

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-256

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-256

SUPPL #

HFD # 170

Trade Name Savella

Generic Name Milnacipran Hydrochloride

Applicant Name Cypress Bioscience, Inc, represented by Forest Laboratories, Inc.

Approval Date, If Known January 14, 2009

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 years

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. 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 2 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

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:

Name of person completing form: Diana L. Walker, PhD
Title: Regulatory Project Manager
Date: January 14, 2009

Name of Office/Division Director signing form: Curt Rosebraugh, M.D., M.P.H.
Title: Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Curtis Rosebraugh
1/14/2009 02:50:03 PM

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA #: 22-256 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DAARP PDUFA Goal Date: _____ Stamp Date: December 18, 2007
October 18, 2008

Proprietary Name: Savella

Established/Generic Name: Milnacipran HCL

Dosage Form: Tablets: 12.5-mg, 25-mg, 50-mg, 100-mg

Applicant/Sponsor: Forest Laboratories, Inc. on behalf of Cypress Bioscience

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Treatment of fibromyalgia

Q1: Is this application in response to a PREA PMC/PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMC/PMR #: _____

Does the division agree that this is a complete response to the PMC/PMR?

- Yes. Please proceed to Section D.
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
 No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 No: Please check all that apply:
 Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 Deferred for some or all pediatric subpopulations (Complete Sections C)
 Completed for some or all pediatric subpopulations (Complete Sections D)
 Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit*	Ineffective or unsafe [†]	Formulation failed ^Δ	
<input checked="" type="checkbox"/>	Neonate	0 wk. __ mo.	__ wk. 1 mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	0 yr. 1 mo.	12 yr. 11 mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children (**Neonates**)
 - Too few children with disease/condition to study (**0-12 years**)
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cdcrpmhs@fda.hhs.gov) OR AT 301-796-0700.

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

Justification: *The prevalence of juvenile primary fibromyalgia syndrome (JPFS) in patients less than 13 years of age is low, and the diagnosis is controversial. Milnacipran is not likely to be used in a substantial number of pediatric patients in this age group.*

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input checked="" type="checkbox"/> Other	13 yr. 0 mo.	17 yr. 0 mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cdcrpmhs@fda.hhs.gov) OR AT 301-796-0700.

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

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

/s/

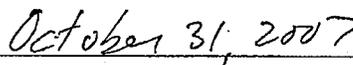
Diana Walker
9/24/2008 11:56:00 AM

DEBARMENT CERTIFICATION

Cypress Bioscience, Inc hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



R. Michael Gendreau, M.D., Ph.D.
Vice President, Clinical Development
& Chief Medical Officer
Cypress Bioscience, Inc.



Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 22-256 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Savella Established/Proper Name: Milnacipran hydrochloride Dosage Form: 12.5-, 25-, 50- and 100-mg		Applicant: Cypress Bioscience, Inc. Agent for Applicant (if applicable): Forest Laboratories, Inc.
RPM: Diana L. Walker, PhD		Division: DAARP
<p>NDA: 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 NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(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"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</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> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
❖ User Fee Goal Date Action Goal Date (if different)		October 18, 2008 January 14, 2009
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (<i>specify type and date for each action taken</i>)		<input checked="" type="checkbox"/> None
❖ Advertising (<i>approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), advertising MUST have been submitted and reviewed (<i>indicate dates of reviews</i>)		<input type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

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.

❖ Application ² Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): Type I (NME)	
<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	
NDAs: 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	
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	
<input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC	
Comments:	
❖ Application Integrity Policy (AIP) http://www.fda.gov/ora/compliance_ref/aip_page.html	
• 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 checked="" type="checkbox"/> No
• If yes, exception for review granted (<i>file Center Director's memo in Administrative/Regulatory Documents section, with Administrative Reviews</i>)	<input type="checkbox"/> Yes
• If yes, OC clearance for approval (<i>file communication in Administrative/Regulatory Documents section with Administrative Reviews</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain: <input type="checkbox"/>	September 24, 2008
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input checked="" type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² All questions in all sections pertain 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: _____
❖ 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).

If "No," continue with question (5).

<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>
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist ³	Yes
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/nonconsent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Approval January 14, 2009
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
❖ Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	January 8, 2009
❖ Original applicant-proposed labeling	December 18, 2007
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use (<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"/> None

³ Fill in blanks with dates of reviews, letters, etc.
Version: 5/29/08

❖ Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	January 8, 2009
❖ Original applicant-proposed labeling	September 5, 2008
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date at upper right of first page of each submission</i>)	
❖ Most-recent division proposal for (only if generated after latest applicant submission)	
❖ Most recent applicant-proposed labeling	October 16, 2008
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> RPM May 20, 2008 <input checked="" type="checkbox"/> DMEDP September 5, 2008 <input checked="" type="checkbox"/> DRISK October 8, 2008 <input checked="" type="checkbox"/> DDMAC April 18, 2008 <input checked="" type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	RPM Filing Review : March 27, 2008
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> • Center Director's Exception for Review memo • If approval action, OC clearance for approval 	<input checked="" type="checkbox"/> Not on AIP
❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)	<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
❖ Postmarketing Requirement (PMR) Studies	<input type="checkbox"/> None
• Outgoing communications (<i>if located elsewhere in package, state where located</i>)	October 8, 2008
• Incoming submissions/communications	October 9, 2008
❖ Postmarketing Commitment (PMC) Studies	<input type="checkbox"/> None
• Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>)	
• Incoming submission documenting commitment	
❖ Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>)	January 14 & 17, 2008 February 6 (2), 12, 20 & 22, 2008 March 3 & 19, 2008 April 3, 7, & 8, 2008 May 9, 20, 27 & 28, 2008 June 6, 2008 July 11, 21, 23, 28, 30 & 31, 2008 August 5, 6, 7 (2), 8, 11, 15 & 25, 2008 September 2, 2008

⁴ Filing reviews for other disciplines should be filed behind the discipline tab.

