

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204760Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 204760

SUPPL #

HFD # 180

Trade Name Movantik

Generic Name naloxegol

Applicant Name AstraZeneca Pharmaceutical LP

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒

NO ☐

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

505(B)1

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

YES ☒

NO ☐

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

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

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

Applicant claims an exclusivity period of five years from the date of approval of this New Drug Application pursuant to 21 CFR 314.108(b)(2).

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☐

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES ☐ NO ☒

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

NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

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

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets

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

YES ☐ NO ☐

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted

or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

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

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

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

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

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

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

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

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

in interest provided substantial support for the study?

Investigation #1

YES ☐

Explain:

!

!

! NO ☐

! Explain:

Investigation #2

YES ☐

Explain:

!

!

! NO ☐

! 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: Maureen Dewey

Title: Regulatory Project Manager

Date: September 4, 2014

Name of Office/Division Director signing form: Joyce Korvick, M.D., M.P.H.

Title: Deputy Director for Safety

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/

MAUREEN D DEWEY
09/12/2014

JOYCE A KORVICK
09/12/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 204760 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: MOVANTIK Established/Proper Name: naloxegol Dosage Form: Tablets		Applicant: AstraZeneca Pharmaceuticals LP Agent for Applicant (if applicable):
RPM: Maureen Dewey		Division: Gastroenterology and Inborn Errors Products
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<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>09/16/2014</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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 1
(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 | |

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 (approvals only)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters (including approval letter with final labeling)	Action and date 09/16/2014
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☒ Included
Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☒ Included
Original applicant-proposed labeling	☒ Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
Most-recent draft labeling	☒ Included
❖ Proprietary Name	
- Acceptability/non-acceptability letter(s) (indicate date(s)) - Review(s) (indicate date(s))	11/01/2013 10/31/2013
❖ Labeling reviews (indicate dates of reviews)	RPM: ☒ None DMEPA: ☐ None 08/18/2014 DMPP/PLT (DRISK): ☐ None 08/22/2014 OPDP: ☐ None 08/20/2014; 08/22/2014 SEALD: ☒ None CSS: ☐ None 06/03/2014 Other: ☐ None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	11/15/2013
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary (signed by Division Director)	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
Applicant is on the AIP	☐ Yes ☒ No

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

- 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>07/16/2014</u> If PeRC review not necessary, explain: _____	
❖ 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, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	
❖ 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>)	☐ No mtg 04/23/2013
EOP2 meeting (<i>indicate date of mtg</i>)	☐ No mtg 01/26/2010
Mid-cycle Communication (<i>indicate date of mtg</i>)	☐ N/A 03/13/2014
Late-cycle Meeting (<i>indicate date of mtg</i>)	☐ N/A 06/18/2014
Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	n/a
❖ Advisory Committee Meeting(s)	☐ No AC meeting
Date(s) of Meeting(s)	06/11-12/2014
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☐ None 09/16/2014
Division Director Summary Review (<i>indicate date for each review</i>)	☐ None 09/16/2014
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None 09/16/2014
PMR/PMC Development Templates (<i>indicate total number</i>)	☐ None (2)
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>)	10/29/2013; 05/11/2014; 09/09/2014
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>)	Clinical Review Clinical Addendum 09/09/2014
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	☐ None 09/09/2014 NEURO 08/14/2014 DRISK 05/14/2014 PMHS 04/15/2014 DCARP

❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☐ N/A 06/03/2014	
❖ 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 06/10/2014	
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	☐ None requested Review: 05/07/2014 Letters: 07/17/2014; 5/2/2014; 3/31/14 (2); 3/20/14	
Clinical Microbiology ☒ None		
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review	
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	☐ None	
Biostatistics ☐ None		
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	☒ No separate review	
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review	
Statistical Review(s) (<i>indicate date for each review</i>)	☐ None 11/06/2013; 06/20/2014	
Clinical Pharmacology ☐ None		
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	☒ No separate review	
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review	
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	☒ None 10/30/2013 05/14/2014 Part 1 and 2 (2) 09/05/2014	
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	☐ None requested 06/27/2014	
Nonclinical ☐ None		
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) (<i>indicate date for each review</i>)	☐ No separate review 05/13/2014	
• Supervisory Review(s) (<i>indicate date for each review</i>)	☒ No separate review	
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	☐ None 10/30/2013; 05/15/2014; 09/04/2014	
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	☐ None	
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	☐ No carc	
❖ ECAC/CAC report/memo of meeting	☐ None 02/07/2014 Included in P/T review, page 144	
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	☒ None requested	

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	☒ No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	☒ No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	☐ None 11/15/2013; 05/16/2014 06/12/2014; 07/08/2014; 09/12/2014
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	☐ Not needed 10/17/2013; 06/06/2014
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	07/18/2014
☐ Review & FONSI <i>(indicate date of review)</i>	
☐ Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>	Date completed: 06/23/2014 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable Establishment Inspection Report: 07/17/14
☐ BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	☒ Completed 08/25/2014 ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

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
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☐ Done
❖ 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	☐ Done

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

/s/

MAUREEN D DEWEY
09/16/2014

From: [Thinnes, Lynley K](#)
To: [Dewey, Maureen](#)
Cc: [Prosser, Judith](#)
Subject: RE: NDA 204760 MOVANTIK Action Letter
Date: Tuesday, September 16, 2014 9:59:21 AM

Dear Maureen

I confirm receipt of the action letter.

Can you provide clarification on what is meant by the market package? I just want to make sure I know what is expected.

Thank you again for helping to make this process go so smoothly

Kind Regards

Lynley

"When you can do the common things of life in an uncommon way, you will command the attention of the world."
-- George Washington Carver, American scientist and inventor

Lynley Thinnes, RAC

Director, Global Regulatory Affairs, GRAPSQA

AstraZeneca | Global Regulatory Affairs

1800 Concord Pike C4C-121, Wilmington DE, 19850

T: +1 (302) 886-7607 F: +1 (302) 886-2822 M: +1 (b) (6)

lynley.thinnes@astrazeneca.com

Please consider the environment before printing this e-mail

Confidentiality Notice: This message is private and may contain confidential and proprietary information. If you have received this message in error, please notify us and remove it from your system and note that you must not copy, distribute or take any action in reliance on it. Any unauthorized use or disclosure of the contents of this message is not permitted and may be unlawful.

From: Dewey, Maureen [<mailto:Maureen.Dewey@fda.hhs.gov>]

Sent: Tuesday, September 16, 2014 9:50 AM

To: Thinnes, Lynley K

Cc: Prosser, Judith; Dewey, Maureen

Subject: NDA 204760 MOVANTIK Action Letter

AstraZeneca Pharmaceuticals LP

Attention: Lynley K. Thinnes

Director, Regulatory Affairs

1800 Concord Pike, P.O. Box 8355

Wilmington, DE 19803-8355

Dear Ms. Thinnes:

Please refer to your New Drug Application (NDA) dated and received September 16, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for MOVANTIK (naloxegol) tablets, 12.5 mg and 25 mg.

Attached please find a courtesy copy of the Action Letter for NDA 204760 MOVANTIK.

We request a prompt reply confirming receipt of this correspondence.

Please call me if you have any questions.

Thanks,

Maureen Dewey, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Center for Drug Research and Evaluation
FDA
Office: (301) 796-0845
Fax: (301) 796-9904

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

/s/

MAUREEN D DEWEY
09/16/2014



NDA 204760

**METHODS VALIDATION
MATERIALS RECEIVED**

Astra Zeneca
Attention: Barry Sickels
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

Dear Barry Sickels:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Movantik (Naloxegol) tablets 12.5 mg and 25 mg and to our November 13, 2013 letter requesting sample materials for methods validation testing.

We acknowledge receipt on June 11, 2014, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
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/

MICHAEL L TREHY
06/17/2014



NDA 204760

MID-CYCLE COMMUNICATION

AstraZeneca Pharmaceuticals LP
ATTENTION: Lynley K. Thinnes
Director, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Thinnes:

Please refer to your New Drug Application (NDA) dated and received September 16, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for MOVANTI[®] (naloxegol oxalate tablets), 12.5 mg and 25 mg.

We also refer to the teleconference between representatives of your firm and the FDA on March 13, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

We further refer to an email correspondence from Jean Surian dated April 21, 2014 requesting revisions to the AstraZeneca attendees.

An updated record of the teleconference is enclosed for your information.

If you have any questions, please contact Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Maureen Dewey
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

AMENDED MID-CYCLE COMMUNICATION

Meeting Date and Time: March 13, 2014
Application Number: NDA 204760
Product Name: MOVANTIK
Indication: Treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.
Applicant Name: Astra Zeneca
Meeting Chair: Anil Rajpal, M.D.
Meeting Recorder: Maureen Dewey, M.P.H.

FDA ATTENDEES

Office of Drug Evaluation III

Julie Beitz, MD, Director

Maria Walsh, RN, MS, Associate Director for Regulatory Affairs

Division of Gastroenterology and Inborn Errors Products

Donna Griebel, MD, Director

Joyce Korvick, M.D., MPH, Deputy Director for Safety

Anil Rajpal, MD, MPH, Clinical Team Leader

Aisha Peterson-Johnson, MD, Clinical Reviewer

Yuk-Chow Ng, Nonclinical Reviewer

Maureen Dewey, M.P.H. Senior Regulatory Project Manager

Office of New Drugs Quality Assessment

Bogdan Kurtyka, Ph.D., Chemistry Reviewer

Office of Clinical Pharmacology (OCP)

Sue Chih Lee, Ph.D., Team Leader

Elizabeth Shang, PhD, RPh, Clinical Pharmacology Reviewer

Sandhya Apparaju, Ph.D., Clinical Pharmacology Reviewer

OCP- Division of Pharmacometrics

Nitin Mehrotra, Ph.D, Team Lead

Justin Earp, PhD., Reviewer

Office of Biostatistics/Division of Biometrics III

Freda Cooner, PhD, Acting Team Leader

Wen-Jen Chen, PhD, Reviewer

Division of Anesthesia, Analgesia and Addiction Products

Ellen Fields, MD, MPH, Clinical Team Leader

Elizabeth Kilgore, MD, Medical Officer

Pediatric and Maternal Health Staff

Jeanine Best, MSN, RN, PNP , Team Leader
Ethan D. Hausman, MD, Clinical Reviewer
Carrie M. Ceresa, Pharm D., MPH, Regulatory Reviewer
Millie Wright, RN, MSN, Senior Regulatory Health Project Manager

Office of Surveillance & Epidemiology (OSE)

Office of Pharmacovigilance, Division of Epidemiology I

Carolyn McCloskey, MD, MPH, Medical Officer Epidemiologist
Christian Cao, MPAS, PA-C, Safety Evaluator, Division of Pharmacovigilance 1

OSE - Division of Risk Management

Reema Mehta, PharmD, MPH, Team Leader
Nyedra W. Booker, PharmD, M.P.H., Risk Management Analyst

Division of Medical Policy Programs (DMPP)

Karen Dowdy, RN, BSN, Patient Labeling Reviewer

Controlled Substance Staff

Katherine Bonson, PhD, Pharmacologist

Eastern Research Group, Inc.

