DAVID JACOBSON KRAM
03/28/2013



NDA 204168

INFORMATION REQUEST

Forest Laboratories Inc.
Attention: Alexander Bischoff, Ph.D., Associate Director, Regulatory Affairs CMC
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, NJ 07311

Dear Dr. Bischoff:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levomilnacipran Hydrochloride Sustained-Release Capsules.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide information on analytical methods used to accept the drug substance from Pierre Fabre Medicament. If the methods are not the same as those described in DMF (b) (4) appropriate validation data should also be provided.
2. Provide the stability protocol for the first three commercial batches. According to ICH Q1A(R2), a commitment should be made to place the first three production batches on long term stability studies through the proposed shelf life and on accelerated studies for 6 months. Where intermediate testing is called for by a significant change at the accelerated storage condition for the primary batches, testing on the commitment batches can be conducted at either the intermediate or the accelerated storage condition. However, if significant change occurs at the accelerated storage condition on the commitment batches, testing at the intermediate storage condition should be conducted.
3. Justify your proposed dissolution acceptance criteria using your IVIVC model. Otherwise tighten the dissolution acceptance criteria to the target (b) (4) at 2 h and 4 h. Provide updated drug product specification.

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAMESH K SOOD
02/28/2013



NDA 204168

FILING COMMUNICATION

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

Dear Dr. Howell:

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

We also refer to your amendments dated October 3, 2012, November 9, 2012, and November 12, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is July 25, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 27, 2013.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

Clinical

- Please provide a comprehensive literature review pertaining to the levomilnacipran (LVM) Sustained Release Capsules. Please include search methodology (search terms, databases, etc.), summary of findings, comments on the relevance of these findings to the safety or pharmacology of the drug, and overall conclusion.

Biopharmaceutics

- Because of the anticipated exposure with the 120 mg SR formulation in an alcohol dose dumping situation may be even higher based on your simulation, we require that the increased GI adverse events with alcohol be appropriately labeled in product labeling.

Labeling

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

- The length of Highlights (HL) of Prescribing Information must be limited to no more than one-half page. Please reduce the length of the HL or request a waiver.
- Delete the month from the Initial U.S. Approval in HL.
- Subsection 9.2 Abuse and Dependence should be separated: 9.2 Abuse and 9.3 Dependence.
- The language in the Boxed Warning (except the title) should have a left margin.

We request that you respond to the above requests and resubmit labeling within 3 weeks from the date of this letter. The resubmitted labeling will be used for further labeling discussions.

While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

The Pediatric Research Equity Act (PREA) requires that all NDAs, BLAs, or supplemental applications for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration contain a pediatric assessment unless a waiver or deferral has been obtained. A pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required, and other data that are adequate to: 1) assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations and 2) support dosing and administration for each pediatric subpopulation for which the product has been assessed to be safe and effective.

We acknowledge receipt of your request for a partial waiver of pediatric studies for pediatric patients 0 to 6 years for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We also acknowledge your request for a partial deferral for pediatric patients 7 to 17 years; however, it is not complete. Within 30 days of the date of this letter, you will need to provide:

1. The certification required by FDCA Sections 505B(a)(3) and (4).
2. A pediatric plan, which is a statement of intent which outlines the Pediatric Studies (PK/PD, efficacy and safety) that you plan to conduct. It must include a timeline for submission of studies (protocol, initiate studies, submit studies) and address development of age appropriate formulation. Furthermore, it should address under what grounds you are requesting deferral of pediatric studies.

Once we have reviewed your request, we will notify you if the partial deferral request is denied.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Psychiatry Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

If you have any questions, email Juliette Touré, PharmD, Senior Regulatory Project Manager, at Juliette.Toure@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

THOMAS P LAUGHREN
11/27/2012



NDA 204168

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Forest Laboratories Inc.
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, NJ 07311

Attention: Ann Howell, PharmD, MS,
Senior Manager, Regulatory Affairs

Dear Dr. Howell:

Please refer to your New Drug Application (NDA) dated September 25, 2012, received September 25, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Levomilnacipran Extended-release Capsules, 20 mg, 40 mg, 80 mg and 120 mg.

We also refer to your correspondence, dated October 3, 2012, and received October 4, 2012, requesting review of your proposed proprietary name, (b) (4). We have completed our review of (b) (4) and have concluded that this name is unacceptable for the following (b) (4)

(b) (4)

(b) (4)

(b) (4)

We note that you have proposed an alternate proprietary name in your submission dated October 3, 2012. In order to initiate the review of the alternate proprietary name, (b) (4) submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sandra Rimmel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Juliette Toure, at (301) 796-5419.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
10/31/2012



NDA 204168

NDA ACKNOWLEDGMENT

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

Dear Dr. Howell:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: levomilnacipran hydrochloride 20 mg, 40 mg, 80 mg and 120 mg sustained-release capsules

Date of Application: September 24, 2012

Date of Receipt: September 25, 2012

Our Reference Number: NDA 204168

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 24, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, email Juliette Touré, PharmD, Senior Regulatory Project Manager, at Juliette.Toure@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Juliette Touré, PharmD
CDR, United States Public Health Service
Senior Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

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/s/

JULIETTE T TOURE
10/01/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 104483

MEETING MINUTES

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

Dear Dr. Howell:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for levomilnacipran (F2695) for the treatment of Major Depressive Disorder (MDD).

We also refer to the meeting between representatives of your firm and the FDA on May 4, 2012. The purpose of the meeting was to discuss the proposed safety and efficacy content of the NDA and to obtain agreement with the Division that the pivotal and supportive studies to be included in the NDA are sufficient to permit the review of levomilnacipran for the treatment of MDD.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, email LCDR Juliette Touré, PharmD, Senior Regulatory Project Manager at Juliette.Toure@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: May 4, 2012
Meeting Location: Food & Drug Administration
White Oak, Bldg 22, Rm 1315
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Application Number: IND 104483
Product Name: levomilnacipran (F2695)
Indication: Major Depressive Disorder
Sponsor/Applicant Name: Forest Laboratories, Inc.