	October 6, 8 (2), 2008
❖ Internal memoranda, telecons, etc.	February 28, 2008
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) 	<input checked="" type="checkbox"/> Not applicable included in wrap-up meeting September 4, 2008, memo included, October 10, 2008
<ul style="list-style-type: none"> • Regulatory Briefing (<i>indicate date</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date</i>) 	<input type="checkbox"/> No mtg March 16, 2007
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date</i>) 	<input type="checkbox"/> No mtg April 8, 2003
<ul style="list-style-type: none"> • Other (e.g., EOP 2a, CMC pilot programs) 	Type A, Post-SPA review October 14, 2003
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) 	
<ul style="list-style-type: none"> • 48-hour alert or minutes, if available 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None January 14, 2009
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None original: October 16, 2008 addendum: January 14, 2009
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None September 14, 2008
Clinical Information⁵	
❖ Clinical Reviews	
<ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	
<ul style="list-style-type: none"> • Clinical review(s) (<i>indicate date for each review</i>) 	Filing Review, February 20, 2008 Clinical Review, August 28, 2008
<ul style="list-style-type: none"> • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	Included in ADRA Review, September 29, 2008
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None Biometrics QT study review, June 18, 2008 Division of Cardio-renal Products QT Study review, June 22, 2008 Second Biometrics QT study review, September 2, 2008
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input type="checkbox"/> Not needed August 1, 2008 September 23, 2008 October 8, 2008

⁵ Filing reviews should be filed with the discipline reviews.
Version: 5/29/08

❖ REMS <ul style="list-style-type: none"> REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) Review(s) and recommendations (including those by OSE and CSS) (<i>indicate location/date if incorporated into another review</i>) 	<input type="checkbox"/> None October 9, 2008
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested
<ul style="list-style-type: none"> Clinical Studies 	Summary: August 28, 2008 Addendum: January 13, 2009 Letters to Investigators: July 10, 2008 July 11, 2008 (2 letters) August 21, 2008 (3 letters) September 8, 2008 January 14, 2009
<ul style="list-style-type: none"> Bioequivalence Studies Clinical Pharmacology Studies 	
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None January 8, 2009
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None September 8, 2008
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None August 29, 2008
❖ DSI Clinical Pharmacology Inspection Review Summary	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
<ul style="list-style-type: none"> ADP/T Review(s) (<i>indicate date for each review</i>) 	<input type="checkbox"/> None October 6, 2008
<ul style="list-style-type: none"> Supervisory Review(s) (<i>indicate date for each review</i>) 	<input type="checkbox"/> None Filing review: January 31, 2008 Supervisory Review: September 24, 2008
<ul style="list-style-type: none"> Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) 	<input type="checkbox"/> None August 27, 2008 September 17, 2008
❖ 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 June 30, 2008
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None July 3, 2008 Included in P/T review, pageN/A

❖ DSI Nonclinical Inspection Review Summary	<input checked="" type="checkbox"/> None requested
CMC/Quality <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None September 2, 2008
• Branch Chief/TeamLeader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None Filing review, January 25, 2008
• CMC/product quality review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None August 29, 2008 DMF reviews: April 29, 2008 July 31, 2008 August 29, 2008
• BLAs only: Facility information review(s) <i>(indicate dates)</i>	<input type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ 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>	August 29, 2008 (included in CMC Review)
<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	
• NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date)</i>	Date completed: January 18, 2008 - Acceptable January 22, 2008 - Acceptable January 30, 2008 - Acceptable April 15, 2008 - Acceptable June 26, 2008 - Acceptable <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
• BLAs: > TBP-EER > Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) <i>(date completed must be within 60 days prior to AP)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

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

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

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

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

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

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

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

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

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

/s/

Diana Walker

1/14/2009 02:52:02 PM

IR ltr 5/20/08

**REGULATORY PROJECT MANAGER LABELING REVIEW
(PHYSICIAN LABELING RULE)**

Division of Anesthesia, Analgesia and Rheumatology Products

Application Number: 22-256/000
Name of Drug: BRAND (Milnacipran hydrochloride) Tablets
Applicant: Cypress Bioscience, Inc.
Authorized Agent: Forest Laboratories, Inc.

Material Reviewed:

Submission Date(s): December 18, 2007

Receipt Date(s): December 18, 2007

Submission Date of Structure Product Labeling (SPL): December 18, 2008

Type of Labeling Reviewed: WORD

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in the Sponsor's proposed labeling.

Highlights

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b(4)

└

1 Page(s) Withheld

 Trade Secret / Confidential (b4)

X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Full Prescribing Information (FPI)

1. 17

5.

b(4)

Recommendations

The Sponsor must address the identified deficiencies/issues and re-submit labeling. This updated version of labeling will be used for further labeling discussions.

Lauren P. Tornetta, M.S., M.B.A.
Regulatory Project Manager

Supervisory Comment/Concurrence:

Parinda Jani
Chief, Project Management Staff

CSO LABELING REVIEW OF PLR FORMAT: NDA 22-256/Milnacipran

Drafted: LPT/13May08
Revised/Initialed: PJani: 5/20/08
Finalized: LTornetta: 5/20/08
Filename: CSO Labeling Review_NDA 22256.doc

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

/s/

Lauren Tornetta
5/20/2008 10:37:26 AM
CSO

Parinda Jani
5/20/2008 02:40:25 PM
CSO



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

Date: October 8, 2008

To: Bob A. Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Rheumatology Products

From: Jodi Duckhorn, M.A., Team Leader
Sharon R. Mills, BSN, RN, CCRP
Patient Product Information Specialist

**Patient Labeling and Education Team
Division of Risk Management (DRISK)**

Subject: Review of Patient Labeling (Medication Guide)

Drug Name(s): Savella (milnaciparan HCl) Tablets

Application Type/Number: NDA 22-256

Applicant/sponsor: Forest Laboratories, Inc.

OSE RCM #: 2008-1432

1 INTRODUCTION

Forest Laboratories, Inc. submitted an original New Drug Application, NDA 22-256, for milnacipran HCl tablets. Savilla (milnaciparan HCl) Tablets is indicated for the management of fibromyalgia. Savilla is a Selective Serotonin and Norepinephrine Reuptake Inhibitor. As such Savilla is required to carry the anti-depressant Medication Guide (MG) that is also required of antidepressant class products including the SSRIs and other SNRIs.

The sponsor submitted a draft proposed MG for Savilla on September 5, 2008. The draft proposed Medication Guide submitted by the sponsor includes the antidepressant class MG language. The reviewing division felt that the antidepressant class language is all that is necessary for this product.