So Hyun Kim, Independent Assessor, Eastern Research Group
Melissa Bouatene, Independent Assessor, Eastern Research Group

APPLICANT ATTENDEES

AstraZeneca

Lynley Thinnies, Regulatory Affairs Director
Kathleen Cantagallo, Vice President, GMED, naloxegol
Mark Sostek, Medical Science Director
Tim Sullivan, Patient Safety Medical Director
Robert Timko, Regulatory CMC Director
Sue-Ellen Wingertz, Global Project Manager
Raj Tummala, Director Clinical Research
Jaakko Lappalainen, Director Clinical Research
Catherine Datto, Director Clinical Research
Khahn Bui, Sr. Clinical Pharmacology Scientist
Peter Barker, Statistical Science Director
Robert Sepeylak, Pharmaceutical Development Project Director
Mike Hutchinson, Director of Drug Safety and Metabolism
Judith Prosser, Associate Director, Regulatory Project Management
Jean Surian, Associate Director, Regulatory Project Management

Nektar Therapeutics Attendees:

Robert Medve, Chief Medical Officer
Carlo Di Fonzo, Vice President, Drug Development and Regulatory Affairs

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

2.1 NONCLINICAL

Pregnancy Category ^(b)₍₄₎ appears to be inappropriate for MOVANTIK, based on our preliminary assessment of the fetal skeletal changes in the segment II developmental study in rabbits.

Additional Discussion:

The Applicant requested clarification of which pregnancy category the Agency would recommend. The Agency stated that Pregnancy category C appears to be appropriate.

2.2 CLINICAL PHARMACOLOGY

The frequency of high naloxegol systemic exposures in four individuals with moderate or severe renal impairment within the small renal impairment groups in study D3820C00009 is still of concern to the Division. While naloxegol PK in general appear to exhibit moderate variability, there appears to be no evidence of outliers in other completed studies who displayed up to 8-fold higher systemic exposures, as were noted in the renal impairment study. For this reason, we remain concerned that renal impairment of moderate or worse severity may render some patients more susceptible than others.

In this regard, we are considering recommending that patients with renal impairment (moderate or worse) should start on a lower dose, and potentially can increase their dose under the physician's guidance if the drug is well tolerated and a clear need for additional efficacy has been found.

2.3 CLINICAL

Potential labeling issues:

- a) [REDACTED] (b) (4)
[REDACTED] based upon our analysis, we identified patients who experienced symptoms consistent with opioid withdrawal who were on maintenance opioids [REDACTED] (b) (4). Therefore, this should be reflected in the proposed label to include a statement such as: [REDACTED] (b) (4)

Additional Discussion:

The Applicant requested clarification on the source of data reviewed to make the determination that opioid withdrawal occurred in study subjects taking opioids [REDACTED] (b) (4). FDA reviewed the Applicant's analyses and data using the preferred terms based on an expanded list of symptoms consistent with opioid withdrawal, which included terms from the DSM-IV, COWS and SOWS.

- b) The current language in Section 10 "OVERDOSAGE" section is vague. Consider revising the language to include more specific symptoms associated with opioid withdrawal, such as "If a patient on opioid therapy receives an overdose of naloxegol, the patient should be monitored closely for the signs and symptoms of opioid withdrawal such as chills, rhinorrhea, diaphoresis or reversal of central analgesic effect. Base treatment on the degree of opioid withdrawal symptoms, including changes in blood pressure and heart rate, and on the need for analgesia."

- c) [REDACTED] (b) (4)

Additional Discussion:

FDA noted that in Study 005 the 12.5 mg dose did not show a statistically significant difference versus placebo for the primary endpoint (Applicant's analysis).

- d) We are considering if there is a role for the low dose in patients who cannot tolerate the high dose.

Additional Discussion:

FDA clarified that we are considering a recommendation for dose reduction in the Dosage and Administration section for patients who are unable to tolerate the 25 mg dose due to common adverse events such as abdominal pain which was observed in the trials at higher frequency with the 25 mg dose than with the 12.5 mg dose. The Applicant proposed to submit pharmacometric modeling data.

- e) Because there was evidence of opioid withdrawal in study subjects receiving naloxegol, the proposed [REDACTED] (b) (4)

(b) (4)

is not fully supported by the data.

Additional Discussion:

FDA clarified that the data collected on daily opioid dose and average pain intensity were not analyzed as pre-specified endpoints

(b) (4)

Additionally, as stated under Item a) above, there was evidence of opioid withdrawal in some patients.

(b) (4)

- f) We are reviewing the potential for fetal effects (both human and animal) with maternal use of opioid antagonists. In your proposed labeling you state the theoretical risk of fetal opioid withdrawal with the use of naloxegol because of the immature blood-brain barrier. See Information Request 3.1 seeking further clarification on this point.
- g) The efficacy results assessed by the additional secondary endpoints that were not controlled by the multiplicity adjustment method should only be descriptive and should not be associated with p-values if they are ultimately included in the labeling.

During labeling negotiations it will be important to determine how best to address each of these issues in the package insert.

3.0 INFORMATION REQUESTS

3.1 Maternal Health:

We note that three pregnancies occurred during the phase 3 trials with naloxegol. Only one pregnancy is reported in your Summary of Clinical Safety and that pregnancy occurred in the placebo arm. Please provide the two additional pregnancy reports.

Please provide a summary of published data of fetal effects (both human and animal) with maternal use of opioid antagonists. Provide all references reviewed and summarized.

Additional Discussion:

The Applicant requested further clarification about the scope of data requested. FDA clarified that the applicant should submit a summary of, as well as the references on, all fetal effects with the use of opioid antagonists with a special emphasis on opioid withdrawal. FDA noted that the review of the data submitted may have an impact on the final pregnancy category classification.

3.2 Clinical Pharmacology:

Provide information on the following two aspects of the renal impairment PK study D3820C00009:

Detail the dietary restrictions in the renal PK study since foods such as grapefruit juice may also impact exposures. Address whether dietary restrictions were strictly adhered to by the trial participants.

Provide explanation for roughly two-fold higher mean naloxegol exposures in the 'normal' group of renal PK study when compared to healthy volunteers of other phase I clinical trials.

3.3 Chemistry, Manufacturing and Controls:

I. Drug Substance:

a) Specification

- You have not included testing for all potential genotoxic impurities. While you explain this (b) (4) you have not provided sufficient data regarding the origin (b) (4) to justify their use. Provide test results for genotoxic impurities in all batches produced (b) (4)
- The official regulatory methods have not been identified in the specification. Identify which of the listed methods are the regulatory methods and which are alternate methods.
- You have not included testing for polymorphic form. Provide data from polymorph screening studies to demonstrate that such testing is not required.

b) Manufacturing Process

You propose to replace testing for residual (b) (4) in the future, (b) (4) any changes to the control strategy based on this model should be reported to the Agency, along with development and validation data.

c) Stability

- Reporting only the largest unspecified impurity is not sufficient. All impurities above the reporting threshold should be included in batch results and stability tables
- Please revise the retest date to (b) (4) months. The limited stability data that you have submitted for drug substance manufactured (b) (4) does not warrant a (b) (4) month retest period, as you propose
- The proposed stability commitment is not acceptable. Commit to place the first three commercial batches on stability testing, with testing for all attributes in the approved stability protocol. According to ICH Q1A(R2), add an 18 months sampling point to the protocol. In addition, commit to place one commercial batch on stability testing annually. Commit to report all out of specification results to the Agency.

II. Drug Product:

a) **Composition**

- Your proposal (b) (4) with magnesium stearate (b) (4) is not acceptable. Define a (b) (4) composition for your product that is the same as the composition of bioequivalence and stability batches.
- Your commercial product will need to be manufactured with the same coating and same thickness as in stability and bioequivalence batches. Remove statements from the composition table (and other locations in the submission) (b) (4). Any significant changes in coating will need to be reported to the Agency. Please note that the composition table and executed batch records are not in agreement, showing different amounts of coating per tablet. Revise to correct this.
- Specify the amount (b) (4) in the composition table

b) **Manufacturing Process**

- According to CFR 314.50 (d)(ii)(c) the application should include a master batch record or a comparably detailed description of the production process. The information you have submitted is incomplete and requires inclusion of the following steps in a description of the process (b) (4)
- Provide data to support use (b) (4) as included in your manufacturing process description. The use of this size is not supported by data in the pharmaceutical development report.
- The proposed holding times (b) (4) require justification. Please note that the expiration dating period starts (b) (4)
- Please revise the finished drug product specification to include testing of the finished, coated product. Your proposal (b) (4) is not acceptable.

c) **Specification**

- Reporting only the largest impurity is unacceptable. Add specification limits for all impurities, including unidentified impurities as recommended in ICH Q3B(R2).
- Add testing (b) (4) to the specification.
- The proposed limit (b) (4) is not acceptable. Based on toxicology considerations, lower the limit (b) (4)
- Confirm that reported content uniformity data are based on single tablet analyses, not on analysis of composite samples. Please add a statement to that effect to the content uniformity procedure

d) **Analytical Methods**

- Your design of experiments data for both the drug substance and drug product are too limited to give you the flexibility you propose in running your analytical procedures. Therefore, provide the exact conditions that were used in the submitted validation studies and make them the routine operationing conditions for analysis of the commercial product. This applies to all analytical methods for which you have submitted DoEs.
- For the (b) (4) procedure, although you did not use a DoE approach, you recommend (b) (4). This approach is not acceptable. Therefore, provide the exact conditions that were used in the validation studies that you submitted and make them the routine operational conditions
- Your plan (b) (4) is not acceptable. Method changes, with validation data, need to be submitted to the Agency through standard reporting procedures.
- You have not provided sufficient detail (b) (4). Provide additional information including the description of your calibration/validation samples and detailed description of the calibration model and calibration statistics.

e) Stability

- Your stability data suggest that (b) (4) specification limit (b) (4) should be based on batch and stability data. Therefore, your proposed limit (b) (4) is excessive and should be lowered (b) (4).
- The proposed expiration dating period of 24 months for tablets packaged in aluminum/aluminum blister (b) (4) is acceptable. However, you do not have sufficient data to support the proposed 24 month expiration dating period for product packaged in 30 and 90 count HDPE bottles. Based on the submitted data, an (b) (4) months expiration dating period is more appropriate.

Additional discussion:

The sponsor asked for clarification on the Agency's evaluation of the proposed expiration dating periods for drug product stored in various containers. FDA stated that (b) (4)

it is FDA's position that a 24 month expiration dating period based on 12 months of stability data obtained in matrixed studies is not justified.

III. Others Issues

a) DMF

DMF (b) (4) for the coating mixture is inadequate to support your application.

b) Comparability Protocol

Your comparability protocol for new drug substance manufacturing sites is not acceptable. It does not address impurity profiles (in particular genotoxic impurities) of drug substance manufactured at the new site. In addition, the proposed change needs to be submitted as Prior Approval Supplement.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

At this time, we do not anticipate that this application will require a REMS. However, we will make a final determination as to the need for a REMS upon completion of our review of your application.