Meeting Chair: Thomas Laughren, M.D., Director, Division of Psychiatry Products (DPP)
Meeting Recorder: Juliette Touré, PharmD, Senior Regulatory Project Manager, DPP

FDA ATTENDEES

Thomas Laughren, M.D.	Division Director
Mitchell Mathis, M.D.	Deputy Division Director
Jing Zhang, M.D.	Clinical Team Leader
Jenn Sellers, M.D.	Clinical Reviewer
Linda Fossom, Ph.D.	Pharmacology/Toxicology Supervisor
Arippa Ravindran, Ph.D.	Pharmacology/Toxicology Reviewer
Hao Zhu, Ph.D.	Clinical Pharmacology Team Leader
Andre Jackson, Ph.D.	Clinical Pharmacology Reviewer
Peiling Yang, Ph.D.	Statistics Team Leader
Andrejus Parfionovas, Ph.D.	Statistics Reviewer
Doug Warfield	Regulatory Information Specialist, Office of Business Informatics, CDER Data
Valerie Gooding	Regulatory Information Specialist, Office of Business Informatics, ESUB
Erica Radden, MD	Clinical Reviewer, Pediatric and Maternal Health Team (PMHS)

FDA ATTENDEES (continued)

Elizabeth Durmowicz, MD	Clinical Reviewer (PMHS)
Juliette Touré, PharmD	Senior Regulatory Project Manager

SPONSOR ATTENDEES

Forest Research Institute

June K. Bray, RPh, MBA	Senior Vice President, Regulatory Affairs
Michael Olchaskey, PharmD	Senior Director, Regulatory Affairs
Ann Howell, PharmD	Manager, Regulatory Affairs
Nadia Success	Associate Regulatory Affairs
Anjana Bose, PhD	Executive Director, Clinical Development
William Greenberg, MD	Director, Clinical Development
Laishun Chen, PhD	Senior Principal Scientist, Clinical Pharmacology and Drug Dynamics
Dayong Li, PhD	Senior Director, Biostatistics
Changzheng (Richard) Chen, PhD	Associate Director, Biostatistics
Pomy Shrestha, MD	Associate Director, Pharmacovigilance and Risk Management

Pierre Fabre Medicament

Valérie Brunner	Head of Clinical Pharmacokinetics, Pierre Fabre
Nathalie Rouziq	Global Project Manager, Pierre Fabre
Marie-Caroline Gilly Leclere, PharmD	Project Manager, International Regulatory Affairs

1.0 BACKGROUND

Levomilnacipran hydrochloride (HCl) is being developed for the treatment of major depressive disorder (MDD). Levomilnacipran HCl is also referred to as F2695 in studies conducted by Forest Laboratories, Inc. (Forest) and as F02695 in studies conducted by the partner, Pierre Fabre Médicament. As such, levomilnacipran HCl, levomilnacipran, F2695 and F02695 are used interchangeably throughout this briefing book.

Levomilnacipran is a selective inhibitor of norepinephrine (NE) and serotonin (5-hydroxytryptamine [5-HT]) uptake with high binding affinity at the NE and 5-HT transporters ($K_i = 71$ nM and 2.4 nM, respectively) that preferentially inhibits reuptake of NE over 5-HT by approximately 2-fold. Levomilnacipran (1S, 2R) is the more active of the two enantiomers present in the racemate Savella® (also known as milnacipran and F2207), which was approved by the Food and Drug Administration (FDA) for the management of fibromyalgia on 14 Jan 2009.

Forest has completed the clinical development program and is seeking the Agency's feedback on the proposed NDA for levomilnacipran HCl for the treatment of MDD. The objective of this

meeting is to discuss the contents of this briefing package and to receive feedback on the plans for the proposed NDA. Forest is working towards a September 2012 NDA submission date for levomilnacipran HCL.

The MDD indication will be supported by data from subjects in 26 studies: 19 completed clinical pharmacology studies (including the TQT study LVM-PK-07 [Section 11.0]); 5 short-term placebo controlled studies (one Phase 2 and four Phase 3 studies [Section 7.2.1]); 1 long-term open-label safety study (Section 7.2.2); and 1 relapse prevention study (Section 7.2.3):

- Studies LVM-MD-01 and LVM-MD-03: The primary efficacy data supporting levomilnacipran for the treatment of MDD was demonstrated in these 2 pivotal, 8-week, placebo-controlled studies using levomilnacipran 40-120 mg/day
- Study F02695 LP 2 02: Forest's partner, Pierre Fabre Médicament, conducted a 10-week, placebo-controlled study in Europe, India, and South Africa (F02695 LP 2 02) that will be used as a supportive study
- Studies LVM-MD-02 and LVM-MD-10 are 2 additional, 8-week placebo-controlled studies. LVM-MD-02 was a negative study. Study LVM-MD-10 has been clinically completed but results are unavailable as of the date of this Briefing Book

Additional safety information will be provided from two studies of levomilnacipran in indications other than MDD:

-  (b) (4)
-  (b) (4)

2. DISCUSSION

Question 1. Does the Division concur that the two positive pivotal studies, LVM-MD-01 and LVM-MD-03, can support the submission of the NDA for levomilnacipran for the treatment of MDD?

Preliminary Comments: Yes. You will need two positive, adequately designed and well controlled studies to support your submission. We agree that studies LVM-MD-01 and LVM-MD-03 should, in principle, be able to support the submission of an NDA for levomilnacipran for the treatment of MDD.

Discussion at Meeting: No further discussion.

Question 2. Does the Division concur with the proposed structure and statistical analyses planned for the ISE?

Preliminary Comments: *Yes.*

Discussion at Meeting: *No further discussion.*

Question 3. Does the Division concur with integrating pivotal and supportive positive short-term, placebo-controlled studies in MDD for the purpose of subgroup analyses in the ISE?

Preliminary Comments: *We have no objection to your proposed plan, with the acknowledgment that such analyses are exploratory. However, we ask that you also explore subgroup analyses by separately pooling positive and negative trials together. We remind you that we will also evaluate subgroup analysis results from individual trials.*

Discussion at Meeting: *We clarified to the Sponsor that the purpose of subgroup analyses is to explore whether treatment effects appear to be consistent across subgroups and we are not interested in p-values from subgroup analyses that the Sponsor was planning to produce. After clarification, the Sponsor decided to focus on providing descriptive summaries for the studies.*

Question 4. Does the Division concur with the proposed structure, study groupings, and statistical analyses for the ISS?

Preliminary Comments: *Yes. The proposed structure, the study groupings and statistical analyses for the ISS are acceptable.*

Discussion at Meeting: *No further discussion.*

Question 5. Forest proposes to not integrate the Phase 1 safety data in the ISS. Does the Division concur?

Preliminary Comments: *Yes. It is acceptable for the Phase 1 studies to be described individually and not be pooled in the ISS due to their different designs and doses.*

Discussion at Meeting: *No further discussion.*

Question 6. Does the Division concur that the estimated exposure data in MDD subjects is adequate to support the NDA?

Preliminary Comments: *Yes. The estimated exposure data consisting of approximately 202 subjects exposed to levomilnacipran for at least 1 year and over 600 subjects for at least 6 months is acceptable.*

Discussion at Meeting: *No further discussion.*

Question 7. Does the Division concur with the submission of CRFs and narratives only for deaths, SAEs, dropouts due to adverse events and other clinically significant important events?

Preliminary Comments: *Yes.*

Discussion at Meeting: *No further discussion.*

Question 8. Does the Division concur with Forest's plan for submitting study-level datasets in the NDA?

