

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208271Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA #: 208271

SUPPL #:

HFD #: 180

Trade Name: RELISTOR

Generic Name: Methylnaltrexone bromide

Applicant Name: Salix Pharmaceuticals

Approval Date, If Known: 24 Apr 2008

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); SE3

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?

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# 021964 RELISTOR (Methylnaltrexone bromide 12mg/0.6mL and 8mg/0.4mL solution for SC injection)

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#

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:

MNTX3201: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of Oral Methylnaltrexone for the Treatment of Opioid-Induced Constipation in Subjects with Chronic, Non-Malignant Pain

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 (MNTX3201)

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 (MNTX3201)

YES

NO

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

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

MNTX3201: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of Oral Methylnaltrexone for the Treatment of Opioid-Induced Constipation in Subjects with Chronic, Non-Malignant Pain

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

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

Investigation #1:

IND # 067452 YES !
! ! NO
! Explain:

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

Investigation #1

YES !
! ! NO
Explain: ! Explain:

(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: Lawrence Allan
Title: Regulatory Project Manager
Date: 12 Jul 2016

=====

Name of Office/Division Director signing form: Donna Griebel
Title: Deputy Division Director

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

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

/s/

LAWRENCE W ALLAN
07/19/2016

DONNA J GRIEBEL
07/19/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208271	NDA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: RELISTOR Established/Proper Name: Methylnaltrexone bromide Dosage Form: 150 mg tablets		Applicant: Salix Pharmaceuticals Agent for Applicant (if applicable):
RPM: Lawrence Allan/James Carr		Division: DGIEP
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☐ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: <i>Note: 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.</i>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>19 Jul 2016</u>		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☐ Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

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

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only): *Type 3 – New Dosage Form*
 (confirm chemical classification at time of approval)

☐ Fast Track	☐ Rx-to-OTC full switch
☐ Rolling Review	☐ Rx-to-OTC partial switch
☐ Orphan drug designation	☐ Direct-to-OTC
☐ Breakthrough Therapy designation	

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	☐ Yes ☐ No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE	
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>)	☒ Included
❖ Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s): 19 Jul 2016
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	☒ Included
• Original applicant-proposed labeling (19 Jun 2015)	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	☒ Medication Guide ☐ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	☒ Included
• Original applicant-proposed labeling (19 Jun 2015)	☒ Included
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>)	12 Aug 2015 11 Aug 2015
❖ Labeling reviews (<i>indicate dates of reviews</i>)	☐ RPM: ☒ DMEPA: 16 Feb 2016 ☒ DMPP/PLT (DRISK): 22 Jun 2016 ☒ OPDP: 21 Jun 2016 ☐ SEALD: ☐ CSS: ☐ Product Quality: ☐ Other:
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	2 Sep 2015
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary (<i>signed by Division Director</i>)	☒ Included

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) • Date reviewed by PeRC <u>17 Feb 2016</u> If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) (<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	☒ Review Extension – Major Amendment 16 Mar 2016
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☒ N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☒ 3 Nov 2014 ☒ 7 Mar 2012 ☒ 2 Apr 2012 ☒ 4 Apr 2011 ☒ 12 May 2010 ☒ 26 Jul 2006
• EOP2 meeting (<i>indicate date of mtg</i>)	☒ No mtg
• Mid-cycle Communication (<i>indicate date of mtg</i>)	☒ N/A
• Late-cycle Meeting (<i>indicate date of mtg</i>)	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	

❖ Advisory Committee Meeting(s) • Date(s) of Meeting(s)	☒ No AC meeting
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
Division Director Summary Review (<i>indicate date for each review</i>)	☒ 19 Jul 2016
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☒ 28 Jun 2016
PMR/PMC Development Templates (<i>indicate total number</i>)	☒ 01
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	☒ 3 Jun 2016
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Refer to pg. 27 in clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	☒ DPMH (Pediatric) – 2 Feb 2016 ☒ DPMH (Maternal Health) – 16 Mar 2016 ☒ DAAAP – 21 Mar 2016 ☒ OSE (ARIA sufficiency) – 9 Jun 2016
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	☒ None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	☒ 21 Jan 2016 – Clinical inspection summary ☒ 8 Jan 2016 – Site inspection letter ☒ 2 Sep 2015 – Recommendation to accept data w/o on-site inspection

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

Clinical Microbiology		☒ None
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)		☐ No separate review
Clinical Microbiology Review(s) (indicate date for each review)		☐ None
Biostatistics		☐ None
❖ Statistical Division Director Review(s) (indicate date for each review)		☒ No separate review
Statistical Team Leader Review(s) (indicate date for each review)		☒ No separate review
Statistical Review(s) (indicate date for each review)		☒ 25 Jun 2016
Clinical Pharmacology		☐ None
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)		☒ No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)		☒ No separate review
Clinical Pharmacology review(s) (indicate date for each review)		☒ 8 Jun 2016
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)		☒ None requested
Nonclinical		☐ None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) (indicate date for each review)		☒ No separate review
• Supervisory Review(s) (indicate date for each review)		☒ 23 Mar 2016
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)		☒ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)		☒ None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)		☒ No carc
❖ ECAC/CAC report/memo of meeting		☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)		☒ None requested
Product Quality		☐ None
❖ Product Quality Discipline Reviews ⁶		
• Tertiary review (indicate date for each review)		☒ None
• Secondary review (e.g., Branch Chief) (indicate date for each review)		☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (indicate date for each review)		☒ 15 Mar 2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (indicate date of each review)		☒ None

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	Refer to pg. 96 of the IQA
☐ Review & FONSI (<i>indicate date of review</i>)	
☐ Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
☒ Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	☒ Acceptable Re-evaluation date: 8 Jun 2016 Refer to 12 Jul 2016 email PDF ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity (<i>Notify CDER OND IO</i>)
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Courtesy copy emailed to applicant on 19 Jul 2016
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☐ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Email sent on 19 Jul 2016

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

/s/

LAWRENCE W ALLAN
07/19/2016

From: Allan, Lawrence
To: ["Harrell, Mary E"](#)
Subject: NDA 208271 - RELISTOR - Revised labeling (18 Jul 2016)
Date: Monday, July 18, 2016 10:48:00 AM
Attachments: [NDA 208271 RELISTOR - Labeling revisions \(18 Jul 2016\) - CLEAN.docx](#)
[NDA 208271 RELISTOR - Labeling revisions \(18 Jul 2016\) - TRACK CHANGES.pdf](#)

Good morning Mary,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for RELISTOR (methylnaltrexone bromide) 150 mg tablets and 8 mg/0.4 mL and 12 mg/0.6 mg injections for subcutaneous use.

At this time we are communicating comments and revisions to the proposed labeling for RELISTOR (methylnaltrexone bromide). Attached you will find the updated labeling documents; one PDF with revisions and comments marked for your review (track changes) and one WORD document without (clean). Please use the "clean" copy for further edits and resubmission to the application. Please provide your reply as promptly as possible, due to the pending action date of 19 Jul 2016.

Please do not hesitate to contact me if you have any questions concerning the revised labeling.

Regards,

Lawrence Allan

Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
ODE III | OND | CDER | FDA
10903 New Hampshire Ave.
WO22, Room 5353
Silver Spring, MD 20993
Phone: (240) 402 – 2786 | E-mail: lawrence.allan@fda.hhs.gov

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/s/

LAWRENCE W ALLAN
07/18/2016

From: Allan, Lawrence
To: "Mary.Harrell@bausch.com"
Subject: RE: NDA 208271 - RELISTOR - Revised labeling (1 Jul 2016)
Date: Wednesday, July 06, 2016 9:20:00 AM
Attachments: [NDA 208271 - RELISTOR - IFU Vial and syringe tray - 1 Jul 2016 \(track changes\).pdf](#)
[NDA 208271 - RELISTOR - IFU Vial and syringe tray - 1 Jul 2016 \(clean\).docx](#)
[NDA 208271 - RELISTOR - IFU Pre-filled syringe - 1 Jul 2016 \(track changes\).pdf](#)
[NDA 208271 - RELISTOR - IFU pre-filled syringe - 1 Jul 2016 \(clean\).docx](#)
[NDA 208271 - RELISTOR - Med Guide - 1 Jul 2016 \(clean\).docx](#)
[NDA 208271 - RELISTOR - Med Guide - 1 Jul 2016 \(track changes\).pdf](#)
[NDA 208271 - RELISTOR - IFU Vial - 1 Jul 2016 \(clean\).docx](#)
[NDA 208271 - RELISTOR - IFU Vial - 1 Jul 2016 \(track changes\).pdf](#)
Importance: High

Good morning Mary,

I apologize for the confusion on my part, as I thought that all of the labeling documents were still incorporated into one WORD file when I sent it to you.

At this time we are communicating comments and revisions to the proposed labeling for RELISTOR (methylnaltrexone bromide). Attached you will find the following labeling documents; one PDF with revisions and comments marked for your review (track changes) and one WORD document without (clean):

- Medication Guide
- Instructions for Use – Vial
- Instructions for Use – Pre-filled syringe
- Instructions for Use – Vial & syringe tray

Please use the "clean" WORD file for further edits and resubmission to the application.

Please do not hesitate to contact me if you have any questions.

Regards,

Lawrence Allan

Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
ODE III | OND | CDER | FDA
10903 New Hampshire Ave.
WO22, Room 5353
Silver Spring, MD 20993
Phone: (240) 402 – 2786 | E-mail: lawrence.allan@fda.hhs.gov

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authorized. If you have received this document in error, please notify me immediately by telephone at (240) 402 – 2786.

From: Allan, Lawrence
Sent: Friday, July 01, 2016 2:06 PM
To: 'Mary.Harrell@bausch.com'
Subject: NDA 208271 - RELISTOR - Revised labeling (1 Jul 2016)

Good afternoon Mary,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for RELISTOR (methylnaltrexone bromide) 150 mg tablets and 8 mg/0.4 mL and 12 mg/0.6 mg injections for subcutaneous use.

At this time we are communicating comments and revisions to the proposed prescribing information (PI) for RELISTOR (methylnaltrexone bromide). Attached you will find the Prescribing Info labeling documents; one PDF with revisions and comments marked for your review (track changes) and one WORD document without (clean). Please use the "clean" copy for further edits and resubmission to the application.

Please do not hesitate to contact me if you have any questions concerning the revised labeling.

Regards,

Lawrence Allan

Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
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Silver Spring, MD 20993
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/s/

LAWRENCE W ALLAN
07/06/2016

From: Allan, Lawrence
To: ["Mary.Harrell@bausch.com"](mailto:Mary.Harrell@bausch.com)
Subject: NDA 208271 - RELISTOR - Revised labeling (1 Jul 2016)
Date: Friday, July 01, 2016 2:05:00 PM
Attachments: [NDA 208271 - RELISTOR - Draft label \(clean\) - 1 Jul 2016.docx](#)
[NDA 208271 - RELISTOR - Draft label \(track changes\) - 1 Jul 2016.pdf](#)

Good afternoon Mary,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for RELISTOR (methylnaltrexone bromide) 150 mg tablets and 8 mg/0.4 mL and 12 mg/0.6 mg injections for subcutaneous use.

At this time we are communicating comments and revisions to the proposed prescribing information (PI) for RELISTOR (methylnaltrexone bromide). Attached you will find the Prescribing Info labeling documents; one PDF with revisions and comments marked for your review (track changes) and one WORD document without (clean). Please use the "clean" copy for further edits and resubmission to the application.

Please do not hesitate to contact me if you have any questions concerning the revised labeling.

Regards,

Lawrence Allan

Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
ODE III | OND | CDER | FDA
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LAWRENCE W ALLAN
07/01/2016



NDA 208271

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Salix Pharmaceuticals, Inc.
Attention: Mary Harrell
Director, Regulatory Affairs
400 Somerset Corporate Boulevard
Bridgewater, New Jersey 08807

Dear Ms. Harrell:

Please refer to your New Drug Application (NDA) dated June 19, 2015, received June 19, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Relistor (methylnaltrexone bromide tablets).