The Division of Anesthesia, Analgesia, and Rheumatology requested that the Patient Labeling and Education Team review the sponsor's proposed MG and make it consistent with the antidepressant class MG. This review is written in response to that request.

b(4)

2 MATERIAL REVIEWED

- DRAFT SAVELLA Medication Guide (MG) submitted by the sponsor on September 5, 2008 and further revised by the review division and provided on October 2, 2008
- DRAFT SAVELLA Professional Information (PI) submitted by the sponsor on January 4, 2008, and further revised throughout the review cycle. Version provided by the review division on October 2, 2008.

3 DISCUSSION

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

In our review of the MG, we have ensured that the MG is consistent with the PI and with the antidepressant class MG.

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the MG document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG. Comments to the review division are **bolded, underlined and italicized**.

We are providing the review division a marked-up and clean copy of the revised MG. We recommend using the clean copy as the working document.

4 CONCLUSIONS AND RECOMMENDATIONS

1. Savella is packaged as bottles of 60 and 180 film-coated tablets, and in a _____
_____ 4-week starter pak. Unless Savella is packaged in unit-of-use packaging with the MG enclosed, it is unlikely that patients will receive the MG. The sponsor should state their plan to ensure distribution of the MG in accordance with 21 CFR 208.24(d). b(4)
2. The sponsor must comply with all of the Medication Guide regulations as specified in 21 CFR 208. In particular, the carton and container labels must comply with 21 CFR 208.24(a)(2)(d).
3. We have added the class language to the end of MG stating "Not all antidepressant medicines prescribed for children are FDA approved for use in children."
4. In the section "C" J we have added the following language to the end of the section:
"Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088." b(4)
This verbatim statement is required for all Medication Guides effective January 2008 (see 21 CFR 208.20 (b)(7)(iii); also see Interim Final Rule, Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products in Federal Register Vol. 73, No. 2, p.402-404, 1/3/2008).

Please let us know if you have any questions.

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 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Jodi Duckhorn
10/8/2008 01:42:15 PM
DRUG SAFETY OFFICE REVIEWER

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/s/

Jodi Duckhorn
10/8/2008 01:42:15 PM
DRUG SAFETY OFFICE REVIEWER

10/29/08

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

Memorandum

Date: October 29, 2008

To: Diana Walker – Project Manager
Division of Anesthesia, Analgesia, and Rheumatology
Products (DAARP)

From: Michael Sauers – Consumer Promotion Analyst
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

Subject: NDA 22-256
DDMAC labeling comments for Milnacipran Medication Guide

DDMAC has reviewed the proposed Medication Guide for Milnacipran and have no comments at this time.

• Thank you for this opportunity to provide comments. If you have any questions, please contact Mike Sauers at (301) 796-1035 or michael.sauers@fda.hhs.gov

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/s/

Michael A Sauers
10/29/2008 01:24:46 PM
DDMAC REVIEWER



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

Date: October 3, 2008

To: Bob Rappaport, MD,
Director, Division of Anesthesia, Analgesia and Rheumatology
Products

Thru: Linda Y. Kim-Jung, PharmD, Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol A. Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Denise V. Baugh, PharmD, BCPS, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Savella (Milnacipran Hydrochloride) Tablets
12.5 mg, 25 mg, 50 mg and 100 mg

Application Type/Number: NDA# 22-256

Applicant: Forest Laboratories, Inc.

OSE RCM #: 2008-1255

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b(4)

EXECUTIVE SUMMARY

The results of the Label and Labeling Risk Assessment found that the presentation of information and design of the proposed container labels and carton labeling appears to be vulnerable to confusion that could lead to medication errors. Specifically, we feel the cluttered presentation, lack of prominence of important information, incomplete instructions, and lack of differentiation between strengths increase the potential for confusion leading to medication errors. The Division of Medication Error Prevention and Analysis believes the risks we have identified can be addressed and mitigated prior to drug approval, and provide recommendations in Section 5 that aim at reducing the risk of medication errors.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Anesthesia, Analgesia and Rheumatology Products (HFD-170), for assessment of the proposed label and labeling for the proprietary name Savella. Container label, carton and insert labeling were provided for review and comment. The proposed proprietary name, "Savella" (Milnacipran HCL) was completed in OSE review # 2007-1969 (dated September 5, 2008).

1.2 PRODUCT INFORMATION

Savella (Milnacipran HCL) is indicated for the treatment of fibromyalgia syndrome. Savella will be available as 12.5 mg, 25 mg, 50 mg, and 100 mg oral tablets. The proposed titration schedule is listed below. The package insert labeling states to administer Savella in two divided doses per day. Begin dosing at 12.5 mg on the first day and increase to 100 mg per day over a 1 week period. The proposed titration schedule is listed below.

Day 1: 12.5 mg
Days 2-3: 25 mg/day (12.5 mg twice a day)
Days 4-7: 50 mg/day (25 mg twice a day)
After Day 7: 100 mg/day (50 mg twice a day)

Target maintenance dose is 100 mg/day

The maintenance dose may be increased to 200 mg/day based on individual patient response.

It is recommended that patients with severe renal impairment have their daily maintenance dose reduced by 50%.

We note that per e-mail from the Division dated December 10, 2007, due to tolerability issues the sponsor has investigated titration schedules ranging from [] 1 weeks.

b(4)

2 METHODS AND MATERIALS

This section describes the methods and materials used by the Division of Medication Error Prevention and Analysis medication error staff to conduct a label, labeling, and/or packaging risk assessment. The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as

any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.¹

2.1 CONTAINER LABEL, CARTON AND INSERT LABELING

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container label and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the United States Pharmacopeia-Institute of Safe Medication Practices Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.²

Because the Division of Medication Error Prevention and Analysis staff analyze reported misuse of drugs, we are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. The overall risk assessment is based on the findings of a Failure Mode and Effects Analysis (FMEA) of the label and labeling, and is focused on the avoidance of medication errors. FMEA is a systematic tool for evaluating a process and identifying where and how it might fail. The Division of Medication Error Prevention and Analysis uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provides recommendations that aim at reducing the risk of medication errors.

The Applicant submitted the following labels and labeling for Savella on December 1, 2007.