Preliminary Comments: *The study-level datasets described in 10.1 of the Pre-NDA Meeting Briefing Book generally conform to the requirements of the Study Data Specifications guidance. However, the FDA expects the Sponsor to follow the current Study Data Specifications guidance for all study data when submitting the application.*

Clinical trials research study designs should define the protocol for data collection. The Agency's methodology and submission structure supports research study design, as indicated in the Guidance to Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications and the Study Data Specifications. In addition, the Agency's methodology and submission structure supports integrating study data collection for Safety and Efficacy study submission.

The Agency requires implementation of analyses datasets to tabulations datasets traceability. In addition, the Agency requires each study submitted to be complete and evaluated on its own merits. The Agency prefers studies be maintained independently in the SDTM datasets, and that analyses (ADaM) datasets provide traceability to the study's SDTM, including analyses that combine multiple studies (e.g. Safety and/or Efficacy analyses) (See SDTM and ADaM as referenced in Study Data Specifications).

The Sponsor should submit program files in ASCII format, consistent with the Study Data Specifications (pg. 5). The Sponsor should locate the files under the [m3, m4, or m5]\datasets\[studyname]\analysis\programs directory, again per the Study Data Specifications (pg. 8). SAS program (.sas) files that are viewable as ASCII formatted files are acceptable.

Discussion at Meeting: *The Sponsor has studies (PK/PD and Phase 2) to include in the NDA for which legacy (raw) data were used to generate analysis datasets. For purposes of traceability from study data to datasets used for analyses (analyses datasets), the Sponsor will submit legacy datasets (raw), the standardized (SDTM) datasets, and corresponding analyses datasets for these PK/PD and Phase 2 studies. For all other studies the Sponsor will submit SDTM datasets and the corresponding generated analyses datasets.*

Question 9. Does the Division concur that the clinical pharmacology and biopharmaceutic package is adequate to support the registration of levomilnacipran for the treatment of MDD?

Preliminary Comments: Yes, the package has the requisite intrinsic and extrinsic factor studies. OCP would like the firm to complete the attached review tool and submit it with the firm's NDA.

We request you consider using "forest plots" instead of the text and/or table to present the changes in drug PK at Sections 7 (Drug Interactions) and 8 (Use in Specific Populations) of the label. The SAS code to make the forest plot is provided for your reference [See attached SAS code].

Please provide a table for the original PK information in Sections 7 and 8 in the label associated with forest plots for the label in the format below.

Factor (e.g. age, gender, renal impairment, inhibitors of CYP3A4, etc)	Type (e.g. female under gender, and mild under renal impairment, etc)	Moiety	PK (Cmax and AUC)	Geometric Mean Ratio*	90% CI		Recommendation
					Lratio	Uratio	

*Change relative to the reference

Using forest plots in drug labeling may communicate more effectively intrinsic and extrinsic factors effects on pharmacokinetics than using texts. For information on the use of forest plots in Drug label please refer to the following article: Essential Pharmacokinetic Information for Drug Dosage Decisions: A Concise Visual Presentation in the Drug Label, Clinical Pharmacology and Therapeutics, Sep;90(3):471-4. 10.1038/clpt.2011.149.

Supplementary material

Sample SAS code to create forest plots



Discussion at Meeting: *No further discussion.*

Question 10. Does the Division agree that the completed nonclinical pharmacology, ADME, and toxicology studies comprise a comprehensive nonclinical package to support the registration of levomilnacipran HCl for the treatment of MDD?

Preliminary Comments: *Yes; on face, your non-clinical package appears adequate to support filing of an NDA.*

Discussion at Meeting: *No further discussion.*

Question 11. Does the Division agree with the organization of the studies listed in the draft Modules 4 and 5 Table of Contents?

Preliminary Comments:

- *Providing Module 4 and 5 Table of Content is not necessary. Instead, providing a linked reviewer's aid/ reviewer's guide for an original application in module 1.2, as a separate document from the cover letter, to briefly describe where information can be found throughout the application can be helpful to the reviewers.*
- *The tabular listing in m5.2 should be hyperlinked to the referenced studies in m5.*
- *Study Tagging Files (STF) files is required for submissions to the FDA when providing study information in modules 4 and 5 with the exception of module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References and 5.3.6 if the Periodic Report is a single PDF document.*
- *Each study should have an STF and all components regarding that study should be file tagged and placed under the study's STF including case report forms (crfs). Case report forms need to be placed in the appropriate study's STF to which they belong, organized by site as per the specifications and tagged as "case report form". Please refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008).*
- *Please ensure that the leaf title of Postmarketing report includes the reporting period, since each report is for a specific time period.*
- *When naming files, it is important to avoid file truncation. The length of the entire path of the file should not exceed 230 characters. Please refer to Page 7 of the eCTD Specifications, located at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072349.pdf>*

Discussion at Meeting: *The Sponsor stated that levomilnacipran has not yet received approval for marketing in the US or abroad and can disregard the comment about Postmarketing Reporting since they will not be submitting any information in m5.3.6. The Sponsor confirmed that they will comply with the other organizational requirements as noted in the preliminary comment for Question 11.*

Question 12. Does the Division agree with the approach of using the text from the Integrated Analyses of Safety and Integrated Analyses of Effectiveness to fulfill the requirements of both the SCS (2.7.4) and SCE (2.7.3) documents and the narrative portions of the ISS and ISE and placing the supporting summary tables, listings, figures, and datasets for Section 2.7.4 and Section 2.7.3 in Section 5.3.5.3.?

Preliminary Comments: *Yes. Both your proposed document placement and the source of documents are acceptable.*

Discussion at Meeting: *No further discussion.*

Question 13. Does the Division concur with the proposed safety cut-off dates for the NDA and for the 120-day safety update?

Preliminary Comments: *Yes.*

Discussion at Meeting: *No further discussion.*

Question 14. Does the Division concur with the scope of the 120-day safety update?

Preliminary Comments: *Yes. The scope of the 120-day safety update is acceptable.*

Discussion at Meeting: *No further discussion.*

Question 15. Does the Agency agree to a waiver for pediatric studies in patients 0-6 years of age and a deferral in patients 7-17 years of age until after safety and efficacy have been demonstrated in adults?

Preliminary Comments: *The Pediatric Research Equity Act (PREA) requires that all NDAs, BLAs, or supplemental applications for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration contain a pediatric assessment unless a pediatric plan has been submitted and a request for a waiver or deferral has been granted.*

A pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required, and other data that are adequate to: 1) assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations and 2) support dosing and administration for each pediatric subpopulation for which the product has been assessed to be safe and effective.

A pediatric plan should address all relevant pediatric subpopulations and the development of an age-appropriate formulation. Furthermore, it should address whether and, if so, under what grounds, you plan to request a waiver or deferral of pediatric studies.