5.0 ADVISORY COMMITTEE MEETING

Correction:

At this time there are no plans for an Advisory Committee meeting specifically for this application.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

The late cycle meeting (LCM) will be held no less than 12 calendar days before the Advisory Committee Meeting. The proposed labeling and post-marketing requirements or post-marketing commitments will be communicated to you by May 11, 2014.

Correction:

The proposed date for the late cycle meeting is June 18, 2014.

In addition, please note the following projected milestone dates:

Labeling, PMR/PMC to Applicant:	May 30, 2014
LCM Background Package:	June 6, 2014
PDUFA Action:	September 16, 2014

7.0 SPONSOR QUESTIONS

- Understanding the process between the Mid-cycle and the Late Cycle reviews; when will the late Cycle meeting be scheduled?

FDA Response:

The late cycle meeting will be held no less than 12 calendar days before the Advisory Committee Meeting.

Correction:

Please see response to Section 5.0 and 6.0

- What is the status of the CSS review? What will the approved label reflect? Will it reflect the CSS recommendation for scheduling or current scheduling status?

FDA Response:

FDA stated that naloxegol is currently a Schedule II substance under the Controlled Substances Act. If FDA approves the NDA for naloxegol, and if a scheduling action on naloxegol has not been completed by DEA at the time of approval, the labeling of naloxegol will reflect its current scheduling status under the CSA. If a scheduling action is completed by DEA following an approval of the naloxegol NDA, the Sponsor should request a label change to reflect its new scheduling status.

FDA aims to have the abuse potential review complete prior to the PDUFA goal date, but the final DEA decision regarding scheduling is not subject to the PFUDA timeline. FDA further clarified that the review of the Sponsor's petition request for decontrol of naloxegol under the CSA could not be finalized prior to submission of the NDA, given that the Sponsor stated in the petition that additional human data would be submitted in the NDA.

- Have all of the RFI's and Day 74 responses to date addressed the questions asked by the reviewers?

FDA Response:

Yes.

- Status update (b) (4)

FDA Response:

The request is under review. (b) (4)

- For the RFIs included in the Mid Cycle Communication is there an anticipated timing for submission?

FDA Response:

FDA recommends submitting the responses to information requests in a timely manner, no later than 3 months prior to the PDUFA goal date.

- Will the agency accept responses on a rolling basis as there are some that can be addressed sooner than others?

FDA Response:

FDA will accept responses on a rolling basis.

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

/s/

MAUREEN D DEWEY
04/29/2014



NDA 204760

MID-CYCLE COMMUNICATION

AstraZeneca Pharmaceuticals LP
ATTENTION: Lynley K. Thinnes
Director, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Thinnes:

Please refer to your New Drug Application (NDA) dated and received September 16, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for MOVANTI^K (naloxegol oxalate tablets), 12.5 mg and 25 mg.

We also refer to the teleconference between representatives of your firm and the FDA on March 13, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, please contact Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Maureen Dewey
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: March 13, 2014
Application Number: NDA 204760
Product Name: MOVANTIK
Indication: Treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.
Applicant Name: Astra Zeneca
Meeting Chair: Anil Rajpal, M.D.
Meeting Recorder: Maureen Dewey, M.P.H.

FDA ATTENDEES

Office of Drug Evaluation III

Julie Beitz, MD, Director

Maria Walsh, RN, MS, Associate Director for Regulatory Affairs

Division of Gastroenterology and Inborn Errors Products

Donna Griebel, MD, Director

Joyce Korvick, M.D., MPH, Deputy Director for Safety

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Pediatric and Maternal Health Staff

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Carrie M. Ceresa, Pharm D., MPH, Regulatory Reviewer
Millie Wright, RN, MSN, Senior Regulatory Health Project Manager

Office of Surveillance & Epidemiology (OSE)

Office of Pharmacovigilance, Division of Epidemiology I

Carolyn McCloskey, MD, MPH, Medical Officer Epidemiologist
Christian Cao, MPAS, PA-C, Safety Evaluator, Division of Pharmacovigilance 1

OSE - Division of Risk Management

Reema Mehta, PharmD, MPH, Team Leader
Nyedra W. Booker, PharmD, M.P.H., Risk Management Analyst

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APPLICANT ATTENDEES

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Lynley Thinnes, Regulatory Affairs Director
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Mark Sostek, Medical Science Director
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Eike Floetmann, Toxicology Project Leader
Robert Timko, Regulatory CMC Director
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Robert Sepeylak, Pharmaceutical Development Project Director
Judith Prosser, Associate Director, Regulatory Project Management
Jean Surian, Associate Director, Regulatory Project Management

Nektar Therapeutics Attendees:

Robert Medve, Chief Medical Officer
Carlo Di Fonzo, Vice President, Drug Development and Regulatory Affairs

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

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2.1 NONCLINICAL

Pregnancy Category (b) (4) appears to be inappropriate for MOVANTIK, based on our preliminary assessment of the fetal skeletal changes in the segment II developmental study in rabbits.

Additional Discussion:

The Applicant requested clarification of which pregnancy category the Agency would recommend. The Agency stated that Pregnancy category C appears to be appropriate.

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The frequency of high naloxegol systemic exposures in four individuals with moderate or severe renal impairment within the small renal impairment groups in study D3820C00009 is still of concern to the Division. While naloxegol PK in general appear to exhibit moderate variability, there appears to be no evidence of outliers in other completed studies who displayed up to 8-fold higher systemic exposures, as were noted in the renal impairment study. For this reason, we remain concerned that renal impairment of moderate or worse severity may render some patients more susceptible than others.

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Potential labeling issues:

a)

(b) (4)
based upon our analysis, we identified

patients who experienced symptoms consistent with opioid withdrawal who were on maintenance opioids (b) (4). Therefore, this should be reflected in the proposed label to include a statement such as: (b) (4)

Additional Discussion:

The Applicant requested clarification on the source of data reviewed to make the determination that opioid withdrawal occurred in study subjects taking opioids (b) (4). FDA reviewed the Applicant's analyses and data using the preferred terms based on an expanded list of symptoms consistent with opioid withdrawal, which included terms from the DSM-IV, COWS and SOWS.

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- c) (b) (4)

Additional Discussion:

(b) (4)

- d) We are considering if there is a role for the low dose in patients who cannot tolerate the high dose.

Additional Discussion:

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- e) Because there was evidence of opioid withdrawal in study subjects receiving naloxegol, the proposed (b) (4) is not fully supported by the data.

Additional Discussion:

FDA clarified that the data collected on daily opioid dose and average pain intensity were not analyzed as pre-specified endpoints (b) (4)

Additionally, as stated under Item a) above, there was evidence of opioid withdrawal in some patients (b) (4)

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3.0 INFORMATION REQUESTS

3.1 Maternal Health:

We note that three pregnancies occurred during the phase 3 trials with naloxegol. Only one pregnancy is reported in your Summary of Clinical Safety and that pregnancy occurred in the placebo arm. Please provide the two additional pregnancy reports.

Please provide a summary of published data of fetal effects (both human and animal) with maternal use of opioid antagonists. Provide all references reviewed and summarized.

Additional Discussion:

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Provide explanation for roughly two-fold higher mean naloxegol exposures in the ‘normal’ group of renal PK study when compared to healthy volunteers of other phase I clinical trials.

3.3 Chemistry, Manufacturing and Controls:

I. Drug Substance:

a) Specification

- You have not included testing for all potential genotoxic impurities. While you explain this (b) (4) you have not provided sufficient data regarding the origin (b) (4) to justify their use. Provide test results for genotoxic impurities in all batches produced (b) (4)
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b) Manufacturing Process

You propose to replace testing for residual (b) (4) in the future (b) (4) any changes to the control strategy based on this model should be reported to the Agency, along with development and validation data.

c) Stability

- Reporting only the largest unspecified impurity is not sufficient. All impurities above the reporting threshold should be included in batch results and stability tables
- Please revise the retest date to (b) (4) months. The limited stability data that you have submitted for drug substance manufactured (b) (4) does not warrant a (b) (4) month retest period, as you propose
- The proposed stability commitment is not acceptable. Commit to place the first three commercial batches on stability testing, with testing for all attributes in the approved stability protocol. According to ICH Q1A(R2), add an 18 months sampling point to the protocol. In addition, commit to place one commercial batch on stability testing annually. Commit to report all out of specification results to the Agency.

II. Drug Product:

a) Composition

- Your proposal (b) (4) with magnesium stearate (b) (4) is not acceptable. Define a (b) (4) composition for your product that is the same as the composition of bioequivalence and stability batches.
- Your commercial product will need to be manufactured with the same coating and same thickness as in stability and bioequivalence batches. Remove statements from the composition table (and other locations in the submission) (b) (4). Any significant changes in coating will need to be reported to the Agency. Please note that the composition table and executed batch records are not in agreement, showing different amounts of coating per tablet. Revise to correct this.
- Specify the amount (b) (4) in the composition table

b) Manufacturing Process

- According to CFR 314.50 (d)(ii)(c) the application should include a master batch record or a comparably detailed description of the production process. The information you have submitted is incomplete and requires inclusion of the following steps in a description of the process (b) (4).
- Provide data to support use (b) (4) as included in your manufacturing process description. The use of this size is not supported by data in the pharmaceutical development report.
- The proposed holding times (b) (4) require justification. Please note that the expiration dating period starts at (b) (4).
- Please revise the finished drug product specification to include testing of the finished, coated product. Your proposal (b) (4) is not acceptable.

c) Specification

- Reporting only the largest impurity is unacceptable. Add specification limits for all impurities, including unidentified impurities as recommended in ICH Q3B(R2).
- Add testing (b) (4) to the specification.
- The proposed limit (b) (4) is not acceptable. Based on toxicology considerations, lower the limit (b) (4).
- Confirm that reported content uniformity data are based on single tablet analyses, not on analysis of composite samples. Please add a statement to that effect to the content uniformity procedure

d) Analytical Methods

- Your design of experiments data for both the drug substance and drug product are too limited to give you the flexibility you propose in running your analytical procedures. Therefore, provide the exact conditions that were used in the submitted validation studies and make them the routine operationing conditions

for analysis of the commercial product. This applies to all analytical methods for which you have submitted DoEs.

- For the (b) (4) procedure, although you did not use a DoE approach, you recommend (b) (4). This approach is not acceptable. Therefore, provide the exact conditions that were used in the validation studies that you submitted and make them the routine operational conditions.
- Your plan (b) (4) is not acceptable. Method changes, with validation data, need to be submitted to the Agency through standard reporting procedures.
- You have not provided sufficient detail (b) (4). Provide additional information including the description of your calibration/validation samples and detailed description of the calibration model and calibration statistics.

e) Stability

- Your stability data suggest that (b) (4) your proposed limit (b) (4) is excessive and should be lowered (b) (4).
- The proposed expiration dating period of 24 months for tablets packaged in aluminum/aluminum blister (b) (4) is acceptable. However, you do not have sufficient data to support the proposed 24 month expiration dating period for product packaged in 30 and 90 count HDPE bottles. Based on the submitted data, an (b) (4) months expiration dating period is more appropriate.

Additional discussion:

The sponsor asked for clarification on the Agency's evaluation of the proposed expiration dating periods for drug product stored in various containers. FDA stated that (b) (4)

(b) (4) it is FDA's position that a 24 month expiration dating period based on 12 months of stability data obtained in matrixed studies is not justified.