Professional Sample (10 count): 50 mg and 100 mg (Appendix A)

Professional Sample 2 week patient 'starter' kit containing five 12.5 mg tablets, eight 25 mg tablets, fourteen 50 mg tablets (Appendix B)

Professional Sample 4 week patient 'starter' kit containing five 12.5 mg tablets, eight 25 mg tablets, and forty-two 50 mg tablets (Appendix C)

Trade 4 week 'starter' pak containing five 12.5 mg tablets, eight 25 mg tablets, and forty-two 50 mg tablets (Appendix D)

Trade Bulk: 12.5 mg (60 count, 180 count); 25 mg (60 count, 180 count); 50 mg (60 count, 180 count); 100 mg (60 count, 180 count). (Appendix E)

Insert Labeling: No image.

On August 25, 2008 the Applicant informed the Agency that the [

[] would be withdrawn from consideration. Therefore those labels are not included in this review.]]

b(4)

3 RESULTS

3.1 LABEL AND LABELING RISK ASSESSMENT

¹ National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/about/MedErrors.html>. Last accessed 10/11/2007.

² Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

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X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

7 REFERENCES

1. ***Micromedex Integrated Index*** (<http://weblern/>)

Contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. This is a database which was created for DMETS, FDA.

3. ***Drug Facts and Comparisons, online version, St. Louis, MO*** (<http://weblern/>)

Drug Facts and Comparisons is a compendium organized by therapeutic Course; contains monographs on prescription and OTC drugs, with charts comparing similar products.

4. ***AMF Decision Support System [DSS]***

DSS is a government database used to track individual submissions and assignments in review divisions.

5. ***Division of Medication Error Prevention and Analysis proprietary name consultation requests***

This is a list of proposed and pending names that is generated by DMETS from the Access database/tracking system.

6. ***Drugs@FDA*** (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name and generic drugs and therapeutic biological products; prescription and over-the-counter human drugs and therapeutic biologicals, discontinued drugs and "Chemical Type 6" approvals.

7. ***Electronic online version of the FDA Orange Book***
(<http://www.fda.gov/cder/ob/default.htm>)

Provides a compilation of approved drug products with therapeutic equivalence evaluations.

8. ***U. S. Patent and Trademark Office website*** <http://www.uspto.gov>.

Provides information regarding patent and trademarks.

9. ***Clinical Pharmacology Online*** (<http://weblern/>)

Contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. Provides a keyword search engine.

10. Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and tradenames that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

11. Natural Medicines Comprehensive Databases (<http://weblern/>)

Contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

12. Stat!Ref (<http://weblern/>)

Contains full-text information from approximately 30 texts. Includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology and Dictionary of Medical Acronyms Abbreviations.

13. United States Adopted Names Stems (<http://www.ama-assn.org/ama/pub/category/4782.html>)

List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

Contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

15. Lexi-Comp (www.pharmacist.com)

A web-based searchable version of the Drug Information Handbook.

16. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

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/s/

Denise Baugh
10/3/2008 03:27:23 PM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
10/3/2008 03:28:34 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
10/3/2008 03:39:01 PM
DRUG SAFETY OFFICE REVIEWER

ADRA Rev #1 of Action Package for NDA 22-256, Savella (milnacipran HCl tablets)

Reviewer: Lee Ripper, ODE II

Date received: 9-25-08

Date of review: 9-29-08

Date original NDA received: 12-18-07

UF goal date: 10-18-08

Proposed Indication: Tx of fibromyalgia

Action type: AP or CR, depending on need for additional data on abuse potential

RPM: Diana Walker

Drug Classification: 1S

505(b) application

Debarment Certification: AC

Financial Disclosure: MOR p. 37. See comment below.

Safety Update: see MOR p. 157

REMS: MedGuide

Clinical Inspection Summary: Eight investigator sites and the CRO Forest Labs were inspected; two reviews are pending final classification, one is NAI and the other VAI. Overall conclusion is that data appear acceptable in support of the application.

DMEPA Review of Proprietary Name: 9/5/08: Do not object to Savella

DMEPA Review of Carton and Container Labels: 10/3/08, emailed to applicant 10/6/08

DDMAC Review: 4/18/08 review of PI and labels; not of MedGuide.

DRISK Review of MedGuide: Consult sent 9/8 *cm 10/8*

DRISK Review of REMS: *cm 10/13*

SEALD Review of PLR: None

CSS: Ongoing discussions between DAARP and CSS

EA: Categorical exclusion granted

EER: 1 facility pending, Pierre Fabre Sante in Gaillac, France; EES shows inspection scheduled for 6/23/08. *AC 10/16*

PSC Mtg: Combined with 9/4/08 WU mtg; RPM is doing minutes *cm 10/14*

CDTL Review: 9/14/08

DR Letters Issued: Thorough QT Study Review: 7/23/08

CMC reviewed by Blair Fraser 9/2/08

P/T reviewed by Paul Brown, 10/6/08

1. Financial disclosure information was not available for two investigators; this information is supposed to be collected from investigators before they begin. Information was also not available for 17 sub-investigators. Add the following to the action letter as a comment, not as a deficiency:

We note that financial disclosure information was not provided for two investigators. We remind you that in accordance with 21 CFR 312.53, financial disclosure information must be collected from investigators before they begin participating in the clinical trial. In addition, financial disclosure information was not provided for 17 subinvestigators. When financial

disclosure information is not available for investigators or subinvestigators, under due diligence, the application should include an explanation of why this information was not obtainable and document the attempts made to collect the information. See our guidance *Financial Disclosure by Clinical Investigators*, <http://www.fda.gov/oc/guidance/financialdis.html>. When financial information is not available, for those investigators and sub-investigators, you should certify as to outcome payments, proprietary interests, and significant payments of other sorts as this information should be available in your files.

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/s/

Leah Ripper
10/7/2008 05:22:13 PM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-256 Supplement # 000 Efficacy Supplement Type SE-

Proprietary Name: Savella (pending)
Established Name: Milnacipran hydrochloride
Strengths: 12.5-, 25-, 50-, and 100-mg, Oral Tablets

Applicant: Cypress Bioscience, Inc.
Agent for Applicant (if applicable): Forest Laboratories, Inc.