Each Pediatric Plan should contain the following:

- (1) certification of the grounds for deferring the assessments;*
- (2) a description of the planned or ongoing studies;*
- (3) evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time; and*
- (4) a timeline including protocol submission date, study completion date, and the date final studies will be submitted.*

We likely would agree to a partial waiver in birth to 6 years of age in the treatment of major depressive disorder, because studies are highly impractical due to the low prevalence of this disorder in this age range, and deferral of studies in patients 7 to 17 years of age. You will need to submit data to support your partial waiver request.

Discussion at Meeting: *The Sponsor requested clarification of the data required to support the partial waiver request. The Agency stated that the partial waiver request should include the rationale or justification for the request, and that this information should be included in the NDA submission.*

Question 16. Given that the proposed indication for the treatment of MDD is distinct from fibromyalgia and that the levomilnacipran NDA package will not rely on milnacipran data, does the Agency concur that Forest's proposed 505(b)(1) NDA for levomilnacipran will be eligible for a period of 5-year NCE exclusivity pursuant to FDC Act § 505(u)?

Preliminary Comments: *As mentioned in the End-of-Phase 2 Meeting Minutes, FDA does not award, comment on or grant exclusivity prior to approval of a drug product; therefore, concurrence at this time would be premature. If you choose to make the election under Section 505(u) to have the single enantiomer treated as a different active ingredient from the approved racemic drug, and the enantiomer is approved as a new drug, the Agency will analyze eligibility for exclusivity at that time.*

Discussion at Meeting: *The Sponsor clarified that the data supporting this NDA application will be stand-alone, i.e., only levomilnacipran data.*

Additional Statistical Comments: *In your future NDA submission, please include the following items for the trials intended to support an efficacy claim:*

- 1) SAS programs by which the derived variables were produced from the raw variables;*
- 2) SAS programs that produced efficacy results;*
- 3) A list of IND number with serial numbers and submission dates of the protocols, SAPs, amendments, and any relevant meetings.*

Discussion at Meeting: *We clarified to the Sponsor that the efficacy variables in items 1) and 2) above refer to the primary and the key secondary endpoints. The Sponsor confirmed that it will submit the information requested in 3) with the NDA application.*

3.0 ATTACHMENTS AND HANDOUTS

Forest representatives presented a summary of the results from a pivotal Phase 3 trial, LVM-MD-10, at the beginning of the meeting. The handout is attached.

LVM-MD-10

Summary Results

May 4, 2012

Study Design

- Multi-center, randomized, double-blind, fixed-dose study in outpatients with MDD
- Three groups (1:1:1 randomization)
 - Placebo
 - Levomilnacipran SR 40 mg/day
 - Levomilnacipran SR 80 mg/day
- Total study duration = 10 weeks
 - 1 week single-blind placebo lead-in
 - 8 week DB treatment
 - 1 week DB down-taper
- Study was conducted in the US and Canada

Outcome Measures at Week 8

- Primary: MADRS Total Score
- Secondary: Sheehan Disability Scale (SDS)
- Additional: CGI-S, HAMD-17, MADRS & HAMD response/remission rates, HAMD17 subscales
- Safety: PE, AE, vital signs, ECG, labs, C-SSRS

Patient Disposition

	Placebo n	F2695 SR 40 mg/d n	F2695 SR 80 mg/d n	Total n
Randomized	189	190	189	568
Safety	186	188	188	562
ITT	185	185	187	557
Completed Study (%)	82.8	77.1	75.5	78.5
Prematurely D/C (%)	17.2	22.9	24.5	21.5
Reason for Premature D/C (%)				
Adverse Event	1.6	6.4	10.1	6.0
ITR	1.6	1.6	1.6	1.6
PV	2.2	5.3	3.2	3.6
WOC	4.3	5.3	3.7	4.4
LTFU	7.5	4.3	5.9	5.9
Other	0	0	0	0

**Primary Efficacy Parameter:
Change from Baseline MADRS Total Score at Wk 8
ITT Population**

	Placebo (N=185)	F2695 SR 40 mg/d (N=185)	F2695 SR 80 mg/d (N=187)
Baseline Mean ± SD	31.0 ± 3.8	30.8 ± 3.4	31.2 ± 3.5
Change at Week 8 (MMRM): Primary			
LS Mean (LSMD) [P-value]	-11.3	-14.6 (-3.30) [0.0027]	-14.4 (-3.14) [0.0043]
Change at Week 8 (LOCF): Sensitivity Analysis			
LS Mean (LSMD) [P-value]	-10.7	-13.1 (-2.42) [0.0247]	-13.1 (-2.38) [0.0244]

Secondary Efficacy Parameter: Change from Baseline in SDS Total Score at Wk 8 ITT Population

	Placebo (N=185)	F2695 SR 40 mg/d (N=185)	F2695 SR 80 mg/d (N=187)
Baseline Mean ± SD	16.4 ± 6.1	16.7 ± 6.6	17.6 ± 6.0
Change at Week 8 (MMRM): Primary			
LS Mean (LSMD) [P-value]	-5.4	-7.3 (-1.83) [0.0459]	-8.2 (-2.72) [0.0028]
Change at Week 8 (LOCF): Sensitivity Analysis			
LS Mean (LSMD) [P-value]	-5.0	-6.7 (-1.68) [0.0607]	-7.4 (-2.45) [0.0055]

Summary of Adverse Events

Safety Population, DB treatment period

	Placebo (N=186)	F2695 SR 40 mg/d (N=188)	F2695 SR 80 mg/d (N=188)
<i>% of Patients with</i>			
Deaths	0	0	0
SAE	0.5	1.6	0
ADO	1.6	6.4	10.1
TEAE	55.4	68.1	79.3

Treatment Emergent Adverse Events Reported in $\geq 10\%$ of Patients in Any Treatment Group - Safety Population

<i>Adverse Event (Preferred Term)</i>	Placebo (N=186)	F2695 SR 40 mg/d (N=188)	F2695 SR 80 mg/d (N=188)
Nausea	5.9	14.4	15.4
Headache	8.6	11.7	13.3
Dry mouth	3.8	10.1	9.6

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/s/

THOMAS P LAUGHREN
05/08/2012



IND 104483

MEETING MINUTES

Forest Laboratories, Inc.
Attention: Michael K. Olchaskey, PharmD
Director, Regulatory Affairs
Plaza V, Suite 1900
Jersey City, NJ 07311

Dear Dr. Olchaskey:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for F2695.

We also refer to the meeting between representatives of your firm and the FDA on March 12, 2010. The purpose of the meeting was to obtain the Division's feedback regarding

(b) (4)

(b) (4)

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, email your Regulatory Project Manager at Juliette.Toure@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: [REDACTED] (b) (4)

Meeting Date and Time: March 12, 2010, 10:00 – 11:00 AM EST
Meeting Location: Food & Drug Administration, White Oak Bldg 22, Rm 1311

Application Number: IND 104,483
Product Name: F2695
Indication: Major Depressive Disorder
Sponsor/Applicant Name: Forest Laboratories, Inc.