On February 5, 2016, February 10, 2016, March 10, 2016, March 16, 2016 and 17 March 2016 we received your major amendments to this application and additional time is needed to verify the responses provided. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is July 19, 2016.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by May 19, 2016.

If you have any questions, call CDR James Carr, Regulatory Project Manager, at (240) 402-6624.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., MBA
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products

Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BRIAN K STRONGIN
03/31/2016

From: Carr, James
To: ["Harrell, Mary E"](#)
Subject: NDA 208271 Relistor-Information Request 3.4.2016
Date: Friday, March 04, 2016 6:46:00 AM
Attachments: [image001.png](#)

Ms. Harrell,

This is an information request:

- ***As previously stated during pre-NDA preliminary meetings comments dated 31October2014, support for the approval of oral methylalntrexone bromide would require the results of the prespecified analyses supporting the proposed dose to first be statistically valid, allowing for evaluation of key secondary analyses of interest for purposes of ultimately approving and labeling the product. In addition, the results of these key analyses of clinical endpoints considered suitable for purposes of labeling would need to be robust (e.g., analyses comparable to the analyses presented in subcutaneous methylalntrexone product labeling for the indication of OIC in chronic pain.)***
- ***During our review, we note that in your oral program, the secondary endpoint, which is the primary endpoint used in your subcutaneous trial (i.e., proportion of patients with ≥ 3 SBMs per week during the 4-week double blind period), did not support the drug's efficacy with nominal statistical significance and you have not provided justification to support that your key analyses from MNTX3201 are comparable to the analyses presented in subcutaneous methylalntrexone product labeling for the indication of OIC in chronic pain.***
- ***Please address the above issue with thorough justification and statistical analyses when needed. We expect to receive your response by 3/10/2016.***

Jay

James B Carr, MPAS, PA-C

CDR, US Public Health Service
Regulatory Health Project Manager
CDER/OND/ODEIII
Division of Gastroenterology and Inborn Errors Products
CDER/FDA

(240) 402-6624 (office)

(301) 796-9904 (fax)

James.Carr@fda.hhs.gov



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/s/

JAMES B CARR
03/04/2016

From: Carr, James
To: ["Harrell, Mary E"](#)
Subject: NDA 208271 Relistor-Statistical Information Request 3.3.2016
Date: Thursday, March 03, 2016 7:41:00 AM
Attachments: [image001.png](#)

Ms. Harrell,
This is an information request:

- As noted in our IR of Jan 29, 2016, we have identified numerous inconsistencies in your data and we have been unable to reproduce your efficacy results. As previously requested, you must submit your efficacy results for the primary endpoint and key secondary endpoints according to the specifications in the Statistical Analysis Plan. In addition, conduct subgroup analyses for gender, geographical area or regional effects, and race subgroups accordingly. These results and analyses should be submitted by next Thursday, March 10, 2016.

Jay

James B Carr, MPAS, PA-C

CDR, US Public Health Service
Regulatory Health Project Manager
CDER/OND/ODEIII
Division of Gastroenterology and Inborn Errors Products
CDER/FDA

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JAMES B CARR
03/03/2016

From: Carr, James
To: [Harrell, Mary E](#)
Subject: NDA 208271 Relistor-Salix ClinPharm Information Request 2.16.16
Date: Tuesday, February 16, 2016 12:44:00 AM
Attachments: [image001.png](#)

Ms. Harrell,

This is an information request please respond by 2.18.16:

We could not locate the following bioanalytical validation report/in study bioanalytical reports. If you have already submitted these reports, please assist us locating them in the submission. If not, please submit them within 2 business days.

- Bioanalytical validation report (b) (4) 10-0301 addendum 1 that demonstrate the long term storage stability of N-Methylnaltrexone in human plasma at -70°C for 259 days and at -20°C for 365 days.
- Bioanalytical study report for measuring plasma concentration of N-Methylnaltrexone in study MNPk1118. It appears that you have only submitted the bioanalytical reports for measuring the urine concentration of N-Methylnaltrexone and plasma concentration of metabolites Methyl-6 α -Naltrexol, Methyl-6 β -Naltrexol, and Sulfate-Methyl-Naltrexone.
- In Bioanalytical validation report (b) (4) 107-0308 "LC/MS/MS Assay Validation of N-Methylnaltrexone in Human Urine", you have indicated that the long-term frozen stability of N-methylnaltrexone in human urine at -70°C will be assessed at a later date and an addendum to the report will be provided. In bioanalytical study report for study MNPk 1004 and study MNPk1118, you have stated that the long term stability of N-Methylnaltrexone in human urine has been established for 613 days at -70°C and for 366 days at -20°C. We could not locate any supporting validation data to demonstrate the long term stability of N-Methylnaltrexone in human urine for 613 days at -70°C and for 366 days at -20°C in the submission.
- In Bioanalytical validation report (b) (4) Study report 388-1502, you have indicated that the long-term storage stability of methyl-6 α -naltrexol, methyl-6 β -naltrexol, and sulfate-methyl-naltrexone in K2EDTA human plasma at -20°C will be assessed at a later date, and data will be provided in an amendment to this report. We could not locate a study report that contains the supporting stability data of these metabolites at -20°C.

Jay

James B Carr, MPAS, PA-C

CDR, US Public Health Service

Regulatory Health Project Manager

CDER/OND/ODEIII

Division of Gastroenterology and Inborn Errors Products

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/s/

JAMES B CARR
02/16/2016

From: Carr, James
To: [Harrell, Mary E](#)
Subject: NDA 208271 Relistor-Salix Information Request Clinical 2.8.16
Date: Monday, February 08, 2016 1:02:00 PM
Attachments: [image001.png](#)

Ms. Harrell,

Below is another clinical information request, please send response by February 10, 2016.

In reference to the table 14.1.6.3.e, please clarify the laxatives used in each category

- Rescue laxative medication
- Other laxative use

using CMDECOD (concomitant medication standardized medication name) . For example, was bisacodyl used as both a Rescue Laxative and an Other laxative? Please fill the document below for the following time periods:

- a. Prescreening
- b. QD dosing period (Days 0-28)
- c. PRN dosing period (Days 29-84)
- d. After day 84 (follow-up)

Prescreening		QD dosing period (Days 0-28)		PRN dosing period (Days 29-84)		After day 84 (follow-up)	
Rescue Laxative	Other laxative	Rescue Laxative	Other laxative	Rescue Laxative	Other laxative	Rescue Laxative	Other laxative
Bisacodyl	Etc Etc etc	Bisacodyl		Bisacodyl			

In the data submitted in Table 14.1.6.3e, the percentages and numbers in the **Prescreening period** were identical to the **After day 84 period** (see table below). Please clarify how many patients were evaluated in the Follow-up period and why these statistics are identical.

Clarify how the **After day 84 period** accounted for drop outs or subjects who did not make it through the entire study to day 84.

	MNTX 150 mg n (%)	MNTX 300 mg n (%)	MNTX 450 mg n (%)	Placebo n (%)
Pre-Screening	N=201	N=201	N=200	N=201
Rescue Laxative Medications	129 (64.2%)	133 (66.2%)	122 (61.0%)	136 (67.7%)

Other Laxative use	192 (95.5%)	191 (95.0%)	194 (97.0%)	195 (97.0%)
Total	198 (98.5%)	197 (98.0%)	197 (98.5%)	197 (98.0%)
QD dosing period (Days 0-28)	N=201	N=201	N=200	N=201
Rescue Laxative Medications	90 (44.8%)	95 (47.3%)	98 (49.0%)	100 (49.8%)
Other Laxative use	0 (64.2%)	1 (0.5%)	0	0(64.2%)
Total	90 (44.8%)	95 (47.3%)	98 (49.0%)	100 (49.8%)
PRN dosing period (Days 29-84)	N=167	N=181	N-169	N=167
Rescue Laxative Medications	80(45.2%)	72 (39.8%)	67 (39.6%)	76 (45.5%)
Other Laxative use	3 (1.7%)	1(0.6%)	5 (3.0%)	0
Total	76(45.5%)	73 (40.3%)	71 (42.0%)	76 (45.5%)
After day 84 (follow-up)	N=201	N=201	N=200	N=201
Rescue Laxative Medications	129(64.2%)	133 (66.2%)	122 (61.0%)	136 (67.7%)
Other Laxative use	192 (95.5%)	191 (95.0%)	194 (97.0%)	195 (97.0%)
Total	198 (98.5%)	197 (98.0%)	197 (98.5%)	197(98.0%)

Source: IR response from Applicant 5 February 2016. Table 14.1.6.3.e

Jay

James B Carr, MPAS, PA-C

CDR, US Public Health Service
Regulatory Health Project Manager
CDER/OND/ODEIII
Division of Gastroenterology and Inborn Errors Products
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JAMES B CARR
02/08/2016

Strongin, Brian K

From: Strongin, Brian K
Sent: Friday, January 29, 2016 1:48 PM
To: 'Mary_harrell@bausch.com'
Cc: Strongin, Brian K
Subject: Information Request for NDA 208271 Methylnaltrexone Bromide

Please respond to the following information request by COB 2/5/16

1. Provide the pre-specified definition for rescue-free bowel movement.
2. Provide a summary table of laxative use in the ITT population during study MNTX3201, as shown in the shell table below, for each of the following study periods.
 - a. Prescreening
 - b. QD dosing period (Days 0-28)
 - c. PRN dosing period (Days 29-84)
 - d. After day 84 (follow-up)

	Placebo (N)	MNTX150 mg (N)	MNTX 300mg (N)	MNTX 450 mg (N)	Total (N)
Rescue Laxative Use (including constipation medication) n (%)					
Other Laxative Use (including general concomitant medication) n(%)					
Total n (%)					

3. Clarify how "other laxative use" (including general concomitant medication) was accounted for in your efficacy analyses? In other words, could patients have a "RFBM" if they used a laxative not classified as a rescue laxative?
 - a. In case the proportion of subjects responding to study drug (responder/non-responder status) is affected by the "other laxative use", please identify those patients and provide the results of the efficacy analysis (re-analysis) using the new dataset.

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BRIAN K STRONGIN
02/04/2016

From: Carr, James
To: "[Harrell, Mary E](#)"
Subject: NDA 208271 Relistor-Information Request 2.1.16 DAAAP Clinical IR
Date: Monday, February 01, 2016 8:15:00 AM
Attachments: [image001.png](#)

Good Morning Ms. Harrell,

The following is an information request is needed by COB February 4, 2016.

With regard to subjects who experienced opioid withdrawal/drug withdrawal (Investigator-identified or DSM-V criteria):

- **Provide narratives for subjects MNTX3201-080-017, MNTX3201-054-017, and 2202-027-1173.**
- **Clarify if there are typographical errors for the following (as the Subject IDs are reported different ways in the ISS):**
 - **Subject MNTX3201 001-010 or 001-011. A narrative was submitted for Subject 001-011. No narrative was submitted for Subject 001-010. If this is not a typo, submit the narrative for Subject 001-010.**
 - **Subject 0200-115-5835 or 0200-115-3835. If this is a typographical error, submit the narrative for the correct subject (s).**

If these narratives are already included in the submission, identify where they may be found for these subjects. All narratives should include total Objective Opioid Withdrawal Scale/Subjective Opioid Withdrawal Scale (OOWS/SOWS) scores, pain intensity scores, and outcome.

Jay

James B Carr, MPAS, PA-C

CDR, US Public Health Service
Regulatory Health Project Manager
CDER/OND/ODEIII
Division of Gastroenterology and Inborn Errors Products
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(240) 402-6624 (office)

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James.Carr@fda.hhs.gov



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/s/

JAMES B CARR
02/01/2016

From: Carr, James
To: ["Harrell, Mary E"](#)
Subject: NDA 208271 Relistor-Salix Clinical Information Request 12.23.15
Date: Wednesday, December 23, 2015 2:15:00 PM
Attachments: [image001.png](#)

Ms. Harrell,

Below is a Clinical Information Request, please respond no later than Monday January 4, 2016.