III. Others Issues

a) DMF

DMF (b) (4) for the coating mixture is inadequate to support your application.

b) Comparability Protocol

Your comparability protocol for new drug substance manufacturing sites is not acceptable. It does not address impurity profiles (in particular genotoxic impurities) of drug substance manufactured at the new site. In addition, the proposed change needs to be submitted as Prior Approval Supplement.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

At this time, we do not anticipate that this application will require a REMS. However, we will make a final determination as to the need for a REMS upon completion of our review of your application.

5.0 ADVISORY COMMITTEE MEETING

Correction:

At this time there are no plans for an Advisory Committee meeting specifically for this application.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

The late cycle meeting (LCM) will be held no less than 12 calendar days before the Advisory Committee Meeting. The proposed labeling and post-marketing requirements or post-marketing commitments will be communicated to you by May 11, 2014.

Correction:

The proposed date for the late cycle meeting is June 18, 2014.

In addition, please note the following projected milestone dates:

Labeling, PMR/PMC to Applicant:	May 30, 2014
LCM Background Package:	June 6, 2014
PDUFA Action:	September 16, 2014

7.0 SPONSOR QUESTIONS

- Understanding the process between the Mid-cycle and the Late Cycle reviews; when will the late Cycle meeting be scheduled?

FDA Response:

The late cycle meeting will be held no less than 12 calendar days before the Advisory Committee Meeting.

Correction:

Please see response to Section 5.0 and 6.0

- What is the status of the CSS review? What will the approved label reflect? Will it reflect the CSS recommendation for scheduling or current scheduling status?

FDA Response:

FDA stated that naloxegol is currently a Schedule II substance under the Controlled Substances Act. If FDA approves the NDA for naloxegol, and if a scheduling action on naloxegol has not been completed by DEA at the time of approval, the labeling of naloxegol will reflect its current scheduling status under the CSA. If a scheduling action is completed by DEA following an approval of the naloxegol NDA, the Sponsor should request a label change to reflect its new scheduling status.

FDA aims to have the abuse potential review complete prior to the PDUFA goal date, but the final DEA decision regarding scheduling is not subject to the PFUDA timeline. FDA further clarified that the review of the Sponsor's petition request for decontrol of naloxegol under the CSA could not be finalized prior to submission of the NDA, given that the Sponsor stated in the petition that additional human data would be submitted in the NDA.

- Have all of the RFI's and Day 74 responses to date addressed the questions asked by the reviewers?

FDA Response:

Yes.

- Status update (b) (4)

FDA Response:

(b) (4)

- For the RFIs included in the Mid Cycle Communication is there an anticipated timing for submission?

FDA Response:

FDA recommends submitting the responses to information requests in a timely manner, no later than 3 months prior to the PDUFA goal date.

- Will the agency accept responses on a rolling basis as there are some that can be addressed sooner than others?

FDA Response:
FDA will accept responses on a rolling basis.

APPEARS THIS WAY ON
ORIGINAL

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/s/

MAUREEN D DEWEY
03/31/2014



NDA 204760

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

AstraZeneca Pharmaceuticals LP
Attention: Lynley K. Thinnies
Director, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Thinnies:

Please refer to your New Drug Application (NDA) dated and received September 16, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Movantik (naloxegol oxalate) Tablets, 25 mg.

We also refer to your amendments dated September 27, 2013, October 15 & 17, 2013, and November 14, 2013.

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**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>). Therefore, the user fee goal date is September 16, 2014.

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 May 30, 2014. In addition, the planned date for our internal mid-cycle review meeting is February 27, 2014. We are currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

1. The proposed metabolism of naloxegol, a pegylated product, is described as formation of partially shortened PEG chain products. Address the potential for the formation and systemic accumulation of ethylene glycol, diethylene glycol as well as their toxic metabolites as by-products of this metabolism.
2. We notice that in the mass balance study the ^{14}C -radiolabel is located on the PEG side chain rather than on naloxone moiety. You have noted in your metabolite profiling report that “No radiochromatographic peak corresponds to naloxone or naloxol indicating that, if formed, these would represent less than 1% of unchanged NKTR-118”. Given the position of the radiolabel, address how you have ensured that no naloxone has formed during in vivo studies in humans.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

1. A certification (b) (4)

2. A SAS transport file of the plasma concentration data from the BE study (D3820C00018). These data should also include the first and last time points used to estimate the elimination constant (K_{el}) for each subject/period as shown. Submit the data in the following format:
SUBJ SEQ PER TRT C1 C2 C3...Cn KE_FIRST KE_LAST T1 T2 T3...Tn
3. A SAS transport file of the pharmacokinetic data from the BE study. The data should include AUC0-t, AUC0-inf, C_{max}, T_{max}, K_{el} , and T_{1/2} as shown. Submit the data in the following format:
SUBJ SEQ PER TRT AUC AUCINF CMAX TMAX KE Thalf

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 Medication Guide. Submit

consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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 indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a (b) (4) waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the (b) (4) waiver request is denied.

(b) (4)

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

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

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/s/

MATTHEW C SCHERER

11/27/2013

Signing for Donna Griebel



NDA 204760

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Astra Zeneca
Attention: Barry Sickels
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-2822
FAX: (302) 886-2822

Dear Barry Sickels:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Movantik (Naloxegol) tablets 12.5 mg and 25 mg.

We will be performing methods validation studies on Movantik (Naloxegol) tablets 12.5 mg and 25 mg, as described in NDA 204760.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

Analytical procedure for assay by UPLC
Analytical procedure for assay by HPLC
Analytical procedure for (b) (4) test by LC
Analytical procedure for (b) (4) by LC

Samples and Reference Standards

5 g Naloxegol oxalate drug substance
500 mg Naloxegol oxalate drug reference standard
300 mg (b) (4) reference standard
200 mg (b) (4) reference standard
50 Movantik (Naloxegol) tablets 12.5 mg
50 Movantik (Naloxegol) tablets 25 mg

Equipment

1 (b) (4) particle size
1 (b) (4) column
1 (b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
11/13/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 204760

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

AstraZeneca Pharmaceuticals LP
1800 Concord Pike, P.O. Box 8355
Wilmington, DE 19803-8355

ATTENTION: Lynley K. Thinnes
Director, Regulatory Affairs

Dear Ms. Thinnes:

Please refer to your New Drug Application (NDA) dated and received September 16, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Naloxegol Oxalate Tablets, 12.5 mg and 25 mg.

We also refer to your correspondence, dated and received September 27, 2013, requesting review of your proposed proprietary name, Movantik. We have completed our review of the proposed proprietary name, Movantik and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your September 27, 2013 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Phong Do, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4795. For any other information regarding this application, contact Matthew Scherer, the Office of New Drugs (OND) Regulatory Project Manager, at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk
Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

KELLIE A TAYLOR
11/01/2013



NDA 204760

NDA ACKNOWLEDGMENT

AstraZeneca Pharmaceuticals LP
Attention: Lynley K. Thinnes
Director, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Thinnes:

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: Movantik (naloxegol oxalate) Tablets, 12.5 mg and 25 mg

Date of Application: September 16, 2013

Date of Receipt: September 16, 2013

Our Reference Number: NDA 204760

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 15, 2013, 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

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

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

If you have any questions, 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

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/s/

MATTHEW C SCHERER
10/08/2013



IND 078781

MEETING MINUTES

AstraZeneca Pharmaceuticals LP
Attention: George Kummeth
Regulatory Affairs Director
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

Dear Mr. Kummeth:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for NKTR-118 (naloxegol) Tablets.

We also refer to the meeting between representatives of your firm and the FDA on April 23, 2013. The purpose of the meeting was to discuss opioid withdrawal and cardiovascular safety as it relates to the development of naloxegol.

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
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: Type C
Meeting Date and Time: April 23, 2013, 10:00 to 11:00 am
Meeting Location: White Oak, Building 22, Room 1309
Application Number: IND 078781
Product Name: Naloxegol (PEG-naloxol) Tablets
Indication: Opioid induced constipation
Sponsor/Applicant Name: AstraZeneca Pharmaceuticals, LP
Meeting Chair: Anil Rajpal
Meeting Recorder: Matthew Scherer

FDA ATTENDEES

Joyce Korvick, MD, MPH, Deputy Safety Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Andrew Mulberg, MD, FAAP, CPI, Deputy Director, DGIEP
Anil Rajpal, MD, Medical Team Leader, DGIEP
Aisha Johnson, MD, MBA, Medical Officer, DGIEP
Rob Fiorentino, MD, Medical Team Leader, DGIEP
Preston Dunnmon, MD, Medical Officer, Division of Cardiovascular and Renal Products
Ellen Fields, MD, MPH, Medical Team Leader, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Elizabeth Kilgore, MD, Medical Officer, DAAAP
Sharon Hertz, MD, Deputy Director, DAAAP
Clara Kim, PhD, Team Leader, Division of Biometrics VII
Bradley McEvoy, PhD, Statistician, Division of Biometrics VII
Sue-Chih Lee, PhD, Team Leader, Division of Clinical Pharmacology III
Matthew Scherer, Regulatory Project Manager, DGIEP

SPONSOR ATTENDEES

George Kummeth, B.S., M.B.A., Senior Director, Regulatory Affairs
Kathleen Cantagallo, Global Product Vice President, Development Projects
Joseph Cordaro, Executive Director Development
William Mezzanotte, MD, Vice President, CV, GI, Respiratory & Inflammation Products
Barry Sickels, Vice President, US Regulatory Affairs
Raj Tummala, MD, Director Clinical Research
Jaakko Lappalainen, MD, Director Clinical Research
Peter Barker, Global Product Statistician
Christer Gottfridsson, MD, PhD, Cardiac Safety Knowledge Group, Global Clinical Development
(b) (4) Medical and Scientific Consultant, Professor of Medicine

(b) (4)

Robert Medve, MD, Chief Medical Officer, Nektar Therapeutics
Carlo J. DiFonzo, PhD, VP, Drug Development & Regulatory Affairs, Nektar Therapeutics
Maryann Toto, Associate Director, Regulatory Affairs

1. BACKGROUND

AstraZeneca (AZ) is developing naloxegol, a mu-opioid receptor antagonist, for the treatment of opioid-induced constipation (OIC).

In the preliminary responses sent on October 8, 2012 in preparation for a pre-NDA meeting (scheduled for October 10, 2012, subsequently canceled), the FDA informed AZ that it had concerns that there may be a class effect of mu-opioid receptor antagonists precipitating opioid withdrawal and related cardiovascular safety concerns. AZ requested this meeting to discuss available data and how to address the FDA's concerns.

2. DISCUSSION

Question 1: In its October 2012 communication to AstraZeneca (see Appendix 1), the Agency referenced the 2008 alvimopan Advisory Committee Meeting transcript as important to understand the Agency's concern about potential for CV Risk in the μ -opioid antagonist class. Furthermore, the Agency stated that "The effects of opioid withdrawal on the autonomic nervous system, including changes in hemodynamic parameters, are known to increase the risk of cardiovascular adverse events." However, in reviewing the 2008 alvimopan Advisory Committee meeting transcript, AstraZeneca has not found evidence of increased risk of opioid withdrawal as a precipitant for imbalances in MACE rates in Study GSK 14.