Meeting Chair: Thomas P. Laughren, M.D.
Meeting Recorder: Juliette Touré, Pharm.D.

FDA ATTENDEES

Thomas Laughren, M.D.	Division Director
Mitchell Mathis, M.D.	Deputy Division Director
Jing Zhang, M.D.	Clinical Team Leader
Maju Mathews, M.D.	Clinical Reviewer
Linda Fossom, Ph.D.	Pharmacology/Toxicology Team Leader
Arippa Ravindran, Ph.D.	Pharmacology/Toxicology Reviewer
Juliette Touré, Pharm.D.	Senior Regulatory Project Manager

SPONSOR ATTENDEES

Sergei Stankovic, M.D.	Senior Vice President, Clinical Development
Anjana Bose, Ph.D.	Executive Director, Clinical Development
Rana Al-Hallaq, Ph.D.	Clinical Scientist II, Clinical Development
June Bray, R.Ph., M.B.A.	Vice President, Regulatory Affairs
Michael Olchaskey, Pharm.D.	Senior Director, Regulatory Affairs
Dayong Li, Ph.D.	Director, Biostatistics
Hongjie Zheng, Ph.D.	Biostatistics
Pradeep Banerjee, Ph.D.	Senior Director, Pharmacology
Mary Hooper, M.S.	Associate Director, Project Management
Nicole Bradley, Pharm.D.	Post-Doctoral Fellow, St. John's University

1.0 BACKGROUND

F2695 is apparently the more active of the 2 enantiomers present in the racemate milnacipran (F2207), which was approved by the FDA on January 14, 2009 for the management of fibromyalgia under the trade name Savella™. F2695 sustained-release (SR) is currently being developed for the acute and maintenance treatment of major depressive disorder (MDD) under a phase 3 clinical development plan (IND #104,483). The plan for the acute treatment of MDD was discussed and agreed with the Division at the End of Phase 2 meeting on May 18, 2009, and includes 3 randomized, double-blind, placebo-controlled, 8-week studies, as well as an open-label, long-term safety study. A relapse prevention study is also planned to evaluate F2695 SR in the maintenance treatment of MDD.

In contrast to other serotonin and norepinephrine reuptake inhibitors (SNRIs), which are more potent serotonin (5-HT) than norepinephrine (NE) reuptake inhibitors, in vitro studies suggest that F2695 is apparently slightly more potent at inhibiting the uptake of NE than 5-HT.

(b) (4)

3 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

General Comments:

These are the official minutes of our March 12, 2010 meeting. If you have any questions or disagree with the content of these minutes in any particular, it is your responsibility to bring these points to our attention.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

IND-104483

GI-1

FOREST
LABORATORIES
INC

F2695

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

/s/

THOMAS P LAUGHREN
03/15/2010



IND 104,483

Forest Laboratories, Inc.
Attention: Michael K. Olchaskey, PharmD
Director, Regulatory Affairs
Plaza V, Suite 1900
Jersey City, NJ 07311
USA

Dear Dr. Olchaskey:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for F2695, also referred to as levomilnacipran.

We also refer to the teleconference between representatives of your firm and the FDA on May 18, 2009. The purpose of the teleconference was to discuss the development of levomilnacipran as a treatment for Major Depressive Disorder (MDD).

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the teleconference outcomes.

If you have any questions, you may email LCDR Juliette Touré, Senior Regulatory Project Manager, at Juliette.Toure@fda.hhs.gov.

Sincerely,
{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: Monday, May 18, 2009
TIME: 2:00 to 3:00 PM EST
LOCATION: Teleconference# 1-800-411-0160; Pass code (b) (4)
APPLICATION: IND 104,483
DRUG NAME: F2695 (levomilnacipran)
TYPE OF MEETING: Type B, End of Phase 2 Meeting

MEETING CHAIR: Thomas Laughren, M.D.

MEETING RECORDER: Juliette Touré, Pharm.D.

FDA PARTICIPANTS/CONTRIBUTORS: (Title and Office/Division)

Thomas Laughren, M.D.	Division Director, Division of Psychiatry Products (DPP)
Mitchell Mathis, M.D.	Deputy Director, DPP
Gwen Zornberg, M.D.	Clinical Team Leader, DPP
Maju Mathews, M.D.	Clinical Reviewer, DPP
Barry Rosloff, Ph.D.	Pharmacology/Toxicology Supervisor, DPP
Linda Fossom, Ph.D.	Pharmacology/Toxicology Team Leader, DPP
Arippa Ravindran, Ph.D.	Pharmacology/Toxicology Reviewer, DPP
Thomas Oliver, Ph.D.	Pharmaceutical Assessment Lead, DPP
Patrick Marroum, Ph.D.	Biopharmaceutics Expert, DPP
Phillip Dinh, Ph.D.	Statistical Reviewer
Andre Jackson, Ph.D.	Clinical Pharmacology Reviewer
Juliette Touré, Pharm.D.	Senior Regulatory Project Manager, DPP

EXTERNAL CONSTITUENT PARTICIPANTS:

Jingdon Xie, Ph.D.	Associate Director, Biostatistics
Hongjie Zheng, Ph.D.	Executive Director, Biostatistics
Dayong Li, Ph.D.	Director, Biostatistics
Anjana Bose, Ph.D.	Executive Director, Clinical Development
Rana Al-Hallaq, Ph.D.	Clinical Scientist I, Clinical Development
Giovanna Forero, M.S.	Assistant Director, Clinical Development
Pradeep Banerjee, Ph.D.	Sr. Director, Pharmacology
Laishun Chen, Ph.D.	Sr. Principal Scientist, Clinical Pharmacology and Drug Dynamics (CPDD)
Mahendra Dedhiya, Ph.D.	Senior Director, Product Development
June K. Bray, M.B.A., R.Ph.	Vice President, Regulatory Affairs
Michael Olchaskey, Pharm.D.	Director, Regulatory Affairs
Sejal Parikh, Pharm.D.	Senior Manager, Regulatory Affairs
Julie Plotnikov, Pharm.D.	Post Doctoral Fellow, Regulatory Affairs
Anne Gilson, M.S.	Principal Scientist, Toxicology

Maureen Toulon, Ph.D., D.A.B.T. Executive Director, Toxicology
Mary B. Hooper, M.S. Associate Director, Corporate Project Management

BACKGROUND:

F2695 (levomilnacipran) is apparently the more active of the two enantiomers present in the racemate milnacipran (F2207). Milnacipran was approved by the FDA on January 14, 2009 for the management of fibromyalgia under the trade name Savella™. The sponsor states that F2695 is a selective and potent inhibitor of the reuptake of norepinephrine (NE) and serotonin (5-HT). The sponsor notes that this is a pharmacologic mechanism of action shared by other drugs that have been shown to be effective in the treatment of mood disorders, and further, claims that F2695 does not have certain side effects associated with off-target activities (e.g., histamine, muscarinic cholinergic). This meeting is focused on a program to develop this drug for the treatment of MDD. The sponsor seeks guidance on its planned phase 3 development program.