- **Provide case report forms and narratives for all GI adverse events in Study MNOC1111.**

Jay

James B Carr, MPAS, PA-C

LCDR, US Public Health Service
Regulatory Health Project Manager
CDER/OND/ODEIII
Division of Gastroenterology and Inborn Errors Products
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(240) 402-6624 (office)

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JAMES B CARR
12/23/2015

From: Carr, James
To: ["Harrell, Mary E"](#)
Subject: NDA 208271 Relistor-Salix Information Request Clinical Pharmacology 12.8.15
Date: Tuesday, December 08, 2015 4:22:00 PM
Attachments: [image001.png](#)

Ms. Harrell,

This is a Clinical Pharmacology information request please have response by 12.21.2015:

- Reconduct your exposure-response analysis (for laxation with 4 hrs) using data from only the relevant/indicated population (OIC from non-cancer pain).
- Conduct a similar exposure-response analysis for your key secondary endpoint compared to that done for your primary efficacy endpoint:

“Responder endpoint: Proportion of subjects who responded to study drug during Weeks 1 to 4, where a responder is defined as ≥ 3 RFBM/week, with an increase of ≥ 1 RFBM/week over baseline, for ≥ 3 out of the first 4 weeks of the treatment period. “

The analysis should test both Cmax and AUC as metrics of methylnaltrexone exposure. This analysis should also be performed in only the relevant/indicated population (OIC from non-cancer pain).

- For both of the above analyses use the established exposure-response relationship to simulate the dose-response for each study used in the analysis and for the phase three trial MNTX3201.

Jay

James B Carr, MPAS, PA-C

LCDR, US Public Health Service
Regulatory Health Project Manager
CDER/OND/ODEIII
Division of Gastroenterology and Inborn Errors Products
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JAMES B CARR
12/08/2015

From: Carr, James
To: "[Harrell, Mary E](#)"
Subject: NDA 208271 Relistor- Salix Information Request Statistical 12.4.5
Date: Friday, December 04, 2015 9:14:00 PM
Attachments: [image001.png](#)

Ms. Harrell,

The below is an information request from the statistical team. We would like a response as soon as possible but no later than December 11, 2015.

- We are in the process of confirming your derived/analysis data from the raw data provided for Study 3201. We are unable to re-produce your analysis results for the key secondary endpoint, the "Responder Analysis (responder/non-responder) to study drug during Weeks 1 to 4, where responder is defined as having ≥ 3 RFBM/week, with at least 1 RFBM/week increase over baseline, for at least 3 out of the first 4 weeks".
- Please specify which one of the variables in your dataset "EFF" is this (mentioned above) responder variable. Also, please provide your **step by step** algorithm for deriving to this variable. Please include clear explanations of your algorithm and the purpose of the variables used from the raw in a text document and not in a SAS code.
- At each step, provide the variable name in the SAS data that you used, along with the corresponding meaning of that variable name.

Jay

James B Carr, MPAS, PA-C

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Regulatory Health Project Manager
CDER/OND/ODEIII
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JAMES B CARR
12/05/2015

From: Carr, James
To: ["Harrell, Mary E"](#)
Subject: NDA 208271 Relistor-Salix Information Request Clinical Pharmacology 12.3.15
Date: Thursday, December 03, 2015 9:01:00 PM
Attachments: [image001.png](#)

Ms. Harrell,

This is an information request that pertain to clinical pharmacology, please send response by close of business December 11, 2015.

1. **Study MNOC111 appeared to show an increased incidence of GI adverse events in the to-be-marketed formulation (film coated (b)(4) compared to the phase 3 formulation ((b)(4)). In analysis of the total 17 GI AEs in the provided dataset we noted 7 subjects (for a total of 12 AEs) who ingested the (b)(4) formulation, 2 subjects (for a total of 4 AEs) who ingested the (b)(4) formulation, and 1 subject who ingested placebo (report of 1 AE). Please explain the observed safety differences between these two formulations.**
2. **In your current submission, there is no mass balance study with oral administration nor are there other data to link oral formulation to the results of the mass balance study with the IV formulation. In addition, the recovery from the IV mass balance study was low (~70%) to a have meaningful interpretation. Please describe how you will label the oral product in regard to metabolism/elimination and excretion.**
3. **As requested previously in an IR dated 08/07/2015, in order to facilitate our analysis, for pharmacokinetic parameter datasets for all clinical pharmacology studies (i.e., study MNPK1001, MNOC1111, MNPK1004, MNFE1001, MNPK 1114, MNPK 1117, MNPK 1118), please place each PK parameter in a distinct column. In addition, the PK parameter dataset should also include subject ID, treatment, period, and sequence in different columns. Please see below examples for format (PK parameters should not be limited to the ones in the example table).**

Study ID	Subject ID	treatment	Period	Sequence	Cmax	Tmax	AUCt	AUCinf	CL	V	Tlag
X	1	Formulation A	1	AB							
X	1	Formulation B	2	AB							
X	2	Formulation B	1	BA							
X	2	Formulation A	2	BA							

4. **For all concentration time profile dataset in all clinical pharmacology studies (i.e., study MNPK1001, MNOC1111, MNPK1004, MNFE1001, MNPK 1114, MNPK 1117, MNPK 1118), please include the treatment (e.g., formulation and dose) information.**

Jay

James B Carr, MPAS, PA-C
LCDR, US Public Health Service
Regulatory Health Project Manager
CDER/OND/ODEIII
Division of Gastroenterology and Inborn Errors Products

CDER/FDA

(240) 402-6624 (office)

(301) 796-9904 (fax)

James.Carr@fda.hhs.gov



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/s/

JAMES B CARR
12/03/2015

From: Carr, James
To: [Harrell, Mary E](#)
Subject: NDA 208271 Relistor-Salix Information Request Clinical 12.3.15
Date: Thursday, December 03, 2015 12:24:00 PM
Attachments: [image001.png](#)

Ms. Harrell,

This is an information request please send response to no later than one week from receipt.

Provide AE incidence tables for AEs of abdominal pain, hypertension, hypotension, and tachycardia for the SC MNTX 3356 study, using a broad search of these MedDRA terms, specifically:

- abdominal pain should include the following terms: abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, and abdominal tenderness
- hypertension should include the following terms: hypertension, blood pressure systolic increased, blood pressure increased
- hypotension should include the following terms: hypotension, blood pressure decreased
- tachycardia should include the following terms: tachycardia, heart rate increased

Jay

James B Carr, MPAS, PA-C

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JAMES B CARR
12/03/2015

From: Carr, James
To: ["Lomri, Zohra"](#)
Subject: NDA 208271 Relistor Information Request 11.10.15
Date: Tuesday, November 10, 2015 11:14:00 AM
Attachments: [image001.png](#)

Ms. Lomri,

This is an information request please respond no later than one week from receipt.

- Please send a summary of the protocol deviations with the Unique Subject Identifier in study (MNTX3201) categorized by:
 - Dosage arm
 - Treatment period (QD vs. PRN)
- We have reviewed the 537 page document 16.2.2 (Protocol Deviations) associated with Study MNTX3201 Clinical Study Report. Clarify how this information is reflective of the numbers presented in Table 7 of the MNTX3201 CSR (page 63).
- Please provide individual tables subgroup analyses for the key secondary efficacy endpoint #1 for the following subgroups:
 - Age (<40, 40-65; >65)
 - Gender
 - Race
 - Baseline opioid dosage
 - Low (<84.7 mg/day),
 - medium (84.7- <145 mg/day)
 - high (145 - < 260 mg/day)
 - very high (>= 260 mg/day).

Jay

James B Carr, MPAS, PA-C

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/s/

JAMES B CARR
11/10/2015

From: Carr, James
To: ["Lomri, Zohra"](#)
Subject: NDA 208271 Relistor-Information Request 10.14.15
Date: Wednesday, October 14, 2015 9:49:00 AM
Attachments: [image001.png](#)

Ms. Lomri,
Another Information Request for this application. Please respond no later than a week from the day of receipt.

- **How many individuals were screened for study MNTX3201 prior to the enrollment of 804 subjects? Is this data available based upon study site, or any other stratification?**

Jay

James B Carr, MPAS, PA-C

LCDR, US Public Health Service
Regulatory Health Project Manager
CDER/OND/ODEIII
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/s/

JAMES B CARR
10/14/2015

From: Carr, James
To: ["Lomri, Zohra"](#)
Subject: NDA 208271 Relistor-Salix Information Request DAAAP 10.7.15
Date: Wednesday, October 07, 2015 8:40:00 AM
Attachments: [image001.png](#)

Ms. Lomri,

The consultants have sent forward this information request. I asked that be addressed no later than 1 week upon receipt, keeping in mind that there is a holiday next week extend that to Friday of next week:

- **In the CSR for Study MNTX3201, you report that five MNTX-treated subjects and no placebo-treated subject had opioid withdrawal according to DSM-V criteria, if GI symptoms were included in the analysis, and provided a link to Listing 16.2.7.1 for line listings.**
- **Provide narratives, including patient ID, for the five MNTX-treated subjects who experienced opioid withdrawal using the DSM-V criteria.**

Jay

James B Carr, MPAS, PA-C

LCDR, US Public Health Service
Regulatory Health Project Manager
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/s/

JAMES B CARR
10/07/2015

From: Carr, James
To: ["Lomri, Zohra"](#)
Subject: NDA 208271 Relistor General Advice
Date: Monday, September 21, 2015 8:10:00 AM
Attachments: [image001.png](#)

Ms. Lomri,

Per our conversation last week. Here is one comment for advice. The other may be a couple of weeks to answer from clinical pharmacology.

- Please provide a recommendation in Section 8.7 for patients severe hepatic impairment who may need to be treated with the injectable formulation based upon what is known about injection in patients with less severe impairment, the PK changes seen with the oral formulation in patients with moderate and severe impairment, and the overall safety profile of the drug. If no specific dosing adjustment can be provided, then consider a statement such as "Avoid use of RELISTOR in patients with severe hepatic impairment" or "Monitor patients with severe hepatic impairment for methylnaltrexone-related adverse reactions..."

Jay

James B Carr, MPAS, PA-C

LCDR, US Public Health Service
Regulatory Health Project Manager
CDER/OND/ODEIII
Division of Gastroenterology and Inborn Errors Products
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JAMES B CARR
09/21/2015

From: Carr, James
To: ["Lomri, Zohra"](#)
Subject: NDA 208271 Relistor-Information Request 9.15.15
Date: Wednesday, September 16, 2015 9:01:00 AM
Attachments: [image001.png](#)

Ms. Lomri,

This is an information request:

- Please provide and confirm the dates of all protocol amendments and the date of data lock for Study MNTX3201.

Jay

James B Carr, MPAS, PA-C

LCDR, US Public Health Service
Regulatory Health Project Manager
CDER/OND/ODEIII
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JAMES B CARR
09/16/2015

From: Carr, James
To: ["Michael Adam"](#)
Subject: NDA 208271 Relistor Information Request 9.16.15
Date: Wednesday, September 16, 2015 8:54:00 AM
Attachments: [image001.png](#)

Mr. Adams,

This is an information request:

- Please provide and confirm the dates of all protocol amendments and the date of data lock for Study MNTX3201.

Jay

James B Carr, MPAS, PA-C

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/s/

JAMES B CARR
09/16/2015



NDA 208271

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Salix Pharmaceuticals, Inc.
Attention: Zohra Lomri
Director, Regulatory Affairs
400 Somerset Corporate Boulevard
Bridgewater, New Jersey 08807

Dear Ms Lomri:

Please refer to your New Drug Application (NDA) dated June 19, 2015, received June 19, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Relistor (methylnaltrexone bromide tablets).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a) this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is April 19, 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by March 22, 2016.