- a. Would the Agency please clarify how the alvimopan data discussed at the 2008 Advisory Committee meeting supports a link between μ -opioid antagonists and opioid withdrawal leading to MACE?

FDA Response:

These are two separate but related findings.

First, the 2008 AC for alvimopan demonstrated the association between numerically higher CV events and mu-opioid receptor antagonism. There was no signal for CV events in the short duration Post-Operative Ileus (POI) studies with alvimopan. However, the POI studies had design limitations that impaired their ability to detect CV events as noted below:

- **Follow-up by phone call only (except 1/9 studies)**
- **Important safety endpoints such as 30 day and 60 day morbidity/mortality not collected**
- **CV events not prospectively defined nor consistently assessed post exposure**
- **Missing follow-up data did not imply the lack of CV events**

In contrast, from Study 014, the only study with 12 month follow-up and the largest study of the alvimopan development program, there was a notable imbalance in both the number of CV events as well as the number of patients experiencing CV events in the alvimopan treatment arm(s).

Second, FDA has become aware of data from this class that have suggested temporal associations between dosing, CV symptoms and/or events, and withdrawal symptoms.

Further, in publically available postmarketing drug safety evaluations completed from July 2011 through December 2011, AE reports of drug withdrawal syndrome with use of methylnaltrexone were identified. We further note that your product antagonizes opioid receptor subtypes (e.g., δ -opioid) that are known to be present in the cardiovascular system and that are implicated in cardioprotection.

It is unclear if these withdrawal events represent a causal association with the drug or represent a background rate of withdrawal in patients taking opioids. However, given the potential for withdrawal, the above findings, and the elevated baseline risk for CV events in the OIC population (described in the literature), the Agency is concerned about a possible association between withdrawal due to the drug and CV events.

- b. Is opioid withdrawal with precipitation of hemodynamic changes leading to MACE the only mechanism under consideration as an explanation for possible increased CV risk or are other mechanisms under consideration by the Agency?

FDA Response:

Opioid withdrawal with precipitation of hemodynamic effects may be the most likely mechanism to explain the possible increase in CV risk, although we cannot exclude other mechanisms. Precipitation of withdrawal by an opioid antagonist, which may be mediated by interaction with central and/or peripheral opioid receptors, may increase the CV risk in an opioid-tolerant patient due to activation of the autonomic nervous system. The exact mechanism has yet to be unequivocally defined. While mu-opioid receptors are present in the heart, their function is as of yet unclear, so any potential for pro-thrombotic or vasoconstrictive consequences to their blockade would be purely speculative at this point.

Your development program should explore potential mechanisms and the resultant cardiovascular safety concern.

Meeting Discussion

FDA noted that there are limitations in what can be concluded in looking at summary data when the datasets are “small,” i.e., underpowered to detect a CV signal. With smaller datasets, the FDA examines every patient experience (including dropouts).

FDA noted that the associations between opioid withdrawal, CVEs and mu-opioid receptor antagonists, described in the preliminary responses, have been observed in datasets from other mu-opioid receptor antagonist development programs.

Question 2: The study procedures, analysis methods, and preliminary results for assessing CV events and opioid withdrawal risk in the naloxegol Phase III development program have been described in this Briefing Document.

- a. Are there additional analyses or data presentations the Agency would like to see included in the NDA to further assess the CV risk for naloxegol?

FDA Response:

Yes, there are additional analyses or data presentations we would like to see included in the NDA to further assess the CV risk for naloxegol (see below). See also responses to Questions 1a and 2b.

In Table 1 of Appendix 7 (page 4 of that Appendix) which shows categorical shifts in blood pressures, the footnote states that “the sample sizes for the data presented are less than or equal to N”. This implies that there could be data missing from the data tables. For all data entries, please indicate the appropriate N and percent based on that N.

This issue of missing data is important, especially as this relates to the possibility that informative censoring may have impacted the count of CV and/or opioid withdrawal events. Specify clearly in a stand-alone and labelled section of your submission the following:

- **What imputation rules were employed in the efficacy analysis when follow-up data were missing.**
- **What imputation rules and/or censoring rules were used for patients who withdrew early with respect to counting CV outcome events (regardless of severity) and withdrawal events (regardless of severity).**

See also FDA Additional Comments 1 and 2.

- b. **Are there additional analyses or data presentations the Agency would like to see included in the NDA to further assess the opioid withdrawal risk for naloxegol?**

FDA Response:

Yes, there are additional analyses or data presentations we would like to see included in the NDA to further assess the opioid withdrawal risk for naloxegol (see below).

We note the following limitations of your Phase 3 studies:

- **The key Phase 3 studies 04 and 05 were not adequately designed to measure opioid withdrawal due to the infrequent administration of the modified Himmelsbach Opioid Withdrawal Scale (mHS) and lack of a subjective opioid withdrawal assessment scale.**
- **Your analyses did not provide sufficient information to adequately assess whether opioid withdrawal occurred in the Phase 3 studies.**
- **Due to the flaws in study design for assessing opioid withdrawal, there is limited ability to reliably interpret the opioid withdrawal findings.**

See also FDA Additional Comments 3 and 4.

In order to further evaluate whether naloxegol use for OIC is associated with opioid withdrawal (within the confines of the limitations above), you should conduct the following analyses on the completed Phase 3 studies:

- **Display weekly average opioid use (maintenance and breakthrough morphine equivalent doses) along with pain scores and withdrawal symptoms by treatment group for each study.**

- In graphic or tabular form, display information regarding mean weekly opioid dose, mean weekly pain scores, and withdrawal assessments for all patients (as mean scores) and individually for the subjects who experienced an AE of withdrawal by week of treatment in order to compare opioid use and pain scores in patients who experienced a withdrawal AE with the study population as a whole.
- Provide a graph of weekly pain scores over time for patients with AE of drug withdrawal compared to all patients by treatment group in order to assess changes in pain over time for all subjects, without using a cutoff of an increase of at least 2 points in the pain score.
- Provide an analysis of breakthrough/rescue analgesic use by treatment group that includes opioid and non-opioid rescue.
- Perform a post-hoc analysis of drop-outs (discontinuations) due to AEs potentially related to opioid withdrawal during each treatment period by treatment group.
- Include additional preferred term events in the post hoc analysis of adverse events potentially related to opioid withdrawal that include signs and symptoms of withdrawal noted in the DSM- IV Opioid Withdrawal Diagnostic Criteria, COWS, OOWS and other clinical terms associated with opioid withdrawal.
- In order to understand the association of CV AEs and AEs due to withdrawal, include the type and timing (relative to dosing) of the CV events in a table that also includes the withdrawal AEs for those patients identified in the studies as having both types of AEs. In addition, provide narratives for these patients.

For future studies, you should include the following:

- Utilize an opioid withdrawal assessment tool that includes GI symptoms. Analyses should be performed both with and without the GI symptoms.
- We recommend the use of COWS as the analysis of the scores includes identification of the severity of withdrawal.
- Perform opioid withdrawal assessments more frequently, at least weekly for the first two weeks, then intermittently for the duration of the study.
- Include a subjective opioid assessment tool such as the SOWS which should be performed daily for the first two weeks, then intermittently for the duration of the study.

Meeting Discussion

AZ agreed to include the above-listed analyses in the naloxegol NDA; however, AZ noted that based upon its understanding of the data from the naloxegol program, these further analyses will not change the conclusions regarding the cardiovascular safety of naloxegol.

FDA clarified that the completed studies do not appear to be adequate to capture a withdrawal signal.

- c. Blinded, adjudicated data revealed only rare MACE without any imbalance across treatment groups. Further, there was only non-specific reporting of signs and symptoms consistent with opioid withdrawal, and in very few patients. For this reason, it is AstraZeneca's position that a randomized, controlled clinical trial to rule out a specific upper bound of the confidence interval for CV risk associated with opioid withdrawal is neither necessary nor practicable. Does the Agency agree?

FDA Response:

No, we do not agree. It will be necessary to conduct a cardiovascular safety trial given the concerns we described in the responses above. So long as equipoise is maintained after you have reviewed your safety data, we also do not see an ethical limitation to a CV safety trial.

Meeting Discussion

FDA agreed to further discuss internally whether these data will be required to file an NDA submission.

[Post-meeting update: FDA clarifies that the results of a cardiovascular safety trial are not required to successfully file the naloxegol NDA.]

FDA ADDITIONAL COMMENTS

- 1. When you submit your NDA, include a listing of all patients who withdrew from the trial early and who did not have narratives generated for CV outcome and/or opioid withdrawal events, and provide FDA with narratives on all of these patients as well. Complete CRFs (including SAE worksheets or COMIS forms) should be submitted for all patients withdrawing regardless of cause. All CV-EAC packages/dossiers and queries should likewise be submitted at the time of your NDA submission.**

- 2. Your CV-EAC charter states the following:**

A layered approach is used to ensure that any and all relevant CV SAEs/AEs are reviewed by the Adjudication Committee. A primary and conservative guiding principle is that Investigators should be allowed to select any CV-type SAE/AE for adjudication which they feel is appropriate. Investigators are given training and on-site resources to describe this process. Those events requiring review by the CV-EAC (see section 9) will be reported by the Investigator via the Veracity EAS. The Investigator will complete all required Case Report Form pages for the event type.

An additional guiding principle is that all SAEs which are clearly CV in nature will be adjudicated. Quintiles's Safety provides, at a minimum, monthly data output to AstraZeneca's Safety Surveillance group to identify cases which may have been missed by the Investigators. This list will be provided frequently close to database lock. Quintiles's Data Management also runs a programmed check based on MedDRA preferred terms that may trigger for adjudication (see Appendix B). Any events identified through these processes are confirmed by AstraZeneca Safety Surveillance, who then forwards the list to Quintiles CEVA to initiate event processing.

Finally, select non-SAE events may also be adjudicated based on either Investigator selection or by AstraZeneca medical review. Select non-SAE events will be identified through medical reviews conducted by a three person panel comprised of a single representative from each of AstraZeneca's Clinical Development, Patient Safety and the CV special knowledge group. To maintain robustness of the process, AstraZeneca, as directed by the medical review panel, will forward directed queries to Investigators for any CV-type non-SAE of interest to ensure that no potentially adjudicable event is overlooked. To facilitate and document selection of non-SAE CV-type events in an objective and transparent manner, a tracker is used and may be provided on request.

We understand your automated triggers for CV-EAC referral and the PT list for automated scanning appears to be appropriate. However, we are not clear on the process that was used for the manual triggers for CV-EAC referral. This seems to have been investigator discretion and your internal 3 person panel. Were there certain CRF pages and/or adverse events of interest that forced CV-EAC referral? How did the internal process work? Were the internal staff all blinded to and without access to the randomization codes?

In your NDA, include all outputs from your trial steering committees, DMCs, and CV-EACs. For the latter, please include adjudication results for each adjudicator, as well as the ultimate consensus adjudication. Please submit any presentations (PowerPoint, Word, etc.) made by you to any of these committees as well.