The sponsor summarizes the nonclinical pharmacokinetic (PK) studies as follows:

“These studies indicate that levomilnacipran is rapidly absorbed after oral administration and has low binding capacity to plasma proteins. Radioactivity in the administered dose is rapidly eliminated, primarily in the urine. Levomilnacipran did not demonstrate a significant inhibition of major cytochrome P-450 isozymes (CYPs) in human liver microsomes or an induction of major CYP and uridine glucosyltransferase 1A6 enzyme activities in isolated human hepatocytes.”

The sponsor suggests the following regarding the nonclinical toxicity data for levomilnacipran:

“It demonstrated an acceptable safety profile similar to that of its racemate, milnacipran. Major observations in 13-week repeat-dose studies were hypersalivation and liver centrilobular hypertrophy in rats and reductions in body weight, body weight gain, and food consumption in rats and monkeys. Levomilnacipran did not demonstrate clastogenic or mutagenic activity in a standard ICH (International Conference on Harmonisation) battery of in vitro and in vivo tests.”

The sponsor suggests the following regarding reproductive and developmental toxicity for levomilnacipran:

“Reproductive and developmental toxicity studies have not yet been conducted with levomilnacipran. However, studies of the racemate, F2207, in rats demonstrated low-dose perinatal/postnatal maternal toxicity, fetolethality, and failure of offspring to thrive. F2207 did not adversely affect fertility in rats and was not teratogenic to mice or rabbits.

The sponsor suggests the following regarding clinical pharmacology studies:

“The single oral administration of an immediate-release (IR) capsule formulation of levomilnacipran to healthy subjects demonstrated a dose-proportional increase in plasma exposure over the dose range of 12.5 to 75 mg, with peak plasma concentrations occurring at about 2 to 6 hours. The PK behavior of levomilnacipran following multiple-dose administration (12.5-75 mg, twice a day) matches the prediction based on single-dose administration. The terminal elimination half-life ($T_{1/2}$) of the IR formulation was 8 to 10 hours following single-dose administration and was similar after multiple dosing.

Levomilnacipran is primarily excreted in urine as unchanged drug (53%-66% of the administered dose).

Subsequent to the development of an IR capsule of levomilnacipran, modified- or sustained-release (SR) capsule formulations with different in vitro dissolution rates were developed in Europe by Pierre Fabre Médicament. The SR capsule formulation chosen for future clinical studies demonstrated a relative bioavailability of 81% referenced to the IR capsule and a T_{1/2} of 12 hours.”

The sponsor has completed one flexible dose (75-100 mg/day; n=278 levomilnacipran, n=279 pbo) randomized, placebo-controlled trial (RCT) 10-week phase 2 study in patients with MDD that the sponsor considered positive. In this study patients received levomilnacipran titrated up to the target dosage of 100 mg/day starting at 25/mg/day for 3 days; 50 mg/day for 4 days; 75 mg/day for 4 days and 100 mg/day at Day 12 unless tolerability limited the dose to 75 mg/day. A mean change in systolic and diastolic blood pressure were noted, as well as increased ventricular heart rate starting from Day 7 and persisting through the treatment period. The mean QT_c interval increased by 8.0 msec in the levomilnacipran group based on the Bazett formula and decreased by -3.1 msec at endpoint based on the Fridericia formula.

The sponsor plans to conduct three short-term (8-week) phase 3 pbo-controlled RCTs. LVM-MD-01 will be a fixed dose study (40, 80, and 120 mg/day) and LVM-MD-02 and LVM-MD-03 will be identically designed flexible-dose studies (40-120 mg/day). Each study will consist of 3 phases: 1-week single-blind placebo lead-in, followed by 8 weeks of double-blind treatment, and a 2-week double-blind taper down period. The starting dose in all three studies will be 20 mg daily. The sponsor also plans to roll over patients who complete 8 weeks in the short-term studies to an open label extension study (LVM-MD-04); this study will extend to up to 1 year to evaluate the long-term safety and tolerability of levomilnacipran in patients diagnosed with MDD. The sponsor does plan to use the C-SSRS in all studies.

MEETING OBJECTIVES:

- To outline and seek FDA concurrence on a clinical development plan in the treatment of patients for Major Depressive Disorder (MDD) indication
- To obtain feedback from the Division on the questions provided below.

DISCUSSION POINTS:

Forest submitted a MR, received March 19, 2009, to discuss the development of F2695 (levomilnacipran) as a treatment for MDD. DPP sent Preliminary Comments to the sponsor on Friday, May 15, 2009. The sponsor responded with written comments on Monday, May 18, 2009 and elected to hold the meeting as a teleconference, rather than as a face-to-face meeting.

Forest opened the teleconference with a few announcements:

- Forest will no longer call the study drug for IND 104,483 “levomilnacipran”; they will only refer to it as “F2695”. This is to avoid any potential confusion, as the drug formulation has a 1S-2R configuration (the salt is dextrorotary).

- Forest is interested in exercising FDAAA § 505(u), as noted in their response to Question #9, and applying for the 5-year exclusivity, therefore, they will not reference data submitted for approval of Savella™ (milnacipran).
- Forest will only be developing a sustained-release (SR) formulation— no immediate-release (IR) formulation.

Toxicology

Question 1. Nonclinical toxicology studies of levomilnacipran conducted to date indicate that levomilnacipran has a toxicity profile similar to that of its recently FDA-approved racemate, milnacipran (Savella™). Chronic toxicity studies of levomilnacipran will be ongoing when the proposed phase III trials are initiated. Does the Division concur that, while the chronic studies of levomilnacipran are ongoing, the chronic toxicity studies of milnacipran will provide adequate nonclinical safety support for the longer-term phase III trials?

Preliminary Comments: *Yes. However, it is not clear that chronic animal studies would be required for levomilnacipran. Based on the similar pharmacological and toxicological profiles for levomilnacipran and (racemic) milnacipran, which you have already demonstrated, and the complete non-clinical toxicological assessment of milnacipran that supported its approval for treatment of fibromyalgia, typically the only additional non-clinical study that we would require for levomilnacipran would be an embryo-fetal reproductive toxicology study. Additionally, as is always the case, any concerns about impurities/degradants in drug substance or product or novel excipients would need to be addressed.*

FOREST COMMENT:

Based upon the FDA response to Question 9, Forest will include a full chronic animal study package with F2695 in the NDA, in order to be eligible for 5 year NCE exclusivity. This will include the transgenic carcinogenicity study in the mouse identified in the fax dated April 27, 2009 in response to our request for a Special Protocol Assessment.

We do understand that longer-term phase III F2695 trials may proceed, while the chronic studies of F2695 are ongoing.