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

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified labeling issues and have labeling comments or questions in the attached labeling. Please refer to the attached labeling.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by October 1, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

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

PROMOTIONAL MATERIAL

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

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

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

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

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call LCDR James Carr, Regulatory Project Manager, at (240) 402-6624.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DONNA J GRIEBEL
09/04/2015

From: [Nkah, Shila](#)
To: [Carr James](#)
Subject: Acknowledgment of Receipt - Bioequivalence Audit Request Consult- NDA 208271
Date: Friday, August 21, 2015 2:41:00 PM
Attachments: [OSI Bioequivalence Audit Request NDA 208271.pdf](#)

Dear James,
This email acknowledges receipt of the Bioequivalence Audit Request Consult for NDA 208271 submitted on August 19, 2015.

I am the OSIS PM assigned to this NDA.

The consult has been sent for assessment. I will be updating you on the site inspection decision as soon as the information is available.

Feel free to contact me if you have any questions.

Thank you.

Shila Nkah, M.S.

Project Manager

Office of Study Integrity & Surveillance

Office of Translational Sciences

Center for Drug Evaluation and Research

Food & Drug Administration

White oak Bldg. 51, Rm. 5318

Phone: (301)-796-8347

Email: shila.nkah@fda.hhs.gov

Please consider the environment before printing this e-mail.

From: oasfda@fda.gov [mailto:oasfda@fda.gov]
Sent: Wednesday, August 19, 2015 3:56 PM
To: CDER OSI; Bashaw, Edward D; Carr, James; ddrdsi@cdcr.fda.gov; ct.viswanathan@fda.hhs.gov; CDER OSIS BEQ
Subject: Finalized - NDA 208271 Biopharmaceutical Inspections Request (FRM-CONSULT-09)



[Proceed to DARRTS Welcome Screen](#)

Finalized - Biopharmaceutical Inspections Request (FRM-CONSULT-09)

The following communication has been signed and finalized.

Functions

Communication	Communication Group	Communication Name
FRM-CONSULT-09	CONSULT	Biopharmaceutical Inspections Request

Linked Submissions

Application Type and Number	Sponsor	Preferred Product Name	Submission Type and Number	Submission Classification	Group ID
NDA-208271	SALIX PHARMACEUTICALS	METHYLNALTREXONE	ORIG-1	Unknown	

Reference ID: 3812972

INC

BROMIDE

Signers

Signer

CARR, JAMES B.

BASHAW, EDWARD D.

Proxy Signer

Signed Status

signed

signed

Signed Date

08/19/2015

08/19/2015

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/s/

SHILA S NKAH
08/28/2015

From: Carr, James
To: ["Lomri, Zohra"](#)
Subject: NDA 208271 Relistor-Salix Information Request 8-20-15
Date: Friday, August 21, 2015 9:13:00 AM
Attachments: [image001.png](#)

Zohra-this is an information request, please get this back to us as soon as possible.

Jay

Concerning Protocol MNTX3201 entitled, "A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of Oral Methylnaltrexone for the Treatment of Opioid-Induced Constipation in Subjects with Chronic, Non-Malignant Pain":

1. To facilitate our understanding of how subject symptom data was used to determine response, recurrence, and eligibility, and was transmitted from the Interactive Voice System (IVRS) during the clinical trial and prepared for submission to the Agency, please provide a flow diagram and narrative that tracks the course of data generated by the subject using the IVRS. Please describe how the data was collected, transmitted and reviewed. This should include a description concerning data reviewed by the clinical investigator during the trial, data that was used to populate the case report form (CRF) and data that was used for analysis. The diagram should identify who was responsible for each step in the process; including description of what entity (e.g. clinical investigator, automatic population from IVRS, calculation from sponsor program, etc.) was responsible for calculation of eligibility and determination of response. Please note specific points in dataflow where an audit trail exists.
2. Please provide a flow diagram and narrative that tracks the course of the IVRS data to the clinical investigator (CI) for archiving at the end of the trial so that the CI will be able to fulfill the responsibilities under 21CFR312.62.
3. Provide the name of the CRO, if any, responsible for the:
 - a. IVR system for the diary data.
 - b. IVR system for the randomization and treatment dispensing.
4. Provide the location or locations of the documents related to the information request above (e.g. in clinical trial file at sponsor site, at CRO, etc.) and the location of the diary data (e.g. at clinical investigator site, sponsor site, at CRO, etc.)
5. Submit the Patient diary guide for both the paper and electronic diaries. Provide a copy of the paper diary.
6. For each of the revisions in the Protocol Amendments 2 to 4 please provide the specific:
 - a. Changes to the inclusion and exclusion criteria
 - b. Revisions to the prohibited medications and rescue medication procedures
 - c. Revisions to study assessments and visit procedures
 - d. Clarification of the definition of constipation (amendment 4).

James B Carr, MPAS, PA-C

LCDR, US Public Health Service
Regulatory Health Project Manager
CDER/OND/ODEIII
Division of Gastroenterology and Inborn Errors Products
CDER/FDA

(240) 402-6624 (office)

(301) 796-9904 (fax)

James.Carr@fda.hhs.gov



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/s/

JAMES B CARR
08/24/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208271

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Salix Pharmaceuticals, Inc.
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

ATTENTION: Zohra Lomri,
Director, Regulatory Affairs

Dear Ms. Lomri:

Please refer to your New Drug Application (NDA) dated and received June 19, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Methylnaltrexone Bromide Tablets, 150 mg.

We also refer to your correspondence, dated and received July 2, 2015, requesting review of your proposed proprietary name, Relistor.

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

If any of the proposed product characteristics as stated in your July 2, 2015 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Aleksander Winiarski, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5295. For any other information regarding this application, contact James Carr, Regulatory Project Manager in the Office of New Drugs, at (240) 402-6624.

Sincerely,

{See appended electronic signature page}

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

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/s/

TODD D BRIDGES
08/12/2015



NDA 208271

INFORMATION REQUEST

Salix Pharmaceuticals
Attention: Zohra Lomri
Director, Regulatory Affairs
400 Somerset Corporate Boulevard
Bridgewater, New Jersey 08807

Dear Ms. Lomri:

Please refer to your New Drug Application (NDA) for Relistor (methylnaltrexone bromide) Tablets dated 06/19/2015, submitted under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act and 21 CFR §314.50.

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

Statistics

1. Please provide the raw data based on the subjects diary report (CRF) and the appropriate SAS programs that would allow us to verify the derivation of the primary efficacy endpoint (average percentage of the days that resulted in RFBM) and patients' inclusion/exclusion criteria.

Clinical Pharmacology

Please provide response to items 2-4 within 3-5 business days and items 5 within 10 business days.

2. All bioanalytical validation reports that support the PK studies in this NDA submission should be included in the in the NDA submission. We could not locate the following bioanalytical validation reports that you refer to in your NDA submission. Please submit these bioanalytical validation reports and all associated amendment and addendums. If you have already submitted, please assist us locating the reports.
 - (b) (4) 107-0308: "LC/MS/MS Assay Validation of N-Methylnaltrexone in Human Urine"
 - (b) (4) 107-0301: "LC/MS/MS Assay Validation of N-Methylnaltrexone in Human Plasma"
3. We could not locate the PK/PD datasets for NDA 208271. Please submit all the datasets, program codes, definition files associated with the PK/PD modeling reports. If you have

already submitted, please point us to the exact location in the EDR. For general expectations for submitting pharmacometric data and models, please refer to:

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>

4. The following in-vitro studies could not be located in your NDA submission module 4.2.2.3 and 4.2.2.4. Please submit these study reports. If you have already submitted, please assist us locating the reports.
 - Study XT128007
 - Study XT125033
 - Study XT123038
5. In order to facilitate our analysis, please put each PK parameters in different columns in PK parameter dataset in all clinical pharmacology studies. In addition, the PK parameter dataset should also include subject ID, treatment, period, and sequence in different columns.

Pediatrics (iPSP)

Please provide response to item within 3-5 business days.

6. Since this application triggers PREA, you are required to submit an initial pediatric study plan (iPSP). Failure to do so may lead to a refuse-to-file decision. Please refer to: *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>
7. The iPSP section requesting a waiver should include justification with a summary of supporting data, for all age groups for which the waiver will be sought.

We request a prompt written response in order to continue our evaluation of your NDA. If you have any questions, please contact James Carr, MPAS, PA-C, Regulatory Project Manager, at (240) 402-6624.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., MBA
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BRIAN K STRONGIN
08/07/2015

From: Carr, James
To: "[Lomri_Zohra](#)"
Subject: NDA 208271 Relistor-Salix Information Request
Date: Thursday, July 09, 2015 11:12 00 AM
Attachments: [image001.png](#)

Ms. Lomri-please see below request and respond by August 9th, 2015 or sooner:

On December 4, 2014, the Food and Drug Administration published the "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling," also known as the Pregnancy and Lactation Labeling Rule (PLLR) (79 FR 72064). The PLLR went into effect on June 30, 2015. According to PLLR, Risk Summary statements for sections 8.1 (Pregnancy), 8.2 (Lactation), and 8.3 (Females and Males of Reproductive Potential) must be based on available human and nonclinical data. The Risk Summary must also state when there are no human data or when available human data do not establish the presence or absence of drug-associated risk (21 CFR 201.57(c)(9)(i)(B)(1)).

During our preliminary review of your submitted labeling, we found that you have not provided the information to support the labeling content for sections 8.1, 8.2, and 8.3 of the labeling.

We request that you resubmit labeling that complies with PLLR and provide a review and summary of the available published literature, as well as a review and summary of reports from your pharmacovigilance database, with regard to RELISTOR use in pregnancy and lactation. The resubmission should address these issues by August 9, 2015. The revised labeling will be used for further labeling discussions. Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

Jay

James B Carr, MPAS, PA-C

LCDR, US Public Health Service
Regulatory Health Project Manager
CDER/OND/ODEIII
Division of Gastroenterology and Inborn Errors Products
CDER/FDA

(240) 402-6624 (office)
(301) 796-9904 (fax)
James.Carr@fda.hhs.gov



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/s/

JAMES B CARR
07/09/2015



NDA 208271

NDA ACKNOWLEDGMENT

Salix Pharmaceuticals, Inc.
Attention: Zohra Lomri
Director, Regulatory Affairs
400 Somerset Corporate Boulevard
Bridgewater, New Jersey 08807

Dear Ms. Lomri:

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

Name of Drug Product: Relistor (methylnaltrexone bromide tablets)

Date of Application: June 19, 2015

Date of Receipt: June 19, 2015

Our Reference Number: NDA 208271

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 18, 2015 in accordance with 21 CFR 314.101(a)

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

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

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

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

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

If you have any questions, call LCDR James Carr, Senior Regulatory Project Manager, at (240) 402-6624.

Sincerely,

{See appended electronic signature page}

LCDR James Carr, MPAS, PA-C
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

JAMES B CARR
06/22/2015



IND 067452

MEETING REQUEST CANCELLED

Salix Pharmaceuticals, Inc.
Attention: Benjamin M. Burgin, RAC
Associate Director, Regulatory Affairs
8510 Colonnade Center Drive
Raleigh, NC 27615

Dear Mr. Burgin:

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

We also refer to your November 3, 2014, communication requesting cancellation of the meeting we scheduled on November 4, 2014, in response to your September 9, 2014, meeting request because Salix has determined that the Division's preliminary comments are sufficient at this time and will contact the Division if additional discussion is necessary. The November 4, 2014, meeting has been cancelled.

If you have any questions, call me, Regulatory Project Manager at (301) 796-5343.