- 3. We understand that you selected the Himmelsbach scale to assess for withdrawal due to its focus on non-GI components of the withdrawal syndrome, under the rationale that abdominal cramping and/or diarrhea can be due to the action of the drug. However, per the COWS, cramps, nausea, loose stools, vomiting, and diarrhea are also components of the opioid withdrawal syndrome. Likewise, the pulse rate component of COWS is missing from the Himmelsbach scale. Consequently, your analyses of withdrawal AEs, as well as your counts of tachycardia CV events occurring in tandem with withdrawal events may be underestimates of what is truly occurring in your registration trials.**
- 4. The definition of withdrawal adverse events seems very restrictive. Specifically, per table 3, page 25 of the Meeting Package, footnote 1, preferred terms (PT) prospectively identified as potentially related to opioid withdrawal were: Drug withdrawal convulsions, Drug withdrawal headache, Drug withdrawal syndrome, Drug withdrawal syndrome neonatal, Rebound effect, Steroid withdrawal syndrome, Withdrawal arrhythmia, Withdrawal syndrome, Drug withdrawal maintenance therapy, Drug rehabilitation. Preferred terms specifically related to line items in COWS or the Himmelsbach scale were apparently not included in the PT search from which withdrawal narratives were generated (footnote table 3), though a post hoc analysis of the components of the Himmelsbach scale was generated in Table 5 that does suggest the possibility of a dose response in these events.**

3. ADDITIONAL COMMENTS

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 a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

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. For additional guidance on submission of the PSP, including a PSP Template, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm> .

In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

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 following labeling review resources: the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, labeling guidances, and a sample tool illustrating the format for Highlights and Contents (Table of Contents) available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>.

4. ISSUES REQUIRING FURTHER DISCUSSION

On May 7, 2013, AstraZeneca submitted follow-up questions regarding the additional analyses discussed under questions 2a and 2b.

5. ACTION ITEMS

FDA will review and respond to the May 7, 2013 submission. FDA expects to respond by June 28, 2013.

6. ATTACHMENTS AND HANDOUTS

To facilitate meeting discussion, AstraZeneca provided the following comments in advance of the meeting:

“From the totality of FDA’s comments to AstraZeneca to date, we summarize the FDA position as follows:

- FDA has seen an imbalance in CV events in the long-term alvimopan study
- FDA noted that additional data from this class suggests a temporal association between opioid withdrawal and CV events and/or symptoms
- FDA asserts that OIC patients *may* have a higher baseline CV risk (claims database information with potentially confounding factors)
- FDA has stated that “the effects of opioid withdrawal on the autonomic nervous system, including changes in hemodynamics, are known to increase the risk of CV events”
- FDA suggests that the modified Himmelsbach is a narrow definition for opioid withdrawal. By extrapolation, the Agency seems to suggest that an expanded definition of opioid withdrawal would increase the incidence of CV events.
- Based upon the above, the FDA has indicated that additional study of cardiovascular safety is necessary

During our interaction on Tuesday, we would like to further explore FDA’s comments with the following:

- Experts (b) (4) will attend the meeting and will, based upon their long-term clinical and research experience, challenge the assumption that opioid withdrawal is associated with increased CV morbidity and mortality.
- Summaries of vital sign data, CV AE’s and ECG data demonstrate no clinically meaningful treatment imbalance. Further investigation in this area is unlikely to demonstrate substantive differential autonomic effects from naloxegol versus placebo.
- AstraZeneca will include as part of the NDA filing the additional analyses suggested in the Preliminary Responses; however, it is noted that based upon our understanding of the data from the naloxegol program, these further analyses will not change our conclusions regarding the cardiovascular safety of naloxegol.
- Adjudicated MACE were balanced between naloxegol, placebo, and usual care across the program. No MACE were associated with GI adverse events typically associated with opioid withdrawal or an AE of opioid withdrawal. Thus, neither further analyses nor

expansion of the definition of opioid withdrawal are likely to uncover a relationship between opioid withdrawal and an imbalance in CV events in our program.

- Forty-percent of patients in the phase 3 program were categorized as high baseline CV risk based on traditional CV risk factors. In this population, adjudicated MACE were also balanced between naloxegol, placebo, and usual care.
- The most recent pharmacology data from AstraZeneca demonstrate that naloxegol is about 30-fold more selective for mu- versus delta-opioid receptors. These data will be included in the NDA.
- Importantly, naloxegol's pharmacology at the mu-opioid receptor is one of neutral antagonism which differs from the activity of both alvimopan and methylnaltrexone. Thus, it is not appropriate to generalize conclusions from other programs to suggest a class effect; especially as our robust phase III program, including prospective blinded adjudication showed no CV signal.
- Naloxegol consistently demonstrates a benefit to patients with OIC, and these patients have substantial unmet medical need which naloxegol addresses.
- We continue to believe that based upon the totality of our data and absence of a signal for increased CV risk, a CV safety study is not warranted. Further practical medical considerations in this population raise the issue of whether such a study can be completed.”

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
05/22/2013

Scherer, Matthew

From: Scherer, Matthew
Sent: Monday, August 02, 2010 4:23 PM
To: 'Kummeth, George'
Subject: IND 78781 (NKTR-118) - Advice on Mortality Management in Carcinogenicity Study

Dear Mr. Kummeth,

Please refer to your investigational new drug application (IND) for NKTR-118. We have reviewed your submission, dated July 27, 2010, that included a proposed mortality management program for the 2-year carcinogenicity study in rats.

The Executive CAC and the Division of Gastroenterology Products have the following comments and recommendations:

1. We do not concur with your proposed mortality management plan for the ongoing 2-year carcinogenicity study of NKTR-118 in rats.
2. **For deaths in the Control group:** If the survival of one sex reaches 20 animals, then all study animals of the affected sex in the control and treatment groups should be sacrificed.
3. **For deaths in the Treatment groups:** Through week 100, if the number of surviving animals in a treatment group of either sex reaches 15, the affected sex in this group should be sacrificed. After week 100, if the surviving animals in a treatment group of either sex reaches 15, the study animals of the affected sex in all treatment and control groups should be sacrificed.

Please let me know if you have any additional questions.

Best Regards,

-
Matthew C. Scherer
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODEIII
Ph: 301-796-2307
Fax: 301-796-9905

10903 New Hampshire Avenue
Building 22, Room 5137
Silver Spring, MD 20993

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-78781	ORIG-1	NEKTAR THERAPEUTICS	NKTR 118

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/s/

MATTHEW C SCHERER
08/02/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 78,781

MEETING MINUTES

Nektar Therapeutics
Attention: Carlo J. Di Fonzo, Ph.D.
Vice President, Global Regulatory Affairs
201 Industrial Road
San Carlos, CA 94070

Dear Dr. Di Fonzo:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for NKTR-118 (PEG-Naloxol; NKT-10018).

We also refer to the meeting between representatives of your firm and the FDA on January 26, 2010. The purpose of the meeting was to discuss your the End of Phase 2 and Pre-Phase 3 program for NKTR-118.

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

Comments from the Controlled Substances Staff were not available in time to include with these minutes. They will be provided to you in a later communication.

If you have any questions, please call me at (301) 796-1413.

Sincerely,

{See appended electronic signature page}

Heather Buck, MS, MBA
Regulatory Project Manager
Division of Gastroenterology 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: End of Phase 2

Meeting Date and Time: January 26, 2010, 1:30 pm EST
Meeting Location: FDA White Oak, Building 22, Room 1315

Application Number: 78,781
Product Name: NKTR-118 (PEG-Naloxol; NKT-10018)
Indication: Treatment of opioid-induced constipation (OIC) (b) (4)

Sponsor/Applicant Name: AstraZeneca Pharmaceuticals LP

Meeting Chair: John Hyde, PhD, MD
Meeting Recorder: Heather Buck

FDA ATTENDEES

Donna Griebel, MD	Director, Division of Gastroenterology Products (DGP)
Ruyi He, MD	Acting Deputy Directory, DGP
John Hyde, PhD, MD	Medical Team Leader, DGP
Aisha Peterson, MD, MPH, MBA	Medical Officer, DGP
Heather Buck, MS, MBA	Regulatory Project Manager, DGP
David Joseph, PhD	Acting Pharmacology Team Leader, DGP
Niraj Mehta, PhD	Pharmacology Reviewer, DGP
Mike Welch, PhD	Deputy Director, Division of Biometrics 3
Patrick Morroum, PhD	Biopharmaceutics Supervisor, ONDQA
Jane Bai, PhD	Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 3

SPONSOR ATTENDEES

Nektar Therapeutics

Carlo J. Di Fonzo, PhD	Vice President, Global Regulatory Affairs
Lorianne Masuoka, MD	Senior Vice President & Chief Medical Officer
Patricia Murphy, BS	Executive Director, Regulatory Affairs
Theresa Sweeney, PhD	Senior Director, Toxicology

AstraZeneca Pharmaceuticals LP

Eva-Lena Glämsta, PhD	Safety Assessment
Gary Horowitz, PhD	Executive Director, Regulatory Affairs

Clara Hwang, M.ap. Stat	Statistical Science Director
Lori Kreamer, BS	Global Product Vice President, Development Projects
George Kummeth, MBA	Global Regulatory Affairs Director
Jaakko Lappalainen, MD	Director, Clinical Research
James McDermott, MD	Executive Director, Development
Celia Shelton, PhD	Associate Director, Regulatory Affairs
Mark Sostek, MD	Senior Director, Clinical Research
Yi Wang, PhD	Director, Clinical Pharmacology
Scott W. Grimm PhD	Director, Metabolism & Bioanalysis
Noder Youseff	Directory, Clinical Development

BACKGROUND

On September, 3, 2009, the sponsor (AstraZeneca, previously Nektar) requested this End of Phase 2 (EOP2) meeting for NKTR-118 for the treatment of opioid-induced constipation (OIC). The purpose of this meeting is to discuss the adequacy of the Phase 1 and 2 data as a basis for proceeding into Phase 3, and the plans for Phase 3 development.

DISCUSSION

Questions from the meeting package are shown in plain font. FDA preliminary responses sent to the sponsor prior to the meeting are shown in **boldface**. Discussion at the meeting is indicated by ***bold italics***.

The sponsor reminded all of the transfer of ownership for this IND from Nektar Therapeutics to AstraZeneca Pharmaceuticals LP.

Chemistry, Manufacturing and Controls (CMC)

1. The briefing document explains how AstraZeneca plans to use tablet formulation for 25 mg and 12.5 mg dosages, based upon the demonstration of bioequivalence between a liquid 100 mg dosage and a tablet 100 mg dosage. Does the Agency support the introduction of the new immediate release tablet dosage strengths into the Phase 3 program without additional bioequivalence studies for the 25 mg or 12.5 mg tablets?

FDA Response to Question 1:

Yes, we agree, provided that the dissolution profiles of the 25 and 12.5 mg strengths are similar to the 100 mg strength in three media (0.1 N HCL and phosphate buffer pH 4.5 and 6.8).

Discussion of Question 1:

There was no further discussion.

Nonclinical

2. The pre-meeting package describes a complete nonclinical pharmacology and toxicology package intended to support initiation of Phase 3 clinical trials and approval of an NDA.