Date of Application: December 18, 2007
Date of Receipt: December 18, 2007
Date clock started after UN: N/A
Date of Filing Meeting: January 25, 2008
Filing Date: February 16, 2008
Action Goal Date (optional): October 15, 2008 User Fee Goal Date: October 18, 2008

Indication(s) requested: Treatment of Fibromyalgia

Type of Original NDA: (b)(1) (b)(2)
AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) *If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. 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). If the application or efficacy supplement is a (b)(2), complete Appendix B.*

Review Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.) N/A

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:

- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES NO

2. This application is an eNDA or combined paper + eNDA YES
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

- Does the eNDA, follow the guidance? YES NO
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>)

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, 5 Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO
- PDUFA and Action Goal dates correct in tracking system? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 63,736
- Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) April 8, 2003 NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) March 16, 2007 NO
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) SPA submitted July 18, 2003, but, NO
DAARP issued a non-agreement letter on
September 12, 2003
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
N/A YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA YES NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? N/A YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? CSS consulted for potential drug abuse and dependence. YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 25, 2008

NDA #: 22-256

DRUG NAMES: Milnacipran Hydrochloride

APPLICANT: Forest Laboratories, Inc. on behalf of Cypress

BACKGROUND:

Milnacipran was originally discovered by Pierre Fabre Medicament of Cedex, France. In 1997, milnacipran was approved in France for use in patients with major depressive disorder (MDD). As of July 2007, milnacipran has received market approval in 52 countries for MDD. Milnacipran is not currently approved in the US for any indication and it has not been submitted for FMS in any country.

ATTENDEES:

Bob Rappaport, M.D., Sharon Hertz, M.D., Mwango Kashoki, M.D, M.P.H., Jane Filie, M.D., Danae Christodoulou, Ph.D., Craig Bertha, Ph.D., Elsbeth Chikhale, Ph.D., Dan Mellon, Ph.D., Asoke Mukherjee, Ph.D., Elizabeth Bolan, Ph.D., Suresh Doddapaneni, Ph.D., Sayed Al Habet, Ph.D., Dionne Price, Ph.D., Joan Buenconsejo, Ph.D., Parinda Jani, Lauren Tornetta, M.S., M.B.A.

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	Jane Filie, M.D.
Medical Team Leader:	Mwango Kashoki, M.D., M.P.H.
Statistical:	Joan Buenconsejo, Ph.D.
Pharmacology:	Ashoke Mukherjee, Ph.D. and Elizabeth Bolan, Ph.D.
Statistical Pharmacology:	N/A
Chemistry:	Craig Bertha, Ph.D. and Elsbeth Chikhale, Ph.D.
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Sayed Al Habet, Ph.D.
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	Roy Blay
OSE:	TBD
Regulatory Project Management:	Lauren Tornetta, M.S., M.B.A.
Other Consults: DMETS, DDMAC, SEALD, PTOX/Stats. QT/IRT, PeRC and CSS	

- Per reviewers, are all parts in English or English translation? YES NO
If no, explain:

CLINICAL		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
• Clinical site audit(s) needed? If no, explain:		YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
• Advisory Committee Meeting needed?	date if known _____		NO <input checked="" type="checkbox"/>
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?		N/A <input checked="" type="checkbox"/>	YES <input type="checkbox"/> NO <input type="checkbox"/>
CLINICAL MICROBIOLOGY	N/A <input checked="" type="checkbox"/>	FILE <input type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
STATISTICS	N/A <input type="checkbox"/>	FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
BIOPHARMACEUTICS		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
• Biopharm. study site audits(s) needed? YES			<input type="checkbox"/> NO <input checked="" type="checkbox"/>
PHARMACOLOGY/TOX	N/A <input type="checkbox"/>	FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
• GLP audit needed?		YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
CHEMISTRY		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
• Establishment(s) ready for inspection?		YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
• Sterile product?		YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
If yes, was microbiology consulted for validation of sterilization?		YES <input type="checkbox"/>	NO <input type="checkbox"/>

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. Convey document filing issues/no filing issues to applicant by Day 74.

Lauren P. Tornetta, M.S., M.B.A.
Regulatory Project Manager

**APPEARS THIS WAY
ON ORIGINAL**

Appendix A to NDA Regulatory Filing Review

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

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

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

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

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

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

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

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

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**APPEARS THIS WAY
ON ORIGINAL**

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.) YES NO

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product? YES NO

If "Yes" contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.
- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO
- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

If "Yes," to (c), proceed to question 7.

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES NO

If "No," skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").
9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO
10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES NO
11. Is the application for a duplicate of a listed drug whose only difference is YES NO

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? YES NO
(This is different from the patent declaration submitted on form FDA 3542 and 3542a.)

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- Not applicable (e.g., solely based on published literature. See question # 7)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must *subsequently* submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES NO

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A YES NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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/s/

Lauren Tornetta
3/27/2008 03:24:29 PM
CSO

Walker, Diana

From: Walker, Diana
Sent: Wednesday, October 08, 2008 1:34 PM
To: 'Olchaskey, Michael'
Subject: FDA Information Request: NDA 22-256/Savella/Post-Marketing requirements/08Oct08
Importance: High

Dear Michael,

In a teleconference between Forest Laboratories and the Division on September 9, 2008, Dr. Kashoki discussed potential Post-Marketing Requirements that would be put into place if NDA 22-256 were to be approved, including a pregnancy registry and a lactation study. In this email, I am sending you details concerning those studies, and asking you to send your concurrence along with your proposed dates for protocol submission and study start date. Please email me this information as soon as possible, but no later than C.O.B. Thursday, October 9, 2008, followed by an official submission to your NDA. The details of these Post-Marketing Requirements are as follows:

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

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

You will conduct this trial according to the following timetable:

Protocol Submission: xxxxx
Study Start Date: xxxxx
Final Report Submission: Within six months of FDA notification that sufficient data has been collected.

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

A single dose, pharmacokinetic, open-label, clinical study in healthy lactating women. Concentrations of Savella will be assessed in maternal plasma and breast milk so as to estimate potential infant exposure.

You will conduct this trial according to the following timetable:

Protocol Submission: xxxxx
Study Start: xxxxx
Final Report Submission: [

] b(4)

Please acknowledge receipt of this email, and contact me if you have any questions concerning this request.