Sincerely,

{See appended electronic signature page}

CDR Matthew Brancazio, Pharm.D.
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

MATTHEW B BRANCAZIO
11/04/2014



IND 067452

MEETING PRELIMINARY COMMENTS

Salix Pharmaceuticals, Inc.
Attention: Benjamin M. Burgin, RAC
Associate Director, Regulatory Affairs
8510 Colonnade Center Drive
Raleigh, NC 27615

Dear Mr. Burgin:

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

We also refer to your September 9, 2014, correspondence, received August 9, 2014, requesting a meeting to discuss Salix's plans for submitting an sNDA for MNTX 150 mg oral tablets based on a change in formulation (SC injection to oral tablet). Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me, Regulatory Project Manager, at (301) 796-5343.

Sincerely,

{See appended electronic signature page}

CDR Matt Brancazio, Pharm.D.
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: November 4, 2014 at 2:00-3:00 pm EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: 067452
Product Name: Methylnatrexone
Indication: For the treatment of OIC in patients with NCP
Sponsor/Applicant Name: Salix Pharmaceuticals, Inc.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for November 4, 2014, 2:00-3:00 pm EST, at 10903 New Hampshire Avenue, White Oak Building 22, Conference Room: 1415, Silver Spring, Maryland 20903 between Salix Pharmaceuticals, Inc. and the Division of Gastroenterology and Inborn Errors Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Methylnaltrexone bromide (MNTX), a selective mu-opioid receptor antagonist, is a quaternary derivative of the opioid antagonist, naltrexone. MNTX is designed to block undesired adverse effects of opioid pain medications, such as constipation, mediated predominately by the

peripherally located opioid receptors, while sparing the desired centrally mediated analgesic effect. MNTX provides a specific treatment for opioid-induced constipation, targeted at the root cause. The purpose of the meeting is to discuss Salix's plans for submitting an sNDA for MNTX 150 mg oral tablets based on a change in formulation (SC injection to oral tablet). Salix is seeking Agency feedback and approval for the oral tablets formulation use data from SC formulation. The Agency has previously met with Salix regarding this sNDA on March 7, 2012, and June 26, 2006.

2.0 DISCUSSION

2.1. Clinical/Statistical

Question 1: *Based on the efficacy and safety of SC MNTX in OIC in non-cancer pain patients (Studies 3356 and 3358), comparability of pharmacokinetic/pharmacodynamic relationships for SC and oral MNTX, and demonstrated efficacy of the oral MNTX formulation (Study 3201), does the Division concur that these data establish sufficient basis for submission and substantive review of the proposed sNDA for oral MNTX?*

FDA Response to Question 1:

As noted by FDA during our March 7, 2012 meeting, current standards for the design of trials for new drugs to treat OIC in NCP have changed since the completion of the trials listed above. However, we acknowledge that, as described in the label, Relistor SC was approved based on a primary endpoint of the proportion of patients with ≥ 3 spontaneous bowel movements (SBMs) per week during the 4-week double-blind period. In order for Study 3201 to support the approval of an oral Relistor formulation, the results of the prespecified analyses supporting the proposed dose would first need to be statistically valid, allowing for evaluation of key secondary analyses of interest for purposes of ultimately approving and labeling the product. The results of these key analyses of clinical endpoints considered suitable for purposes of labeling would need to be robust (e.g., analyses comparable to the analyses presented in subcutaneous methylnaltrexone product labeling for the indication of OIC in chronic pain). We do not agree that the prespecified primary endpoint of Study 3201 is appropriate for labeling as it does not adequately define an overall responder for a chronic condition and is likely not to be readily interpretable to patients or practitioners. These will be review issues during the NDA review if you choose to submit the completed single oral methylnaltrexone trial as the major trial supporting the NDA. Note that key support for this approach would be persuasive safety data indicating that the oral formulation is better tolerated than the SC formulation (i.e., evidence that you have identified an effective alternative oral dosing formulation with evidence of improved safety compared to the available SC formulation).

2.2. Clinical Pharmacology

Question 2: *In the meeting on March 7, 2012, the Division recommended that drug interaction potential via interaction with transporters be further addressed. Does the*

Division concur that studies XT128007, XT125033, and XT123038 address this recommendation?

FDA Response to Question 2:

It appears that you have addressed the potential interaction of parent drug methylnaltrexone as a substrate with all transporters. However, you only evaluated the potential of parent drug methylnaltrexone as an inhibitor with P-gp and BCRP. Please evaluate whether methylnaltrexone is an inhibitor of OCT2, OAT1, OAT3, OATP1B1, and OATP1B3 in vitro. In addition, please evaluate the potential interaction of methylnaltrexone metabolites with transporters in vitro.

2.3. Regulatory

Question 3: *Does the Division concur with the proposed* [REDACTED] (b) (4) ?

FDA Response to Question 3:

No, we do not agree [REDACTED] (b) (4)

Question 4: *Does the Division concur with the proposed sNDA eCTD submission strategy?*

FDA Response to Question 4:

From a technical standpoint, (not content related) yes, the proposed sNDA submission strategy is acceptable; however, please see general comments below:-

- The new Comprehensive Table of Contents (CTOC) and Hierarchy (dated:-2/14) should not be utilized until the new m1 is implemented. Instead, please refer to the Comprehensive Table of Contents (CTOC) and Hierarchy (dated:- 7/05), located at:- <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM315023.pdf>
- FDA FORM 3674 should reside under m1.2 cover letter section (not m1.1.4), with a clear leaf title
- Providing a single 3.2.S, section with attribute of "ALL" and differentiating documents by leaf title, is acceptable. The preferred method of differentiating documents is with clear and concise leaf titles that indicate the file's true content (e.g. manufacture-[REDACTED] (b) (4), manufacture-Mallinckrodt, etc.).

3.0 FDA ADDITIONAL COMMENTS

3.1 Regulatory

According to the bundling policy included in the guidance for industry, **Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees**: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf> :

Different dosage forms (see the Orange Book, Appendix C) should be submitted in separate original applications unless the products are identical (drugs) or alike (biological products) in quantitative and qualitative composition (e.g., a sterile liquid in a single dose vial that is intended for use as either an injectable or an inhalation solution).

3.2 Clinical Pharmacology

- Please address how you plan to label oral methylnaltrexone in patients with hepatic and renal impairment.
- Please re-evaluate the in-vitro data to determine the need for in vivo DDI studies for oral methylnaltrexone since this is a different route of administration.
- Due to potential pre-systemic drug interactions, you should address the applicability of the in vivo DDI data you have obtained from studies using the SC product.

3.3 Biopharmaceutics

- Provide a head to head comparison of the qualitative and quantitative composition of the (b) (4) formulation tablet formulation used in the Phase 3 study 3201 and the film-coated version of the (b) (4) tablet formulation (tested in Studies MNPk1114, MNPk1117, MNPk1118, and MNPk1001. If changes in the components and composition between the uncoated and film-coated (b) (4) tablet formulations are deemed major, a BE study will be required to bridge these two formulations.
- We have the following comments regarding the dissolution information that should be provided in your submission.
 1. **Dissolution Test:** Include the dissolution method development report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:
 - a. Solubility data for the drug substance covering the physiological pH range;
 - b. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution

- method as the optimal test for your product. If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable;
- c. Provide the complete dissolution profile data (individual, mean, SD, profiles) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim);
 - d. Data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products (aberrant formulations) that are intentionally manufactured with meaningful variations for the most relevant manufacturing variables (i.e., ± 10 -20% change to the specification-ranges of these variables). In addition, if available, submit data showing that the selected dissolution method is able to reject batches that are not bioequivalent; and
 - e. Supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).

2. Dissolution Acceptance Criterion: For the selection of the dissolution acceptance criterion of your product, the following points should be considered:

- a. The dissolution profile data (i.e., 10, 15, 20, 30, 45, and 60 minutes) from the pivotal clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criterion of your product (i.e., specification-sampling time point and specification value). The criterion should be based on average in vitro dissolution data for each lot under study, equivalent to USP Stage 2 testing (n=12).
- b. The in vitro dissolution profile should encompass the timeframe over which at least 85% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.
- c. For immediate release product the selection of the specification time point should be where $Q=(b)(4)\%$ dissolution occurs.

3.4 Statistical

- For the multiplicity adjustment method, you stated in your Meeting package that a truncated Hochberg procedure with parameter $r = 0$ for the hypotheses associated with the primary and first key secondary endpoints and $r = 1$ for the hypotheses associated with the second key secondary endpoint.

Please inform us when and where in the protocol, you pre-specified your proposed multiplicity adjustment method.

4.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

5.0 PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

6.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

7.0 Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

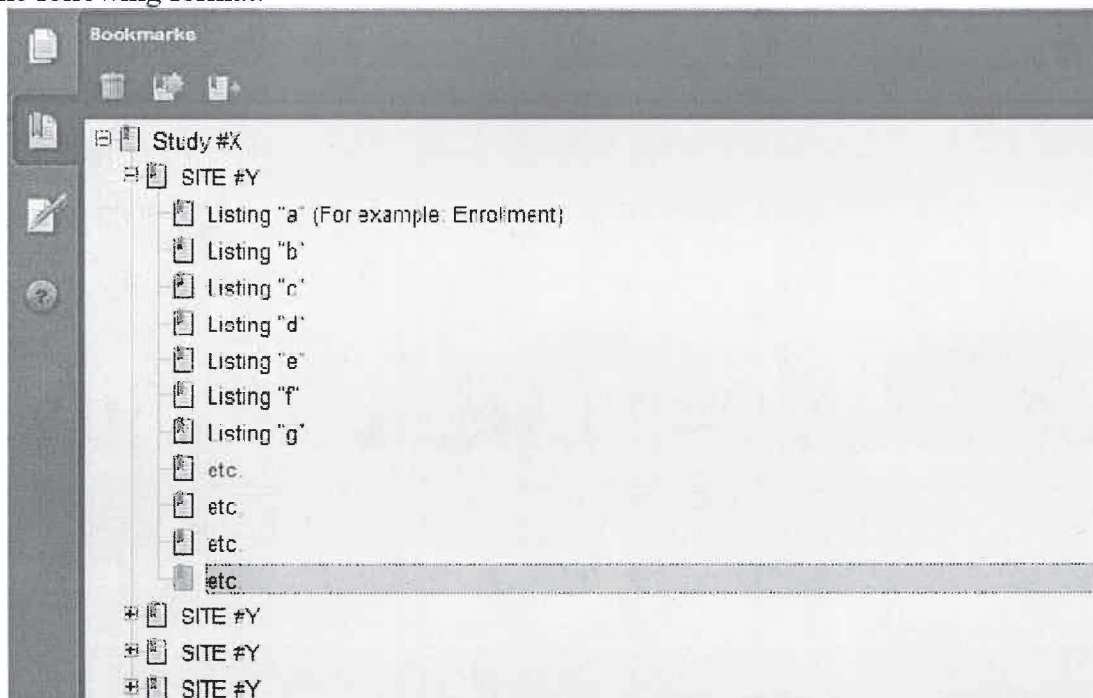
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:

- a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
 3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
 4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
 5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated

- b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to

voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

**Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format**

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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

/s/

MATTHEW B BRANCAZIO
10/31/2014



IND 067452

MEETING MINUTES

Salix Pharmaceuticals, Inc.
Attention: Benjamin Burgin
Senior Manager, Regulatory
1700 Perimeter Park Drive
Morrisville, NC 27560

Dear Mr. Burgin:

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

We also refer to the meeting between representatives of your firm and the FDA on March 7, 2012. The purpose of the meeting was to discuss a planned NDA submission.

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

If you have any questions, call me at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

Matthew Scherer, MBA
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA
Meeting Date and Time: March 7, 2012, 1:30 PM
Meeting Location: Building 22, Room 1313
Application Number: IND 067452
Product Name: Methylalntrexone bromide Tablets
Indication:
Sponsor/Applicant Name: Salix Pharmaceuticals
Meeting Chair: Rob Fiorentino, M.D., M.P.H.
Meeting Recorder: Elizabeth A.S. Ford, R.N.