Discussion during the teleconference: *DPP confirmed that the longer-term phase III clinical trials may proceed while the chronic animal studies are on-going. Regarding the transgenic mouse carcinogenicity study, Forest confirmed that their dose range-finding study will be 4 weeks in duration.*

Chemistry, Manufacturing, and Controls

Question 2. Does the Division agree with the approach of demonstrating equivalency of site transfer batches with the phase III clinical trial batches using an in vitro–in vivo correlation (IVIVC)?

Preliminary Comments: *If the IVIVC is found to be acceptable and predictive of the in vivo performance, then an in vivo bioavailability waiver based on comparability of the in vitro dissolution profiles can be granted. The division agrees with the proposed approach.*

Discussion during the teleconference: *No further discussion.*

Clinical Pharmacology

Question 3. Does the Division concur that the planned clinical pharmacology studies would be adequate to support a New Drug Application (NDA) for levomilnacipran for MDD?

Preliminary Comments: *Your planned studies should be adequate to support an NDA for levomilnacipran for MDD. However, the suitability of the studies will be a review issue.*

FOREST COMMENT

Please clarify that “suitability of the studies will be a review issue” refers to the review of the data and not the study design.

Discussion during the teleconference: *DPP clarified that reviewers will need to review both study design and data.*

(Preliminary Comments continued)
Furthermore:

- *You should determine if there is an exposure response effect for your drug.*

FOREST COMMENT

We will explore an exposure response effect for F2695. We are planning to collect sparse PK samples from Phase III trials. Attempts in establishing a population PK-PD model will be made to understand the relationship between exposure and response.

Discussion during the teleconference: *Forest asked for clarification of DPP’s expectations regarding exposure and response. DPP responded that it would depend on what doses are chosen in order to define the effectiveness of the response.*

(Preliminary Comments continued)

- *You should use the population PK study to study the possible interaction of your drug with any other drugs the patient may be taking.*

FOREST COMMENT

We plan to use the population PK approach to evaluate drug-drug interaction potential with concomitant medications as covariates.

Discussion during the teleconference: *No further discussion.*

(Preliminary Comments continued)

- *The severe renal impairment subjects should have a creatinine clearance < 30 ml/min.*

FOREST COMMENT

Subjects with serum creatinine clearance less than 30 mL/min will be included in the planned renal impairment study.

Discussion during the teleconference: *No further discussion.*

(Preliminary Comments continued)

- *You should consider plans for how this drug will be studied in pediatric patients.*

FOREST COMMENT

We will consider plans for how F2695 will be studied in pediatric patients after safety and efficacy have been demonstrated in adults. (See question 7)

Discussion during the teleconference: *No further discussion.*

(Preliminary Comments continued)

Since you are planning to develop a controlled-release (CR) formulation, we recommend that you conduct the following studies:

FOREST COMMENT

The clinical development program of F2695 is based on the use of a sustained-release (SR) formulation. This formulation has been used in 5 out of 6 clinical trials including 3 Phase I studies and 2 Phase II studies, and will be used in future trials. An investigational immediate-release (IR) product has only been used twice: (a) in the first initial PK study evaluating F2695 PK after single and multiple dose administration (Study F02695 GE 101) and (b) in a study aimed to select an SR formulation for clinical development (Study F02695 GE 102). There is no approved F2695 IR formulation (b)(4). Therefore, we believe that the recommendation of studies aiming to compare the SR to the IR product is not applicable.

Responses to each of the individual study recommendations are provided below.

(Preliminary Comments continued)

- *A single-dose fasting study comparing the CR product at the highest strength to the IR reference when the drug shows linear PK and the CR strengths are compositionally proportional.*

FOREST COMMENT

PK linearity will be addressed in Study LVM-PK-01 which is an ongoing study to evaluate the PK of the SR formulation (b) (4) in healthy subjects following a single dose administration (b) (4) and multiple escalating doses (b) (4) under fasting conditions.

The SR formulation of F2695 is a beaded capsule. Thus, all dosage strengths are (b) (4)

A single dose PK study under fasting conditions will be conducted at the highest dosage strength of the SR product without a comparator of the IR product, provided PK is linear.

Discussion during the teleconference: *The relative BA of any new product is a CFR requirement 320.25(d). More specifically, since your product is a new CR formulation, the question of dose dumping must be addressed which can only be assessed based upon an IR comparator 320.25 f(ii).*

(Preliminary Comments continued)

- (b) (4)

FOREST COMMENT

As stated above, (b) (4) (b) (4) (b) (4) this study is not needed.

(Preliminary Comments continued)

- *A single dose, food-effect study on the highest CR strength*

FOREST COMMENT

We will conduct the food-effect study at the highest SR dose strength.

(Preliminary Comments continued)

- *A steady-state study on the highest strength of the CR product versus an approved IR reference.*

FOREST COMMENT

We will conduct a steady state PK study using the highest strength of the SR product without the IR comparator.

Discussion during the teleconference: *Based upon CFR 320.25 f(2), the reference product to assess a controlled-release product's steady-state relative bioavailability should be a solution or suspension, a currently marketed noncontrolled-release drug product containing the same active drug ingredient or a currently marketed controlled release drug product subject to an approved full new drug application containing the same active drug ingredient.*

(Preliminary Comments continued)

- *For drugs showing non-linear kinetics, there should be a comparison of the controlled release for to an IR reference*
 - *A single dose fasting study for every strength of the CR product compared to the IR reference, or, a single dose study each comparing the highest strength of the CR product to the corresponding IR reference and the lowest strength of the CR product to the corresponding IR reference.*

FOREST COMMENT

If PK is found to be nonlinear, the PK evaluation using each dosage strength will be performed in a single dose study under fasting conditions. We do not feel that comparison to an IR product is applicable.

Discussion during the teleconference: *In addition, if the sponsor's drug exhibits non-linear pharmacokinetics a single dose study must be conducted at the highest and lowest dosage strengths of the CR product each compared to a corresponding reference – see above also, where this was also provided to the sponsor as a Preliminary Comment.*

Clinical

Question 4. Does the Division concur that the proposed phase III program, if successful, would be adequate to support an MDD indication?

Preliminary Comments: *On face, the planned phase 3 studies appear to be acceptable. We will, of course, need to see full protocols and will likely have additional comments at that time. Whether or not the program is ultimately successful would, of course, be a matter of review.*

We have the following additional comments regarding this proposed levomilnacipran in MDD clinical program of 3 studies of acute treatment:

- *You will need to pre-specify a primary efficacy endpoint. If you are also seeking a claim for a secondary endpoint, a key secondary endpoint would need to be prospectively declared and positive findings would need to be replicated, too. Note that secondary endpoints that involve measures of depressive symptoms (e.g. HAMD response rate, MADRS and others) are not considered as acceptable key*

secondary endpoints, since these variables are redundant with the primary efficacy variable. The SDS would be an acceptable key secondary variable.