Regards,

ina

10/8/2008

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
mail: Diana.Walker@fda.hhs.gov

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10/8/2008

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/s/

Diana Walker
10/8/2008 05:49:33 PM
CSO



FOREST LABORATORIES, INC.
Harborside Financial Center
Plaza III, Suite 602
Jersey City, NJ 07311

Direct Line: (201) 386-2142
Fax: (631) 858-7921

October 9, 2008

Bob A. Rappaport, MD
Director
Division of Anesthesia, Analgesia, and Rheumatology Products
Center for Drug Evaluation and Research
US Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA: 22-256 - Milnacipran HCl Tablets
Re: Response to FDA Information Request (dated October 8, 2008) - Postmarketing Commitments (lactation study and pregnancy registry)

Dear Dr. Rappaport:

Reference is made to the e-mail communication sent by Diana Walker, PhD to Michael Olchaskey on October 8, 2008 containing details on the requested post-marketing commitments. We agree to conduct the following two studies according to the timelines provided below.

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

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

We will conduct this trial according to the following timetable:

Protocol Submission:
Study Start Date: _____
Final Report Submission: Within six months of FDA notification that sufficient data has been collected.

11/9

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

A single dose, pharmacokinetic, open-label, clinical study in healthy lactating women. Concentrations of Savella will be assessed in maternal plasma and breast milk so as to estimate potential infant exposure.

We will conduct this trial according to the following timetable:

Protocol Submission:

Study Start:

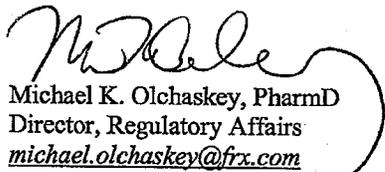
Final Report Submission:

[]

b(4)

If there are any questions related to this submission, please contact me at (201) 386-2142 or in my absence Sejal A. Parikh, PharmD at (201) 386-2123.

Sincerely,


Michael K. Olchaskey, PharmD
Director, Regulatory Affairs
michael.olchaskey@frx.com

Walker, Diana

From: Walker, Diana
Sent: Friday, October 10, 2008 6:30 PM
To: 'Olchaskey, Michael'
Subject: NDA 22-256/Label-PI Comments/10Oct08
Importance: High
Attachments: Savella Draft-PI sent to Forest_10 10 08.pdf

Dear Michael,

The Division review team is reviewing your NDA 22-256, Savella, submission and has comments contained in the attached PDF Package Insert label. Please provide a response to me via email no later than **C.O.B. on Monday, October 13, 2008.**

Please contact me if you have any questions concerning these comments. Because of the government holiday on Monday, I may not be able to contact you with any requested clarifications until Tuesday, October 14, 2008.

Kindly acknowledge receipt of this email, and that you can clearly open and read the attached PDF.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

Diana Walker
11/5/2008 12:55:22 PM
CSO

Walker, Diana

From: Walker, Diana
Sent: Wednesday, October 15, 2008 6:18 PM
To: 'Olchaskey, Michael'
Cc: Jani, Parinda
Subject: FW: FDA Information request/NDA 22-256/Package Insert label (15Oct08)
Importance: High
Attachments: Savella package insert 10-15-08.pdf

Dear Michael,

The review team for your NDA 22-256, Savella, has made comments to the label Package Insert, which is being attached to this email as a PDF file. Please provide a response to Parinda Jani via email no later than 9:00 A.M (EST) on Thursday, October 16, 2008.

Please contact Parinda with any questions regarding your NDA or this information request.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
A/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

Diana Walker
11/5/2008 01:00:00 PM
CSO

Walker, Diana

From: Walker, Diana
Sent: Friday, October 10, 2008 5:42 PM
To: 'Olchaskey, Michael'
Subject: FDA CMC labeling Information Request/10Oct08
Importance: High

Dear Michael,

The Chemistry, Manufacturing, and Controls group has the following comments and requests for information. Please provide a response to me via email (followed by an official submission to your NDA) no later than **8:00 AM, EST, on Tuesday, October 14, 2008.**

1. Submit update d/latest SPL (structured product label).
2. Remove the following statement from all cartons/containers: **Inc".**
3. Remove the logo/drawing on the carton/containers between the word Savella and TM.

b(4)

Please contact me if you have any questions concerning these comments. Because of the government holiday on Monday, I may not be able to contact you with any requested clarifications until Tuesday, October 14, 2008.

Regards,

ana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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Diana Walker
11/5/2008 12:58:55 PM
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Walker, Diana

 **From:** Walker, Diana
Sent: Friday, October 10, 2008 5:33 PM
To: 'Olchaskey, Michael'
Subject: NDA 22-256/DMEPA Carton and Container Comments/10Oct08
Importance: High
Attachments: Savella Labeling Response to Applicant.pdf

Dear Michael,

The Division of Medication Error Prevention (DMEPA) team is reviewing your NDA 22-256, Savella, submission and has comments contained in the attached PDF. Please provide a response to me via email (followed by an official submission to your NDA) no later than **8:00 AM, EST, on Tuesday, October 14, 2008.**

Please contact me if you have any questions concerning these comments. Because of the government holiday on Monday, I may not be able to contact you with any requested clarifications until Tuesday, October 14, 2008.

Please note that, per our teleconference today, I will also be sending you the draft label with comments, although this will follow in a separate email. Kindly acknowledge receipt of this email, and that you can clearly open and read the attached PDF.

Regards,

 Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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Diana Walker
11/5/2008 12:57:48 PM
CSO

Walker, Diana

From: Walker, Diana
Sent: Friday, October 10, 2008 9:43 AM
To: 'Olchaskey, Michael'
Subject: FDA Information Request: NDA 22-256/Savella/Carlton and Container/10Oct08
Importance: High

Dear Michael,

The Division of Medication Errors Prevention (DMEPA) is reviewing your October 8, 2008, submission, and has a clarification request. DMEPA has concerns regarding the patient's ability to read the container instructions, and would like to see a life-sized copy. Please submit the following to me by email as soon as possible, if possible, by noon today, October 10, 2008.