FDA ATTENDEES

Andrew Mulberg, MD, FAAP, CPI, Deputy Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Rob Fiorentino, MD, M.P.H., Medical Team Leader, DGIEP
Helen Sile, MD, Medical Officer, DGIEP
Sushanta Chakder, PhD, Supervisory Pharmacologist, DGIEP
Tamal Chakraborti, PhD, Pharmacologist, DGIEP
Elizabeth A.S. Ford, R.N., Senior Regulatory Project Manager, DGIEP
Wen Jen Chen, Statistics Reviewer, Division of Biometrics III
Michael Welch, PhD, Deputy Director, Division of Biometrics III
Angelica Dorantes, PhD, Biopharmaceutics TL, Office of New Drug Quality Assessment (ONDQA)
Insook Kim, PhD, Clinical Pharmacologist, Division of Clinical Pharmacology III

SPONSOR ATTENDEES

Salix Pharmaceuticals, Inc.

William P. Forbes, Pharm.D. Executive Vice President, Medical, R&D and Chief Development Officer
Enoch Bortey, Ph.D. Vice President, Clinical Operations
Linda Young, R.Ph., J.D. Vice President, Regulatory Affairs

Joseph Lockhart	Associate Vice President, Pharmaceutical Development and Manufacturing
Bob Rolleri, Pharm.D.	Executive Director, Clinical Development
Pam Golden, Ph.D.	Executive Director, Nonclinical and Clinical Pharmacology
Shirley Huang	Associate Director, Biostatistics
Christopher Martin	Associate Director, QC Analytical Science
Benjamin Burgin	Senior Manager, Regulatory Affairs
Xianbin Tian, Ph.D.	Senior Manager, Nonclinical and Clinical Pharmacology
(b) (4) M.D.	Medical Consultant

Progenics Pharmaceuticals, Inc.

Ann Marie Assumma, M.S.	Vice President, Regulatory Affairs
Robert Israel, M.D.	Senior Vice President, Medical Affairs
Paul Maddon, M.D., Ph.D.	Chief Science Officer
Benedict Osorio, M.S., M.B.A.	Senior Vice President, Quality
Nitya Ray, Ph.D.	Senior Vice President, Manufacturing
Nancy Stambler, Dr. P.H.	Senior Director, Biometrics
Vivien Wong, Ph.D.	Vice President, Product Development

1. BACKGROUND

Methylnaltrexone is a mu-opioid receptor antagonist. Salix is developing methylnaltrexone tablets for the following indication (b) (4)

- Treatment of opioid induced constipation (OIC) in patients with non-cancer pain (b) (4)

Methylnaltrexone SC injection is currently approved for treatment of OIC in advanced illness patients (NDA 021964) and there is a pending efficacy supplement (NDA 021964/S010) to add the OIC in patients with non-cancer pain indication.

This pre-NDA meeting was granted on January 20, 2012. The background package was received February 9, 2012. Preliminary comments to the meeting questions were sent March 6, 2012.

2. DISCUSSION

2.1. CLINICAL

Question 1: Does the Agency concur that efficacy data from the phase 3 study 3201, double-blind efficacy study 3356, open-label study 3358, and additional supportive studies are sufficient to allow for a substantive review of this NDA?

FDA Response to Question 1:

No, we do not concur.

We have the following concerns regarding study 3201:

- **A clinically relevant endpoint was not evaluated over an adequate treatment duration (i.e. 12 weeks)**
- **Primary endpoint assessing RFBM within 4 hours of dosing is not acceptable**
- **The 150 mg dose regimen failed to demonstrate a positive result assessed by your primary endpoint based upon your proposed Hochberg multiplicity adjustment procedure**
- **Only the 450 mg dose regimen demonstrated a positive result assessed by an overall responder analyses and using the proposed Hochberg multiplicity adjustment procedure.**
- **Since not all three doses showed significant results and Hochberg procedure is not a separable procedure, no alpha level was left to test secondary endpoints.**

Because the definitive relative bioavailability between SC MNTX and the to-be-marketed oral formulation and the final dose for marketing is not available at this point, it is not clear whether efficacy and/or safety of SC MNTX 12 mg in patients with non-cancer pain could be supportive of the efficacy and/or long term safety of oral MNTX.

In addition, we note that the to-be-marketed formulation is different from the formulation used in study 3201 and will be manufactured at a different site. Bioequivalence should be

demonstrated between the to-be-marketed formulation and the phase 3 formulation. You should include appropriate bridging studies between the various oral formulations and the to-be-marketed formulation if studies conducted using other oral formulations are to be used to support safety and efficacy of the to-be-marketed formulation at the time of your NDA submission.

Given the above concerns, we recommend that you conduct two independent phase 3 trials to demonstrate efficacy and safety of the proposed oral product in the target population. To support an indication for treatment of opioid-induced constipation (OIC) in patients with *chronic* non-cancer pain, the duration of the double-blind treatment period should be at least 12 weeks (see additional comments #1).

Additional Discussion:

Salix provided additional discussion points relative to the FDA preliminary comments (see handout attachment). FDA reinforced content of preliminary comments, no agreements or new comments were provided during the discussion.

FDA agreed to consider a follow-up discussion in the future regarding trial design for as needed dosing.

[Post-meeting comments: Trial design for as needed dosing should be conducted in double blind manner.]

Question 2: Does the Agency concur that the proposed safety pools, safety database and ISS analysis plan (see Attachment 1) are sufficient to provide a substantive review of this NDA?

FDA Response to Question 2:

No we do not concur. Please see our response to question 1. In addition, safety data for the proposed indication and intended target population using the to-be-marketed formulations and doses should be pooled together. Safety data using other formulations (i.e., SC, (b) (4) capsules) (b) (4) would be considered supportive and should be presented separately.

Additional Discussion:

None

Question 3: Does the Agency have questions or recommend any additional analyses beyond those specified in the ISS analysis plan (see Attachment 1)?

FDA Response to Question 3:

We do not have any additional comments or recommendations at this time. Please see our response to question 1.

Additional Discussion:

None

Question 4: Does the Agency concur with the proposed recommended dose (b) (4) 450 mg (3 MNTX tablets) orally QD?

FDA Response to Question 4:
See our response to question 1.

Additional Discussion:
None

2.2. CLINICAL PHARMACOLOGY

Question 5: Does the Agency concur that the clinical pharmacology data and the planned pharmacokinetic studies adequately support an NDA submission?

FDA Response to Question 5:

We recommend that *in vivo* drug interaction potential via interaction with transporters be further addressed. It should be determined whether methylnaltrexone is a substrate of transporters such as BCRP, MRP and OATP and/or an inhibitor of transporters, including but not limited to, p-glycoprotein, BCRP, and OCT. *In vitro* studies may be conducted to determine the necessity of *in vivo* drug interaction studies. Please refer to the FDA Guidance for Industry: Drug Interaction Studies Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.¹

We recommend that you assess *in vivo* drug interaction potential for the major metabolite, M2. *In vitro* studies may be conducted to assess the necessity of *in vivo* drug interaction studies.

We recommend that you submit a PK/PD analysis plan to address our comments prior to NDA submission.

We request that the clinical pharmacology summary according to the provided template be submitted in module 2, section 2.7 with relevant hyperlinks to module 5.

- As different formulations were used throughout the development program, please provide a tabulated list of formulations used in each study.
- We request that non-clinical information obtained using human materials also be summarized in clinical pharmacology section. For example, we note that information about (b) (4) is summarized only in non-clinical summary section in your background package.

Additional Discussion:

Salix understands the rationale for the proposed transporter interaction studies. Salix agreed to go back and perform the additional work that needs to be done.

2.3. NONCLINICAL

¹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>

Question 6: Does the Agency concur that the nonclinical program is complete for NDA submission and is adequate to support the proposed indication?

FDA Response to Question 6:

Yes. We agree.

Additional Discussion:

None

2.4. CHEMISTRY MANUFACTURING AND CONTROLS

Question 7: The Sponsor plans to submit the NDA with 6 months stability data from these studies and intends to amend the application with ongoing data during the review period. Does the Agency agree with this approach?

FDA Response to Question 7:

It will be acceptable for you to submit your application with only six months of stability data and update the data while the application is under review. However, please be aware that any data received beyond the midpoint of the review clock will not be considered for the purpose of expiration dating.

Additional Discussion:

None

Question 8: Considering the rapid dissolution rates of the oral MNTX formulation, the Sponsor believes that an f2 statistical evaluation for demonstrating *in vitro* similarity of drug release between the (b) (4) batches is inappropriate for the oral MNTX 150 mg tablet formulation. Does the Agency agree?

FDA Response to Question 8:

Yes, we agree. The similarity of f2 values are not calculated and reported when the percent of drug dissolved (test and reference products) is > 85% in 15 minutes.

Additional Discussion:

None

Question 9: Considering how both the coated and uncoated tablets rapidly dissolve, does the Agency agree that a presentation of dissolution data at 15, 30, 45, and 60 minutes are sufficient to show comparability in performance between coated and uncoated tablets?

FDA Response to Question 9:

No. In addition to the provided data at pH 6.8, you need to provide dissolution profile comparison data for the coated vs. uncoated tablets at pH 1.2 and 4.5 using the same

testing conditions (i.e., USP Apparatus 2, paddle at 50 rpm (b) (4) (b) (4) sampling times: 15, 20, 30, 45, and 60 minutes).

Also, you should provide the dissolution testing conditions used for the pH 6.8 dissolution data reported in Tables 1 and 2 (page 15/94). If the testing conditions are different than those described above, provide additional dissolution profile comparison data at pH 6.8.

Additional Discussion:

None

Question 10:

Does the Agency agree?

FDA Response to Question 10:

No, we do not agree.

you would need to conduct a bioequivalence study to bridge the Phase 3 and to-be-marketed commercial formulations.

Additional Discussion:

FDA indicated that a bioequivalence study would not be necessary if the phase 3 formulation is the to-be marketed formulation. FDA further indicated that if Salix pursues the marketing of the coated tablet, in which the formulation (b) (4) is the same as the Phase 3 uncoated tablet formulation, Salix may request a biowaiver and provide the supportive data (the formulation information and comparative dissolution profile and f2 data).

Question 11: The Sponsor expects that comparative analyses of physicochemical properties of previously used lots of drug substance and related drug product batches will be sufficient for qualifying the optimized active pharmaceutical ingredient manufacturing process and the active pharmaceutical ingredient supplier for commercial production. Does the Agency concur?

FDA Response to Question 11:

To qualify a new supplier of drug substance, or qualify significant changes to the manufacturing process of drug substance from the current supplier, in addition to submitting the above comparative data, you will need to provide at least three months of long-term and accelerated stability data for drug product manufactured with the new drug substance.

Additional Discussion:

None

2.5. REGULATORY

Question 12: Based on available prevalence data, a pediatric population (b) (4) would be difficult or impractical to enroll sufficient patients to participate in a meaningful clinical study of MNTX. Therefore, the Sponsor is requesting a waiver to conduct pediatric studies (b) (4). Does the Agency concur?

FDA Response to Question 12:

A waiver may be acceptable (b) (4). However, you should submit your strategy to address PREA for all ages (birth through 16 years) (b) (4). Waiver requests should be submitted with adequate justifications at the time of NDA submission.

Additional Discussion:

None

Question 13: (b) (4)
?

FDA Response to Question 13:

You should submit your plan to address PREA (b) (4) with your NDA submission.

Additional Discussion:

None

Question 14: Does the Agency concur with the proposed eCTD submission strategy?

FDA Response to Question 14:

Your proposal is acceptable; however, please follow the FDA Portable Document Format (PDF) Specifications (updated January 20, 2012)² rather than the December 22, 2011 version. In addition, please be sure to provide sufficient navigation (bookmarks, TOC and hyperlinks) when submitting in eCTD format.