Does the Agency agree that the past and planned nonclinical pharmacology and toxicology package is adequate to support:

- a) start of Phase 3?

FDA Response to Question 2a:

Yes, we agree.

Discussion of Question 2a:

There was no further discussion.

b) filing an NDA?

FDA Response to Question 2b:

To support filing of an NDA, nonclinical and/or other types of studies may be needed to evaluate the abuse potential of NKTR-118. This issue is being reviewed by the Controlled Substances Staff. We will provide our recommendations in a future communication.

Discussion of Question 2b:

The FDA reiterated that comments from CSS are forthcoming, and can be expected possibly with the meeting minutes, or in a separate communication.

Clinical

3. The pre-meeting package describes a clinical development plan, including the dose selection for Phase 3, study design, and the primary and secondary endpoints intended to support approval of an NDA.

Does the Agency agree that the clinical development plan supports the following indication: NKTR-118 is indicated for the treatment of opioid-induced constipation?

FDA Response to Question 3

Your general Phase 3 study design appears reasonable; however, without complete Phase 3 protocols, it is premature for us to provide agreement regarding your Phase 3 plans. The specific language in labeling is an issue that would be determined in the course of reviewing the NDA.

Discussion of Question 3:

There was no further discussion.

4. AstraZeneca recognizes the need for expanding the clinical pharmacology knowledge for NKTR-118 before an NDA can be filed. AstraZeneca further believes that the current state of knowledge regarding the safety profile of NKTR-118 provides a solid basis for conducting large-scale efficacy trials while the clinical pharmacology studies are ongoing.

AstraZeneca believes that the known nonclinical and clinical ADME and safety data are sufficient to allow the initiation of Phase 3 studies while further clinical pharmacology studies are conducted in parallel and that this development program will produce data sufficient for an NDA. Does the Agency agree with this assessment?

FDA Response to Question 4:

While you may proceed to the Phase 3 clinical studies without completing your planned clinical pharmacology related studies, the submitted development program is not sufficient for an NDA submission. We have the following recommendations:

- a) You must conduct the food effect study using the to-be-marketed formulation.**

Discussion of Question 4a:

There was no further discussion.

- b) If the formulation used in the Phase 3 clinical studies is different from the to-be-marketed formulation, then a bridging study may be needed.**

Discussion of Question 4b:

There was no further discussion.

- c) We recommend that you investigate the involvement of hepatic transporters in the *in vivo* disposition of NKTR-118 and also study *in vitro* induction potential of your compound on various transporters in the intestine and liver, including g-glycoprotein, OATP1B1, BCRP, and MRP2. Based on the *in vivo* and *in vitro* outcomes, you should determine the need for relevant drug interaction studies. When submitting your NDA, provide all detailed *in vitro* and *in vivo* data and your rationales for studying or not studying certain drug interaction studies.**

Discussion of Question 4c:

There was no further discussion.

- d) We recommend that you conduct a population pharmacokinetic study during the Phase 3 trial and perform a population pharmacokinetic analysis of exposure/response relationship related to efficacy and adverse events, where responses could be any relevant pharmacodynamic (PD) endpoints or biomarkers related to the pharmacological effects of your compound.**

Discussion of Question 4d:

There was no further discussion.

- e) In your proposed Phase 2 study, a dose/response analysis is planned. However it is not clear what response parameters you are referring to. Please clarify the PD parameters mentioned in your synopsis. There appears to be a dose-dependent observation of treatment-related adverse events and discontinuation. Therefore, we strongly recommended that you conduct an exposure/adverse effect relationship analysis.**

Discussion of Question 4e:

The sponsor clarified that the pharmacodynamic parameter will be a change in spontaneous bowel movement from baseline to endpoint.

- f) Given the known contribution of genetics to variability in opioid agonist/antagonist responses, you should consider collection of DNA samples in any subsequent studies. We recommended that you refer to the following *Guidance for Industry* documents on the FDA's web page at

www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

- *Guidance for Industry Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (September 2006)*
- *Guidance for Industry – Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations (March, 2003)*
- *Guidance for Industry – Immediate Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation*

Discussion of Question 4f:

There was no further discussion.

5. The NKTR-118 studies have used diagnostic criteria for OIC that specify an opioid load of 30-1000 MEU, a rate of defecation of ≤ 3 SBM/week and at least 1 of 3 symptoms with a known mechanism of action due to opioid pharmacology (hard lumpy stools, straining or sensation of incomplete evacuation/anorectal obstruction).

Does the Agency agree that the definition of OIC used in the NKTR-118 program is appropriate to define the patient population for the intended labelling: “for the treatment of opioid-induced constipation”?

FDA Response to Question 5:

Based on the synopsis you provided, we assume you intend to define the study population using a criterion of < 3 SBM/week rather than ≤ 3 SBM/week. With this correction, your proposal appears reasonable. Without complete Phase 3 protocols, however, it is premature for us to provide agreement. The specific language in labeling is an issue that would be determined in the course of reviewing the NDA.

Discussion of Question 5:

There was no further discussion.

6. On the basis of physician assessment of patient history and physical examination, patients will be grouped into one of three categories: patients who have adequate response to laxatives (LAR), patients who have inadequate response to laxatives (LIR), and those patients who cannot confirm use of laxatives in the 4 weeks prior to the OIC run-in (LUR). These classifications will provide the basis for separate efficacy analyses with the goal of describing these medically-relevant characteristics of the patient population with respect to responsiveness to laxatives.

Does the Agency agree

(b) (4)

FDA Response to Question 6:

Your proposal appears reasonable for purposes of performing stratified analyses.

(b) (4)

The specific language in labeling is an issue that would be determined in the course of reviewing the NDA.

Discussion of Question 6:

There was no further discussion.

7. The briefing document describes the rationale for the selecting the primary endpoint and the e-diary used to collect the data.

Does the Agency agree

(b) (4)

FDA Response to Question 7:

We do not agree. Your primary endpoint should be based on a responder analysis

(b) (4)

(see also our response to Question 8, below).

(b) (4)

The specific language in labeling is an issue that would be determined in the course of reviewing the NDA.

Discussion of Question 7:

Discussion is captured in Question 8.

8. AstraZeneca is predefining “responder” as a patient showing a change to ≥ 3 SBM/week from a baseline of < 3 SBM/week, in accord with current ROME III criteria for constipation.

Does the Agency agree with the specification of ≥ 3 SBM/week as the definition of a responder?

FDA Response to Question 8:

Your definition should also require an increase of ≥ 1 SBM/week (a two-week run-in could allow patients to qualify with 2.5 SBM/week, and the meaningfulness of an increase of 0.5 SBM/week is questionable). Further, your protocol will need to specify for how many weeks the criterion needs to be met in order for a patient to qualify as being a “responder” for primary endpoint purposes.

Discussion of Question 8:

The sponsor was clear on the primary endpoint, but asked whether 3 out of 4 weeks was an acceptable timeframe for which the criteria should be met in order to be a “responder.” The FDA agreed that this would be acceptable since it was at least 75%.

9. The briefing document presents an outline of a statistical analysis plan that defines the analysis of the primary and secondary endpoints and multiplicity corrections.

Does the Agency agree with the following elements of the statistical analysis plan:

- a) The differences among treatment groups, NKTR-118 12.5 mg vs placebo, NKTR-118 25 mg vs placebo and NKTR-118 37.5 mg vs placebo, in change from baseline in SBM/week will be analysed using mixed model repeated measures (MMRM), where baseline SBM/week (covariate), response to laxatives, week, and treatment will be included in the model

FDA response to Question 9a:

Your proposed approach can serve as a secondary analysis. Please see our response to Question 8. Without complete Phase 3 protocols and statistical analysis plans, however, it is premature for us to provide agreement with your plan.

Discussion of Question 9a:

The FDA recommends that a CMH test (appropriately stratified) be used for the primary analysis of the new responder endpoint. The sponsor agreed to the responder rate for the primary analysis.

- b) To control the overall alpha rate at 0.050 level, Multiple Testing Procedure with Bonferroni-Holm over groups and fix-sequence within group will be applied for the multiple comparisons on the primary and key secondary endpoints

FDA Response to Question 9b:

[Response to be provided at the meeting.]

Discussion of Question 9b:

This may be acceptable; however, it is premature for us to provide agreement with your multiplicity adjustment plan without review of the complete protocol. Because of primary and secondary endpoints changes, details regarding your multiplicity profile may change.

- c) Change from baseline in opioid dose will be summarized

Discussion of Question 9c:

The sponsor agreed to perform an additional exploratory analysis. They will do statistical testing within each treatment group, considering change at baseline in context of the study results. They also agreed not to use the exploratory analysis for labeling. Rather, the primary and secondary key endpoints for efficacy will be used for labeling.

- d) Change from baseline in the composite score of MHS will be summarized

FDA Response (to Questions 9c and 9d):

Please clarify your intentions. We believe these endpoints should be subjected to planned exploratory statistical analysis. Increased need for opioids or emergence of withdrawal symptoms could result from interference with central opioid effect, and these assessments will be important to consider carefully for the overall interpretation of the results of your studies.

Discussion of Question 9d:

Discussion is captured in 9b & 9c.

10. The long-term safety study is designed to compare the safety profile of NKTR-118 with that of current standard-of-care laxatives and to fulfil the requirements of ICH E1A, maintaining at least 100 patients on opioid treatment and on 25 mg/day NKTR-118 for a full year with a provision for a one-time reduction to 12.5 mg/day NKTR-118 or increase to 37.5 mg/day and an additional provision for a possible return to 25 mg/day. It is also expected that 300 to 600 patients will be treated for at least 6 months at dosage levels intended for clinical use.

In order to fulfil ICH E1A recommendations, in the long-term safety study, at least 100 patients will have long-term exposure for 12 months duration and at least 300 will be exposed for at least 6 months to dosage levels of NKTR-118 intended for clinical use. The planned long term safety allows for a single adjustment in dosing (25 mg/day regimen may be reduced once to 12.5 mg/day or increased to 37.5 mg/day with an option to return to 25 mg/day) and thus not all patients will be exposed to the highest planned clinical dose. Does the Agency agree that this scenario will fulfill ICH E1A requirements for long term safety for the dose range of 12.5 mg/day to 37.5 mg/day?

FDA Response to Question 10:

Your proposed studies will span a three-fold range in dose. We would consider the ICH E1A requirements fulfilled only if the numbers of patients near or above the highest dose to be recommended in labeling fulfill the chronic exposure criteria.

We have received reports of bowel perforation in patients administered opioid antagonists for opioid-induced constipation. We recommend that you stay aware of this issue and that you pay special attention to potential for bowel perforation in your safety evaluations. You should plan to address this risk in your NDA submission.

Discussion of Question 10:

There was no further discussion.