Submit by email a "life-sized" copy of the 4-week starter kit, either the professional sample or the trade container.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

Diana Walker
11/5/2008 12:56:38 PM
CSO

Walker, Diana

From: Walker, Diana
Sent: Wednesday, October 08, 2008 5:37 PM
To: 'Olchaskey, Michael'; 'Parikh, Sejal'
Subject: FDA Information Request: REMS Proposal/08Oct08
Importance: High
Attachments: Example_rems.pdf; Attachment A-NDA 22-256 REMS template.doc

Dear Michael,

In a telephone conversation between Sejal Parikh and I on August 28, 2008, we discussed the need for a RISK EVALUATION AND MITIGATION STRATEGIES (REMS) proposal to be submitted to NDA 22-256. At that time, I told Sejal that an official letter would be sent to request this submission, however, it has been determined that this information can be conveyed to you by email. I am providing details below as to the REMS proposal requirement, and I am also attaching a REMS template for you to use for guidance. I am additionally attaching an example REMS proposal for you to look at, which is freely available to the public at drugs@FDA, however please note that the REMS template is the most recent guidance, so use the example as a guide only. Please email me this information as soon as possible, but no later than C.O.B. Thursday, October 9, 2008, followed by an official submission to your NDA as soon as possible. The details of the REMS requirements are as follows:

We are reviewing your NDA submission and have the following comments and information requests.

RISK EVALUATION AND MITIGATION STRATEGIES (REMS) REQUIREMENTS

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

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary to ensure that the benefits of this drug outweigh the risks. Savella is a norepinephrine and serotonin reuptake inhibitor. The known serious risks associated with drugs of this class are serious psychiatric symptoms, including suicidal ideation, particularly in patients with depression. Mood disorders, such as major depression, bipolar disorder, major mood disorder, and anxiety disorders commonly co-occur in patients with fibromyalgia. Your proposed REMS must include the following:

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

We acknowledge receipt on September 5, 2008, of your Medication Guide. The Medication Guide is currently under review, and comments concerning this submission and required revisions will be sent to you from the Division.

Timetable for Assessments: The proposed REMS should describe concisely the actions you will take to manage the risks of Savella, and include a timetable for assessment of the REMS that at a minimum includes assessments that are submitted by 18 months and 3 years, and in the 7th year after the REMS is initially approved, with additional dates if more frequent assessments are necessary to ensure that the benefits of the drug continue to outweigh the risks. The REMS, once approved, will create enforceable obligations.

Our assessment of the REMS should include an evaluation of:

10/8/2008

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

A template for the REMS is included as an attachment.

The REMS Supporting Document should be a document explaining the rationale for each of the elements of the REMS. It should include the following sections:

1. Background Section
2. Goals Section
3. Rationale and Description of Proposed REMS Section
 - a. Medication Guide
 - b. Timetable for Assessment of the REMS Section (505-1(d))
 - c. Information Needed for Assessments

Use the following designator to prominently label all submissions relating to this REMS:

PROPOSED REMS

Please acknowledge receipt of this email, and contact me if you have any questions concerning this request.

Regards,

ana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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Email: Diana.Walker@fda.hhs.gov

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/s/

Diana Walker
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Walker, Diana

From: Walker, Diana
Sent: Tuesday, September 02, 2008 11:02 AM
To: 'Parikh, Sejal'; Olchaskey, Michael
Subject: FDA Information request/NDA 22-256/CMC (02Sep08)
Importance: High

Dear Michael and Sejal,

The CMC team is reviewing your NDA 22-256, Milnacipran, submission and has the below information request. Please provide a response to me via email as soon as possible today Tuesday, September 2, 2008.

1. Please indicate the location of the following in your NDA submission: **Batch Records for the drug product**
2. If these records have not been submitted, please submit them to me via email (followed by an official submission to your NDA) as soon as possible, but no later than **C.O.B. on Tuesday, September 2, 2008.**

Please contact me with any questions regarding your NDA or this information request.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
DA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

Diana Walker
9/17/2008 12:41:37 PM
CSO

Walker, Diana

From: Walker, Diana
Sent: Monday, August 25, 2008 4:54 PM
To: Olchaskey, Michael; 'Parikh, Sejal'
Subject: FDA Information request/NDA 22-256/Clinical (25Aug08)
Importance: High

Dear Michael and Sejal,

The Clinical team is reviewing your NDA 22-256, Milnacipran, submission and has the below information request. Please provide a response to me via email (followed by an official submission to your NDA) as soon as possible, but no later than 10:00 A.M (EST) on Wednesday, August 27, 2008.

1. Please indicate the location of the following narratives in the NDA submission:

Study FMS034: 15908, 12717, 14824,10762, 12702, 13318, 13506,15406,

Study MLN-MD-04: 25003, 22204, 22303, 22317, 22835, 23518, 24307

2. If the narratives are not in the NDA please submit these narratives by 10:00 A.M (EST) on Wednesday, August 27, 2008.

Please contact me with any questions regarding your NDA or this information request.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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Diana Walker
9/17/2008 12:44:00 PM
CSO

Walker, Diana

From: Walker, Diana
Sent: Wednesday, August 13, 2008 2:04 PM
To: 'Olchaskey, Michael'
Subject: NDA 22-256 Milnacipran/Pediatric Plan
Importance: High

Dear Michael,

A pediatric deferral was granted for Milnacipran in a letter from the Division dated September 11, 2007, which was before the FDAA implementation. Under FDAA, you will need to submit a pediatric plan.

The plan should contain (but is not limited to) a summary and commitment of what you plan to do in terms of safety and efficacy studies, address all relevant pediatric subpopulations and the development of an age-appropriate formulation. It should also contain a timing summary. For example, a summary of the safety and efficacy design would include a description (as an example: a randomized, double-blind placebo-controlled, fixed-dosed, 3 month study, number of dose arms, number of patients per arm), the timeframes (for example, dates for the first and last patient visits and the final study report), ages of study participants, etc. Furthermore, it should address whether and, if so, under what grounds, you plan to request a waiver or deferral of pediatric studies, and for what age populations these are being requested.

Please submit a summary Pediatric Plan to me as soon as possible, but no later than August 27, 2008 (if via email, follow with an official submission to your NDA).

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
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Diana Walker
9/17/2008 12:40:12 PM
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Walker, Diana

From: Walker, Diana
Sent: Monday, August 25, 2008 4:54 PM
To: Olchaskey, Michael; 'Parikh, Sejal'
Subject: FDA Information request/NDA 22-256/Clinical (25Aug08)
Importance: High

Dear Michael and Sejal,

The Clinical team is reviewing your NDA 22-256, Milnacipran, submission and has the below information request. Please provide a response to me via email (followed by an official submission to your NDA) as soon as possible, but no later than 10:00 A.M (EST) on Wednesday, August 27, 2008.