Additional Discussion:

None

2.6. ADDITIONAL COMMENTS

1. For your phase 3 trials, we have the following additional comments:

a) Primary and Secondary Endpoints.

² <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163565.pdf>

We recommend that overall responder be defined as the primary endpoint described below:

A weekly responder should be defined as a patient who has ≥ 3 RFBM/week and an increase from baseline of ≥ 1 RFBM/week for that week. A patient is considered to be an overall responder if he/she is a weekly responder for at least 9 weeks out of 12 weeks of treatment and 3 of which are in the last 4 weeks (to show durability).

A method to compute a weekly RFBM frequency rate should be calculated as follows:

$$\text{Number of RFBMs during that week} \div \text{Number of days with non-missing RFBM assessments during that week} \times 7$$

For subjects with fewer than 4 days of RFBM assessments during that week, the number of RFBMs/week should be set to missing for that week. Consequently, in the computation of the primary endpoint, any patient with more than three days of missing RFBM assessments during a given week should be categorized as a “non-responder” for that week.

The definition of RFBM should be a bowel movement that occurs with no laxative use in the previous 24 hours and that is accompanied by a sense of complete evacuation. In addition, it should be emphasized that subjects who receive rescue medication within 24 hours prior to first dose would not be considered as having a RFBM if their bowel movement (BM) occurred during the rescue medication period.

In addition, we recommend that you evaluate these secondary efficacy endpoints in phase 3 trials:

- Responder at least 50% of the weeks (6 out of 12 weeks)
- RFBM frequency rates during each week (weeks 1 to 12)
- Monthly responder analysis for each of the three months of treatment.

Please note that a patient is considered a monthly responder if he/she is weekly responder for at least 3 weeks out of 4 weeks treatment period. You should perform efficacy comparisons for MNTX versus placebo assessed by the monthly responder for each of the 3 months (12 weeks) of treatment.

The secondary and supportive elements should be carefully assessed to ensure that they have not worsened with treatment.

b) Multiplicity of endpoint comparisons

With regard to your schema for multiplicity adjustments, we have the following recommendations:

We note that for the primary and key secondary endpoints in study 3201, the Hochberg procedure was used to control the Type I error rate at 5% for the efficacy comparisons of the 3 oral MNTX doses versus placebo. We would like to remind you that the Hochberg-based procedure is not a separable procedure.³ Accordingly, for your newly proposed phase 3 studies, if any one of the three MNTX dose levels fails to show superiority to placebo, the testing procedure must stop at that endpoint since no alpha level would be preserved, and formal statistical testing would not be possible for the remaining endpoints.

2. You should provide analyses of the primary endpoint and key secondary endpoints using morphine equivalent doses (MED) as a co-variant to assess whether the MED affects the primary and key secondary endpoints.
3. You should not only record daily opioid doses administered by subjects but also capture any changes in doses that occur throughout the 12 week double blind treatment period. In addition, you should assess pain daily using a visual analogue scale (VAS) and analyze for any correlation between the changes in opioids and pain ratings.

Biopharmaceutics

We have the following comments regarding the dissolution information that should be provided in your NDA.

1. **Dissolution Test:** Include the dissolution method report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:
 - a) solubility data for the drug substance covering the pH range;
 - b) detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters used to select the proposed dissolution method as the optimal test for your product (*i.e., selection of the equipment/apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.*). The testing conditions used for each test should be clearly specified. The dissolution profile (*i.e., 15, 20, 30, 45, and 60 minutes*) should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (*i.e., no increase over 3 consecutive time-points*) is reached. We recommend use of at least twelve samples per testing variable;
 - c) provide the complete dissolution profile data (*individual, mean, SD, profiles*) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*); and
 - d) include the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as the supportive validation data for the dissolution method (*i.e., method robustness, etc.*) and analytical method (*precision, accuracy, linearity, stability, etc.*).

³ Alex Dmitrienko, Ajit C. Tamhane, and Brian L. Wiens (2008), General Multistage Gate-keeping Procedures, *Biometrical Journal* 50, 667–677

Please note that you can also provide the dissolution method report under your IND for review and comments.

2. Dissolution Acceptance Criterion:

For the selection of the dissolution acceptance criterion of your product, the following points should be considered:

- a) The dissolution profile data (*i.e.*, 15, 20, 30, 45, and 60 minutes) from the bio-batches (clinical & PK) and primary (registration) stability batches should be used for the setting of the dissolution acceptance criterion of your product (*i.e.*, specification-sampling time point and specification value).
- b) Specifications should be established based on average dissolution data for each lot under study (n=12).
- c) The *in vitro* dissolution profile should encompass the timeframe over which at least 85% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.
- d) For immediate release product the selection of the specification time point should be where Q^{(b)(4)} % dissolution occurs.

Note that the final determination on the acceptability of the proposed dissolution acceptance criterion for your product will be made during NDA review process based on the provided data.

Additional Discussion:

None

3. PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

4. ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (*e.g.*, euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission

[21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

5. MANUFACTURING FACILITIES

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

6. ATTACHMENTS AND HANDOUTS

Salix Handout (attached)

14 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

ELIZABETH A FORD

04/02/2012



IND 067452

MEETING PRELIMINARY COMMENTS

Progenics Pharmaceuticals, Inc.
Attention: Ann Marie Assumma, M.S.
Vice President, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591

Dear Ms. Assumma:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Methylnaltrexone (MNTX; MOA-728) Tablets.

We also refer to your January 25, 2011, correspondence requesting a Type C meeting to discuss drug product impurity specifications. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for April 4, 2011, 3:00 to 4:00 p.m., between Progenics and the Division of Gastroenterology and Inborn Errors Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting

Question: Based on the in silico data presented on (b) (4) and (b) (4) the Sponsor believes that (b) (4) similar to (b) (4) does not present significant genotoxic risk and is of low concern for human safety. Therefore, the Sponsor proposes to control (b) (4) in the MNTX oral drug product as a specified identified degradation product at the lower value of NMT (b) (4)% or (b) (4)mg total daily intake (TDI) in accordance with ICH Q3B(R2). Does the Agency agree?

FDA Response:

We agree, based on our expectation that the human daily dose of MNTX will not be more than 2 g. For daily doses greater than 2 g, the limit should be (b) (4)%.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301)796-2307.

Sincerely,

{See appended electronic signature page}

Matthew Scherer, MBA
Senior Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

MATTHEW C SCHERER

04/04/2011



IND 067452

MEETING PRELIMINARY COMMENTS

Progenics Pharmaceuticals, Inc.
Attention: Ann Marie Assumma, M.S.
Vice President, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591

Dear Ms. Assumma:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Methylnaltrexone (MNTX; MOA-728) Oral formulation.

We also refer to your correspondence, received February 16, 2010, requesting a meeting to discuss a proposed modification to the acceptance criterion for a potential degradant in the methylnaltrexone oral drug product.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for May 17, 2010 at 12:00 pm between Progenics Pharmaceuticals, Inc. and the Division of Gastroenterology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

Question: Based on the data presented, the Sponsor proposes to control (b) (4) in the MNTX oral drug product as a specified identified degradation product at the lower value of

NMT (b) (4)% or (b) (4)mg total daily intake (TDI) in accordance with ICH Q3B(R2). Does the Agency agree?

FDA Response: Yes, we agree. However, in the absence of data demonstrating that impurity (b) (4) is not genotoxic, the acceptance criterion for (b) (4) will need to be NMT (b) (4) ppm (the same as currently used for the sum (b) (4) and (b) (4))

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

Matthew Scherer, M.B.A.
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

IND-67452

GI-1

WYETH
PHARMACEUTICA
LS INC

METHYLNALTREXONE

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

/s/

MATTHEW C SCHERER
05/12/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 67, 452

Wyeth Pharmaceuticals, Inc.
Attention: Joanne Palmisano, M.D., F.A.C.P.
Assistant Vice President, Global Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. Palmisano:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Methylnaltrexone Bromide (MNTX; MOA-728).

We also refer to the meeting between representatives of your firm and the FDA on June 26, 2006. The purpose of the meeting was to obtain the Agency's guidance on your proposed develop plan for the treatment of [REDACTED] (b) (4)

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0871.

Sincerely,

{See appended electronic signature page}

Tanya Clayton, B.S.
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Date: June 26, 2006

Time: 11:00- 12:00 PM

Location: White Oak Building 22, Conference Room 1421

Application: IND 67,452

Type of Meeting: Type C

Meeting Chair: Ruyi He, M.D.

Meeting Recorder: Tanya Clayton, B.S.

FDA Attendees, Titles, and Office/Division:

Division of Gastroenterology Products

Brian E. Harvey, M.D., Ph.D.	Division Director
Joyce A. Korvick, M.D., M.P.H.	Deputy Director
Ruyi He, M.D.	Medical Team Leader
Eric Brodsky, M.D.	Medical Reviewer
Jasti Choudary, Ph.D., B.V.Sc.	Supervisory Pharmacologist
Suliman Al-Fayoumi, Ph.D.	Biopharmaceutical Reviewer
Tanya Clayton, B.S.	Regulatory Project Manager

Office of Biostatistics

Sue-Jane Wang, Ph.D.	Associate Director
Stella Grosser, Ph.D.	Statistical Team Leader
Wen Jen Chen, Ph.D.	Statistical Reviewer

External Constituent Attendees and Titles:

Wyeth Attendees

Joanne Palmisano, M.D., F.A.C.P.,	Assistant Vice President, Global Regulatory Affairs
Bruce Randazzo, M.D., Ph.D.	Sr. Director, Clinical Research
Lisa Jenkins, Ph.D.	Manager, Global Regulatory Affairs
Michael Krams, M.D.	Assistant Vice President, Clinical Development, Adaptive Trials
Xu Meng, Ph.D.	Senior Director, Clinical Pharmacology
Charles Gombar, Ph.D.	Vice President, Project Management, Team Leader
Gerald Fisher, Ph.D.	Senior, Vice President, Office of the President, Research and Development

Wyeth Consultants

(b) (4)

Consultant, Biostatistics
Consultant, Biostatistics

Progenics Pharmaceuticals, Inc.

Robert Israel, M.D.
Alton Kremer, M.D., Ph.D.
Nancy Stambler, M.S.

Senior Vice President, Medical Affairs
Vice President, Clinical Research
Director, Biometrics

Background:

On April 12, 2006, the Sponsor requested a meeting for the purpose of obtaining the Agency's guidance on their proposed develop plan for the treatment (b) (4)

A subsequent May 30, 2006 background package was submitted, which contained 11 questions for discussion.

On June 23, 2006 the Agency's preliminary responses were sent to the sponsor for review.

Following introductions, the Sponsor agreed to proceed directly to the questions for discussion. The sponsor also requested to focus the discussion on questions 8.1.2, 8.2 and 8.3. They required no clarification for the remaining responses.

Discussion Points: (bullet format):

8.1 QUESTIONS RELATED TO THE PROTOCOLS

Wyeth is developing MOA-728 oral for the treatment (b) (4)

The development program for MOA-728 is provided in the Background Package. Wyeth plans to initially conduct a trial designed as a seamless phase 2/3 study, which incorporates a pre-planned interim analysis to decide which doses to carry forward into part 2 of the study (the phase 3 stage). A summary of the clinical phase 2/3 and confirmatory phase 3 trials are included in the Clinical Development Plan in the Background Package. A full phase 2/3 protocol and DRAFT protocol synopsis for the confirmatory phase 3 trial are also provided. There will be criteria that will define eligibility of subjects for participation in active treatment extension studies.