FOREST COMMENT

The primary efficacy endpoint will be pre-specified in the protocol. We plan to use the change from baseline to Week 8 in MADRS total score as the primary efficacy endpoint in all 3 studies (LVM-MD-01, -02, and-03).

In addition, we plan to prospectively define one secondary efficacy endpoint in all 3 protocols. We are considering using

^{(b) (4)} the SDS as the secondary efficacy endpoint.

(b) (4)

(b) (4)

(b) (4)

Discussion during the teleconference:

^{(b) (4)} DPP prefers the SDS (total score would be sufficient), as it more clearly explores a different clinical domain than the primary endpoint.

(b) (4)

Post-Meeting Advice: *For studies that have primary and key secondary endpoints, the sponsor will need to also pre-specify an appropriate multiple testing procedure that strongly controls the studywise type I error rate (for all primary and secondary hypotheses).*

(Preliminary Comments continued)

- *We ask that you include the ASEX that you propose for studies LVM-MD-02 and LVM-MD-03 in study LVM-MD-01 as well. If you think that levomilnacipran may have a unique benefit in lacking sexual side effects, you may consider pre-specifying sexual dysfunction as a key secondary endpoint. Although you noted that no active comparators are planned for these studies, to support such a claim, you would need to show noninferiority to placebo for levomilnacipran and also a positive finding for an active comparator antidepressant known to have prominent sexual dysfunction.*

FOREST COMMENT

(b) (4)

(Preliminary Comments continued)

- *There has been much focus on treatment-emergent suicidality (suicidal ideation and behavior) in recent years, including the question of how best to assess for this in future trials. The Division of Psychiatry Products (DPP) has developed a policy regarding how we will address this issue. All clinical protocols for this product will need to include prospective assessment for suicidality. These assessments would need to be included in every clinical protocol, at every*

planned visit, and in every phase of development. An acceptable instrument would be one that maps to C-CASA (Columbia Classification Algorithm for Suicide Assessment). The C-SSRS (Columbia Suicide Severity Rating Scale) would be an acceptable instrument. We note that you are planning to utilize the C-SSRS, and this is acceptable.

- *In order to provide sufficient geriatric safety data, we recommend that you consider including some patients who are older than 65 years in your phase 3 MDD studies.*

Discussion during the teleconference: *No further discussion.*

FOREST COMMENT

As recommended, we will extend the upper bound of the age limit to 80 years in the two flexible dose studies (LVM-MD-02 and -03) to generate safety data in patients > 65 years.

(Preliminary Comments continued)

- *You should monitor heart rate and blood pressure carefully in all studies, based on the findings of the first trial.*

Discussion during the teleconference: *No further discussion.*

FOREST COMMENT

As requested, heart rate and blood pressure will be carefully monitored in all studies.

Statistical

Question 5. Is the statistical approach to the analyses of the primary efficacy parameter acceptable?

Preliminary Comments: *We agree with your primary analysis model using an MMRM approach with treatment group, study center, visit, and treatment–group-by-visit interaction as fixed effects and the baseline value and baseline-by-visit interaction as the covariates. An unstructured covariance matrix will be used to model the covariance of within-patient scores. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. These analyses will be performed based on all postbaseline scores using only the observed cases (OCs) without imputation of missing values.*

When you submit your Statistical Analysis Plan, please include mock SAS codes for your primary analysis model. Please also provide the details of the sequential multiple-comparison procedure to be used in Study LVM-MD-01. Please also pre-specify an algorithm for pooling small centers with fewer than four patients.

Discussion during the teleconference: *No further discussion.*

Clinical

Question 6. Based on the anticipated safety database, would this be adequate to support an MDD indication?

Preliminary Comments: *The anticipated safety database for the studies in patients with MDD consisting of at least 1500 patients exposed to at least one dose of levomilnacipran and approximately 500 patients with 6 months and 200 patients with 1 year of exposure to study drug is acceptable. Your proposed thorough QTc study should also be informative.*

Discussion during the teleconference: *No further discussion.*

Regulatory

Question 7 (Pediatric Program Deferral). In the NDA, Forest intends to request a deferral of conducting studies required under the Pediatric Research and Equity Act (PREA) in pediatric patients until safety and efficacy have been demonstrated in adults. Does the Agency concur with this approach?

Preliminary Comments: *Yes.*

Discussion during the teleconference: *No further discussion.*

Question 8 (Therapeutic Category). Does the Agency concur that fibromyalgia and depression are in different “therapeutic categories” for purposes of FDC Act § 505(u) concerning 5-year NCE exclusivity for certain enantiomer approvals?

Preliminary Comments: *We agree that MDD is distinct from fibromyalgia.*

Discussion during the teleconference: *No further discussion.*

Question 9 (Exclusivity). Does the Agency concur that Forest’s proposed 505(b)(1) NDA for levomilnacipran will be eligible for a period of 5-year NCE exclusivity pursuant to FDC Act § 505(u)?

Preliminary Comments: *Determination of a product’s eligibility for exclusivity is made at the time of NDA approval. Certain provisions of the FDC Act were amended with the FDAAA (Section 1113) with respect to exclusivity for certain drugs submitted to the agency between Sept 27, 2007, and Sept 30, 2012, containing single enantiomers of*

previously approved racemic mixtures. You may elect to have a single enantiomer (levomilnacipran) not be considered the same active ingredient as a previously-approved racemic drug (milnacipran, SavellaTM) if certain criteria apply, specifically:

- i.) the single enantiomer has not been previously approved except as part of the racemate*
- ii.) the proposed indication is not in the therapeutic category that is approved for the racemic drug or other enantiomer*
- iii.) if the single enantiomer is granted 5-years exclusivity under Sec 1113, it may not be approved for the racemate's indication for 10 years and the labeling must state the single enantiomer has not been shown to be safe and effective for these indications*
- iv.) the NDA must include full reports of new clinical investigations necessary for approval that were conducted or sponsored by the applicant*
- v.) the NDA does not rely on investigations that were part of an application submitted under 505(b) for the approved racemic drug. (This provision may present a problem for a 505(b)(2) application seeking exclusivity; an evaluation at the time of approval would have to be made.)*

Discussion during the teleconference: *No further discussion.*

General Comments:

These are the official minutes of our May 18, 2009 teleconference. If you have any questions or disagree with the content of these minutes in any particular, it is your responsibility to bring these points to our attention.

Linked Applications

Sponsor Name

Drug Name / Subject

IND 104483

FOREST
LABORATORIES INC

F2695

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

/s/

THOMAS P LAUGHREN
05/26/2009

NDA 204168
FETZIMA (levomilnacipran) extended-release 20 mg, 40 mg, 80 mg and 120 mg
capsules for the Treatment of Major Depressive Disorder
Action Package – **APPROVAL**

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