1. Please indicate the location of the following narratives in the NDA submission:

Study FMS034: 15908, 12717, 14824,10762, 12702, 13318, 13506,15406,

Study MLN-MD-04: 25003, 22204, 22303, 22317, 22835, 23518, 24307

2. If the narratives are not in the NDA please submit these narratives by 10:00 A.M (EST) on Wednesday, August 27, 2008.

Please contact me with any questions regarding your NDA or this information request.

Regards,

Diana

Diana L. Walker, Ph.D.
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Diana Walker
8/26/2008 02:42:02 PM
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Walker, Diana

From: Walker, Diana
Sent: Friday, August 15, 2008 4:37 PM
To: 'Olchaskey, Michael'
Subject: FDA Information request/NDA 22-256/Non-Clinical (15Aug08)
Importance: High

Dear Michael,

The Non-Clinical team is reviewing your NDA 22-256, Milnacipran, submission and has the below information request. Please provide a response to me via email (followed by an official submission to your NDA) as soon as possible, but no later than **C.O.B. on Wednesday, August 21, 2008.**

Please provide the name, CAS number, structure and any synonyms for the following compounds:

EC 103.42 (Study #s f220719459, f220719460, and f220719461)

FEL-7 (Study # Min.tx.02000)

FRI-7002207 (Study # Min.tx.02000)

TN-912 (Study #s p142, p143,m0 88)

Please contact me with any questions regarding your NDA or this information request.

Regards,

Diana

Diana L. Walker, Ph.D.
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Diana Walker
8/21/2008 10:48:48 AM
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Walker, Diana

From: Walker, Diana
Sent: Monday, August 11, 2008 9:37 AM
To: 'Olchaskey, Michael'
Subject: URGENT: FDA Information request/NDA 22-256/Clinical Information request (11Aug08)
Importance: High

Dear Michael,

The Clinical team is continuing to review your NDA submission and has the below additional information requests. Please provide a response to me via email (followed by an official submission to your NDA) as soon as possible, but no later than C.O.B. tomorrow, Tuesday, August 12, 2008.

#1. For the placebo-controlled FM studies, provide shift analyses for the tests of liver function, using the following criteria for shifts from baseline to maximum value for each of the treatment arms:

AST and ALT values:

> 1x ULN, < 3x ULN
>/= 3x ULN, < 5 ULN
>/= 5x ULN
>/= 10 x ULN
>/= 20x ULN

Bilirubin:

> 1 x ULN
> 1.5 x ULN
> 2 x ULN

Alkaline phosphatase:

> 1.5 x ULN

Indicate the number and percent of patients in *each cell* of the tables.

#2. For the placebo-controlled FM studies, provide shift analyses for vital signs (systolic blood pressure, diastolic blood pressure and heart rate), using the following criteria for shifts from baseline to maximum value for each of the treatment arms:

Systolic blood pressure (mmHg)

</= 120
> 120-140
>140-160
>160

Diastolic blood pressure (mmHg)

</= 80
>80-90
>90-100
>100-110
>110

Heart rate (bpm)

</= 100

8/11/2008

>100-110
>110-120
>120

Indicate the number and percent of patients in *each cell* of the tables.

Please contact me with any questions regarding your NDA or this information request.

Regards,

Diana

Diana L. Walker, Ph.D.
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Diana Walker
8/11/2008 09:40:05 AM
CSO

Walker, Diana

From: Walker, Diana
Sent: Friday, August 08, 2008 10:06 AM
To: 'Olchaskey, Michael'
Subject: RE: URGENT: FDA Information request/NDA 22-256/Clarification of 06Aug08 Submission (07Aug08)
Importance: High

Dear Michael,

I have received the following clarification in answer to your below email:

For the bilirubin values, the ranges are not mutually exclusive.

For the AST and ALT values (revised, and clarified):

> 1x ULN, < 3x ULN (mutually exclusive)
>/= 3x ULN, < 5 ULN (mutually exclusive)
>/= 5x ULN (not mutually exclusive)
>/= 10 x ULN (not mutually exclusive)
>/= 20x ULN (not mutually exclusive)

I hope this clarifies the information request. Please let me know if you need any further clarification.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

From: Olchaskey, Michael [mailto:Michael.Olchaskey@frx.com]
Sent: Friday, August 08, 2008 7:48 AM
To: Walker, Diana
Subject: RE: URGENT: FDA Information request/NDA 22-256/Clarification of 06Aug08 Submission (07Aug08)

Hi Diana,

Could you clarify whether these ranges are mutually exclusive and also for AST/ALT whether a value of exactly 5 is in the <5xULN or in the >5xULN group?

Thanks,

Michael

From: Walker, Diana [mailto:Diana.Walker@fda.hhs.gov]
Sent: Thursday, August 07, 2008 2:08 PM
To: Olchaskey, Michael
Subject: URGENT: FDA Information request/NDA 22-256/Clarification of 06Aug08 Submission (07Aug08)

8/8/2008

Importance: High

Dear Michael,

Please refer to your NDA 22-256, Milnacipran, submission dated August 6, 2008, entitled "Clinical Shift Tables for Heart Rate, Laboratory Values, and ECG Parameters". The Clinical team is reviewing your submission from August 6, 2008 and has the below clarification requests. Please provide a response to me via email (followed by an official submission to your NDA) as soon as possible, but no later than C.O.B. on Friday, August 8, 2008.

1. For Tables 2 and 3, provide the criteria for which each of the laboratory values were defined as "low," "normal," or "high."
2. Resubmit the shift analyses for the tests of liver function, using the following criteria for shifts from baseline to study end:

AST and ALT:

- > 1x ULN, < 3 x ULN
- >= 3x ULN, < 5x ULN
- > 5x ULN
- > 10x ULN
- > 20 x ULN

Bilirubin:

- > 1 x ULN
- > 1.5 x ULN
- > 2 x ULN

Alkaline phosphatase:

- > 1.5 x ULN

Please contact me with any questions regarding your NDA or this information request.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
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/s/

Diana Walker
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