8.1.1 Protocol definition of opioid-induced bowel dysfunction with constipation as the predominant side effect.

Wyeth will enroll patients with opioid-induced bowel dysfunction with a history of constipation for at least 1 month before the screening visit. Constipation is defined as <3 spontaneous bowel movements per week on average that are associated with 1 or more of the following:

- Hard or lumpy stools for at least 25% of bowel movements
- A sensation of incomplete evacuation following at least 25% of bowel movements.

- Straining during at least 25% of bowel movements.

In addition, during the 14-day single-blind placebo run-in period, constipation will be demonstrated with ≤ 2 spontaneous (no laxative use during the prior 24 hours) bowel movements per week and 1 or more of the following:

- A Bristol Stool Form Scale score of 1 or 2 for at least 1 of the bowel movements.
- A sensation of incomplete evacuation after at least 1 of the bowel movements.
- Straining during at least 1 of the bowel movements.

Does the Agency concur with the eligibility criteria for constipation that will define the baseline condition in our study?

Response

Your eligibility criteria to identify patients with opioid-induced constipation (OIC) in planned Study 3200A3-200-WW (Study 200) and planned Study 3200A3-30A-WW (Study 30A) are acceptable.

8.1.2 Protocol definition of endpoints.

The primary endpoint for these trials [REDACTED] (b) (4)

Does the Agency agree with the proposed primary endpoint for these clinical trials to support registration of MOA-728 oral for the proposed indication?

Response

No. Your proposed primary endpoint in Studies 200 and 30A does not appear to evaluate the efficacy of the study treatments for your proposed indication: “the treatment of [REDACTED] (b) (4) [REDACTED]” for the following reasons:

[REDACTED] (b) (4)

[Redacted] (b) (4)

[Redacted] (b) (4)

To obtain a long-term OIC indication, we recommend you perform and demonstrate efficacy over 12 weeks in two 12-week OIC trials.

The key secondary endpoints are:

- [Redacted] (b) (4)
- [Redacted]
- [Redacted]

Does the Agency agree that if a statistically significant improvement in one or more of the key secondary endpoints is demonstrated that labeling for those endpoints can be considered?

Response

No, statistical significance with appropriate multiplicity adjustments and clinically meaningfulness of the secondary endpoints must be demonstrated for consideration of insertion of secondary endpoints in the label. Multiplicity adjustments must account for the following:

- 1) [Redacted] (b) (4)
- 2) [Redacted]

In addition we have the following concerns/questions regarding your proposed secondary efficacy endpoints for an OIC indication:

- 1) [Redacted] (b) (4)
- 2) [Redacted]
- 3) [Redacted]
- 4) [Redacted]
- 5) [Redacted]

6)

(b) (4)

The bowel movement data and other patient reported daily evaluations would be collected via an Interactive Voice Response System (IVRS) electronic diary. Patients will be required to call into the IVRS to report their bowel movement information daily, including consistency of the stool (via the Bristol Stool Scale), straining, and sensation of complete evacuation associated with each bowel movement. In addition, patients will report daily, their average pain intensity, and if rescue laxative medication was used, including time of use.

Does the Agency agree that endpoint data as described above, reported by patients via an IVRS electronic diary is acceptable for these clinical trials to support registration of MOA-728 oral for the proposed indication?

Response

The use of the IVRS electronic daily diary is acceptable in your proposed trials.

Does the Agency agree

(b) (4)

?

Response

No. Please see our answer to question 8.1.2.1.

(b) (4)

8.2 QUESTION RELATED TO THE STATISTICAL METHODOLOGY

Wyeth proposes to use the methodology as established by

(b) (4)

for analysis of the seamless phase 2/3 study. A full description of the statistical methodology is to be found in Section 4.4.1.3 of the accompanying Background Package.

Is our proposal to conduct a seamless phase 2/3 trial using the methodology of

(b) (4)

?

Response

As written in pages 60-64 of the currently submitted protocol 3200A3-20-WW, only general statements of the adaptive design are given citing the references by (b) (4) While the papers present a framework generally enough that has statistical validity, it has wide range of applications.

In the currently submitted protocol, you consider

(b) (4)

As currently written, they are confusing. Please use the same terminology throughout your proposal. We suggest you provide a flowchart explain the specific adaptive elements and the specific rules for a coherent adaptive design consideration.

In your submission, you indicate that you are still conducting the simulation studies to better understand the operating characteristics of your proposed general strategy. Exactly how you want to apply the method to your specific situation needs to be clearly described. Details in the statistical analysis plan should include clear criteria for each adaptive element that can be followed and reviewed, how the overall family wise type I error rate will be controlled, and how the trial integrity is to be maintained including trial conduct and trial logistics in reference to all pre-specified adaptation elements. It is premature to provide constructive comments as to whether your strategy would be acceptable. Submit the detailed SAP with your simulation results when you are ready, the DMC charter, the DMC SAP, and the documents describing the roles of and the necessary firewalls among all parties including the sponsor and the external independent statistical center for review.

8.3 QUESTION RELATED TO THE DATA MONITORING COMMITTEE (DMC) DRAFT CHARTER

Wyeth has outlined a Data Monitoring Committee (DMC) draft charter that can be found in the Background Package in Section 4.4.1.4. In this draft charter, we describe:

1. The DMC's composition, roles and responsibilities
2. The Independent Statistical Center (ISC)
3. Interactions between the DMC, ISC, and the Sponsor

Wyeth's proposal is the result of extensive scenario planning around the proposed clinical development plan. To enable the proposed design, we envisage that for the deliberations that will result in a recommendation as to which doses to carry forward into part 2 of the seamless phase 2/3 trial, a sponsor non-project senior clinician and statistician will temporarily join the DMC. We would like to offer the possibility of FDA participation to act as independent observers during the deliberations in the context of the interim analysis that will lead to a decision of selection of doses to carry forward into the second part of the phase 2/3 trial.

Does the Agency concur with the Wyeth proposal for the roles and responsibilities of the DMC as described in the DMC draft charter?

Response

Based on your current proposal, an independent statistical center external to the sponsor will perform the unblinded interim analyses and report to DMC. The DMC will then recommend which treatment dose(s) to continue and whether sample size will be increased at the second stage. It is not clear why there is a need of the sponsor non-project personnel's involvement. Clarify what are the roles of the sponsor non-project senior clinician and statistician in joining the DMC.

Is the Agency interested in providing one or two independent observers during the deliberations of the DMC leading to dose selection for the second part of the phase 2/3 trial?

Response

It is not the interest of the Agency to provide observers during the deliberations of the DMC. The role of the Agency is to provide its objectivity in the review process when the study results, interim meeting minutes, etc. are submitted for review.

8.4 QUESTION RELATED TO HUMAN EXPOSURE FOR LONG-TERM SAFETY

At the time of filing the NDA for the oral development program, Wyeth and Progenics expect to have at least (b) (4) patients exposed to MOA-728 (all dosage forms) across all phase 2 and 3 studies. (b) (4)

(Table 5.0-1 in the Background Package). This exposure is in accordance with ICH E1 Guidance: *The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions October 1994*. Wyeth believes that the planned patient exposure and adherence to ICH E1 Guidance will provide data on long-term safety sufficient to support registration for the proposed indication of the treatment of (b) (4) use of MOA-728.

Does the Agency concur?

Response

Your proposed safety exposure to methylnaltrexone (MNTX) may be acceptable. However, we have the following comments:

- 1) **It is not clear from your proposal if the (b) (4) patients exposed to MNTX (b) (4), respectively will be exposed to relevant doses (i.e., doses generally in the therapeutic range);**
- 2) **Other clinical development programs for the treatment of OIC have proposed much larger safety databases for the multiple dose, 6 month, and 12 month exposures; and**
- 3) **More than 1500 multiple-dose exposures to MNTX may be needed if the benefit from MNTX is small or if significant safety signals are seen in the trials. Please see the March 2005 Premarketing Risk Assessment Guidance for more details (<http://www.fda.gov/cder/guidance/6357fnl.htm>).**

8.5 QUESTION RELATED TO CLINICAL PHARMACOLOGY STUDIES

Wyeth plans to submit the data from the proposed clinical pharmacology studies (Table 4.1-1 in the Background Package) relevant to an understanding of the pharmacokinetics and pharmacodynamics of MOA-728 in support of the New Drug Application for MOA-728 oral for the treatment of (b) (4). While some of these studies were originally conducted in support of (b) (4), others were specifically designed for the proposed oral use of MOA-728. Wyeth believes that the data from these clinical pharmacology studies will be

sufficient for supporting the New Drug Application for the proposed oral use of MOA-728 for the treatment of constipation (b) (4) associated with chronic opioid therapy.

Does the Agency concur?

Response

The Clinical Pharmacology studies listed in Table 4.1-1 maybe sufficient; however, as the actual study design features and results have not been presented in this package, we cannot comment as to whether or not additional studies will be needed. We note that there are still some key studies to be completed (final formulation study, radiolabel, methadone patient study, IV QTc, etc.) and they will be key to determination of the adequacy the Clinical Pharmacology/Biopharmaceutics program.

8.6 QUESTION REGARDING ADEQUACY OF QTc STUDY.

Progenics has conducted a thorough QTc study for MOA-728 given subcutaneously (Progenics protocol MNTX (b) (4) in accordance with the *Guidance for Industry E14: Clinical Evaluation of QT/QTc Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (October 2005). (b) (4)

(b) (4)
A
full study report is in preparation.

The MOA-728 concentrations in plasma following oral dose administration of MOA-728 are likely to be substantially lower at the expected therapeutic doses than those achieved for parenteral uses of MOA-728. Wyeth plans to conduct metabolic profiling in the ongoing multiple ascending oral dose study (Wyeth protocol 3200A3-100-US) and a radiolabeled ADME study with oral MOA-728 administration. If the oral administration of MOA-728 achieves plasma concentrations that are lower than those that occur with parenteral dose administration and no unique metabolites are identified following oral dose administration, then Wyeth believes that the completed thorough QTc study is sufficient to cover the proposed oral use of MOA-728.

Does the Agency concur?

Response

Study MNTX (b) (4) (the QT/QTc Study) may be acceptable to “cover” the MOA-728 dose(s) proposed for the OIC indication. To determine the acceptability of Study MNTX (b) (4), we will evaluate the cardiovascular safety of MNTX including, but not limited to, the following:

- 1) If the concentrations of the (b) (4) mg/kg subcutaneous MNTX dose ((b) (4)) and relevant metabolites are at substantial multiples than the concentrations of your proposed oral MOA-728 dose(s) and relevant metabolites (including assessment of changes in the parent:metabolite ratio);
- 2) If there are any cardiovascular signals in Study MNTX (b) (4), the clinical development program, and nonclinical testing; and
- 3) Analysis of Study MNTX (b) (4) according to the E14 Guidance.

Additional Comments/Questions:

- 1) We recommend that your proposed Studies 200 and 30A include a mandatory follow-up safety clinic visit that includes the following: a physical exam, vital signs, laboratory tests, opioid withdrawal instrument(s), and assessment of adverse events;
- 2) [REDACTED] (b) (4), we recommend you add an appropriate subjective opioid withdrawal scale as part of the safety monitoring and add an analysis showing the range of calculated difference in subjective opioid withdrawal scale scores for individual patients in one or both of your proposed studies;
- 3) We are concerned that your proposed MAO-728 doses for Study 30A will be based on the first interim analysis from Study 200; not both the safety and efficacy analyses in Study 200 (see page 50 of your briefing package);
- 4) Clarify if you plan to conduct Studies 200 and 30A concurrently;
- 5) Clarify your proposed number of patients in Study 200. In the briefing package you stated that [REDACTED] (b) (4); and
- 6) Submit the final reports of the Segment I fertility and general reproductive performance study in rats and the nine month oral toxicology study in dogs for review and evaluation prior to initiation of any Phase 3 study.

i [REDACTED] (b) (4)

ii [REDACTED]

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

/s/

Tanya Clayton
7/26/2006 01:26:52 PM

Ruyi He
7/26/2006 01:43:34 PM