FDA ADDITIONAL COMMENTS:

- 11. Please describe any actions you have taken regarding the scheduling of NKTR-118 and any plans you have to evaluate and address the potential for diversion and abuse. The Controlled Substances Staff will provide their advice in a future communication.**

Discussion of Comment 11:

The sponsor summarized the chemical structure and behavior of NKTR-118 and naloxone. The FDA is interested in the abuse or diversion potential of NKTR-118. Unlike a general opioid antagonist, the ability to alleviate peripheral side effects while preserving the CNS opioid effect might make the product attractive for facilitating opioid abuse. It would be good if any potential for diversion could be avoided. The sponsor agreed to consider this concern, but pointed out that constipation is not the limiting adverse event that keeps opioid abusers using. This topic needs further consideration, and the Controlled Substances Staff (CSS) will provide their comments on this issue in a future correspondence (see Action Items).

- 12. The FDA strongly recommends that you submit the data for your NDA in CDISC format. You should plan according in designing the data collection procedures for your clinical studies.**

Discussion of Comment 12:

There was no further discussion.

ISSUES REQUIRING FURTHER DISCUSSION

CSS may recommend that this should be a scheduled drug. The FDA advised the sponsor to contact DEA to receive an assessment of scheduling. The FDA may request additional studies (e.g., binding data, *in vitro* studies) to track antagonist properties.

ACTION ITEMS

When available, comments from CSS will be communicated to the sponsor. A teleconference is possible for further discussion of these comments.

ATTACHMENTS AND HANDOUTS

None.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-78781	GI-1	NEKTAR THERAPEUTICS	NKTR 118

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/s/

HEATHER G BUCK
02/25/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 78,781

Nektar Therapeutics
Attention: Carlo Di Fonzo, Ph.D.
Vice President, Global Regulatory Affairs
201 Industrial Road
San Carlos, CA 94070

Dear Dr. Di Fonzo:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for NKTR-118.

We also refer you to your April 7, 2009 submission that included 16-week mortality data from your mouse carcinogenicity study (LS-2006-006).

The Executive Carcinogenicity Assessment Committee and the Division of Gastroenterology Products have the following comments and recommendations:

We agree that you should reduce the high dose in males from 200 to 100 mg/kg/day, and reduce the high dose in females from 400 to 160 mg/kg/day. In addition, the intermediate dose in males and females should be lowered to 50 and 80 mg/kg/day, respectively, to allow for adequate dose separation and to reduce the risk of mortality. It is also acceptable to remove the high-dose male and female groups from the study.

We recommend that you choose between the following dosing regimens:

- Option A: Males: 25, 50 and 100 mg/kg/day
Females: 40, 80 and 160 mg/kg/day
- Option B: Males: 25 and 50 mg/kg/day
Females: 40 and 80 mg/kg/day

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience

associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports (21 CFR 312.33).

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at 301-796-2307.

Sincerely,

{See appended electronic signature page}

Ruyi He, M.D.

Acting Deputy Director

Division of Gastroenterology Products

Office of Drug Evaluation III

Center for Drug Evaluation and Research

Linked Applications

Sponsor Name

Drug Name / Subject

IND 78781

NEKTAR
THERAPEUTICS

NKTR 118

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/s/

RUYI HE

06/09/2009

Executive CAC

Date of Meeting: November 25, 2008

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul C. Brown, Ph.D., OND IO, Member
Barbara A. Hill, Ph.D., DDDP, Alternate Member
David B. Joseph, Ph.D., DGP, Pharmacology Team Leader
Niraj R. Mehta, Ph.D., DGP, Presenting Reviewer

Coordinator: Sam Habet, R.Ph., Ph.D., OND IO, Senior Clinical Pharmacologist/
Science Policy Analyst (Detail)

Author of Draft: Niraj R. Mehta, Ph.D.

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

The committee did not address the sponsor's proposed statistical evaluation for the 2-yr carcinogen bioassays, as this does not affect the sponsor's ability to initiate the bioassays. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following the CDER/CBER Guidance for Industry, Providing Regulatory Submission in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions using the eCTD Specifications (June 2008) and the associated Study Data Specifications Document.

IND # 78,781
Date of submission: November 4, 2008
Drug Name: NKTR-118
Sponsor: NEKTAR Therapeutics, Inc.

NKTR-118 (PEG-naloxol) is a pegylated derivative of the opioid antagonist drug naloxone. NKTR-118 binding to peripheral μ -opioid receptors of the GI tract has the potential to reverse opioid-induced effects on bowel function. NKTR-118 is being developed for the treatment of opioid-induced constipation and other manifestations of opioid-induced bowel dysfunction in patients taking opioids in acute and chronic settings. The anticipated clinical dose will be 100 mg QD. NKTR-118 was positive in a bacterial mutation test, however results of the *in vivo* mouse bone marrow micronucleus assay and the *in vitro* mammalian cell mutation assay were negative.

Mouse Carcinogenicity Study Protocol and Dose Selection

The sponsor has proposed to conduct a 2-year oral (gavage) carcinogenicity study with NKTR-118 in CD1 mice (b) (4). In the 13-week oral dose-range finding study with NKTR-118 in CD-1 mice, groups of animals received doses of 0, 50, 400, 600, and 800 mg/kg/day. There were five treatment-related deaths or unscheduled sacrifices; two males given 600 mg/kg/day NKTR-118, two males and one female given 800 mg/kg/day NKTR-118. There was a $\geq 10\%$ reduction in body weight gain in males (-13% and -28% at 400 and 600 mg/kg/day, respectively). In the 800 mg/kg/day males, the final body weight was lower than their initial body weight taken before the dosing period (-1.3 g), and there was a robust decrease (19%) in total body weight during the last two weeks of the dosing period. The sponsor proposed the high dose for the 2-year mouse carcinogenicity study on the basis of the MTD, 400 mg/kg/day in male and female mice.

Rat Carcinogenicity Study Protocol and Dose Selection

The sponsor has proposed to conduct a 2-year oral (gavage) carcinogenicity study with NKTR-118 in Sprague-Dawley rats at 0 (water), 40, (b) (4) and 400 mg/kg/day. The sponsor's data indicate that metabolite levels in rats will likely exceed that of human metabolites. In the 13-week oral dose-range finding study with NKTR-118 in Sprague-Dawley rats, groups of animals received doses of 0, 50, 400, 600 and 800 mg/kg/day. The only treatment related death in the main group was one high dose male. There was a dose-dependent reduction in body weight gain in males (-8%, -9%, and -12% decrease relative to controls at 400, 600, and 800 mg/kg/day, respectively) without a significant change in food consumption. The sponsor's selection of 400 mg/kg/day as the highest dose for the 2-year carcinogenicity study is based on a greater than 25-to-1 exposure ratio of rodent to human plasma AUC of NKTR-118 (236-fold exposure ratio at the maximum proposed clinical dose of 100 mg QD).

Executive CAC Recommendations and Conclusions:

Mouse:

- For male mice, the Committee recommended doses of 0, 25, 70, and 200 mg/kg/day by oral gavage, based on mortality. For female mice, the Committee recommended doses of 0, 40, 120, and 400 mg/kg/day by oral gavage, based on adverse histopathology observations. Furthermore, the sponsor should use one (constant) dose volume for all dose groups.

Rat:

- The Committee recommended doses of 40, 120, and 400 mg/kg/day by oral gavage, based on the rodent to human plasma AUC ratio of NKTR-118 exceeding 25-fold. Furthermore, the sponsor should use one (constant) dose volume for all

dose groups.

Mouse and Rat:

- Lastly, the sponsor has proposed to do a histopathologic examination on specific organs/tissues in only the control and high-dose groups, however histopathologic examination of other dose groups will be required under any of the following circumstances:
 - (a) For any macroscopic findings in the low and mid dose groups for a given tissue, they will need to look at that tissue for all of the dose groups.
 - (b) For an increase in the incidence of tumors (rare or common) in the high dose group for a tissue, even if not statistically significant, they will also need to look at the next lower dose group.
 - (c) For an increase in tumors in an organ for a tumor type that should be analyzed across tissue sites as well as by tissue site, they should look at all relevant tissues for that dose level and the next lower dose level.
 - (d) For an excessive decrease in body weight or survival in the examined dose group, they should examine lower dose groups.

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

cc:\

- /Division File/DGP
- /Dr. Joseph/DGP
- /Dr. Mehta/DGP
- /Matthew Scherer/PM/DGP
- /D. Jacobson-Kram, OND IO
- /A. Jacobs, OND IO
- /P. Brown, OND IO
- /SHabet, OND IO

Linked Applications

Sponsor Name

Drug Name

IND 78781

NEKTAR
THERAPEUTICS

NKTR 118

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/s/

SAYED AL HABET

11/26/2008

DAVID JACOBSON KRAM

11/26/2008

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 204760

LATE-CYCLE MEETING MINUTES

AstraZeneca Pharmaceuticals LP
Attention: Lynley K. Thinnes
Director, Regulatory Affairs
1800 Concord Pike, P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Thinnes:

Please refer to your New Drug Application (NDA) dated and received September 16, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for MOVANTIK (naloxegol) tablets, 12.5 mg and 25 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on June 18, 2014.

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

If you have any questions, call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Deputy Director for Safety
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes
Study Concept Table



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: June 18, 2014, 11:00 AM – 12:30 P.M.
Meeting Location: White Oak Building 22, Room 1419
10903 New Hampshire Avenue
Silver Spring, MD 20993

Application Number: NDA 204760
Product Name: Movantik (naloxegol) tablets
Indication: For the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain

Applicant Name: AstraZeneca Pharmaceuticals LP
Meeting Chair: Anil Rajpal, M.D.
Meeting Recorder: Maureen Dewey, M.P.H.

FDA ATTENDEES

Office of Drug Evaluation III

Julie Beitz, MD, Director
Amy Egan, MD, Deputy Director
Maria Walsh, RN, MS, Associate Director for Regulatory Affairs

Division of Gastroenterology and Inborn Errors Products

Donna Griebel, MD, Director
Joyce Korvick, M.D., MPH, Deputy Director for Safety
Anil Rajpal, MD, MPH, Clinical Team Leader
David Joseph, Ph.D., Supervisory Pharmacologist
Yuk-Chow Ng, Nonclinical Reviewer
Maureen Dewey, M.P.H. Senior Regulatory Project Manager

Office of New Drugs Quality Assessment

Marie Kowblansky, Ph.D., Chemistry Team Leader
Bogdan Kurtyka, Ph.D., Chemistry Reviewer
Tapash Ghosh, Ph.D., Biopharm Team Leader
Kareen Riviere, Ph.D., Biopharm Reviewer

Office of Clinical Pharmacology (OCP)

Sue Chih Lee, Ph.D., Team Leader
Elizabeth Shang, PhD, RPh, Clinical Pharmacology Reviewer
Sandhya Apparaju, Ph.D., Clinical Pharmacology Reviewer

OCP- Division of Pharmacometrics

Nitin Mehrotra, Ph.D., Pharmacometrics Team Leader
Justin Earp, PhD., Pharmacometrics Reviewer

Office of Biostatistics

Freda Cooner, PhD, Acting Team Leader
Wen-Jen Chen, PhD, Reviewer

Division of Anesthesia, Analgesia and Addiction Products

Ellen Fields, MD, MPH, Clinical Team Leader
Elizabeth Kilgore, MD, Medical Officer

Pediatric and Maternal Health Staff

Ethan Hausman, MD, Clinical Reviewer
Carrie Ceresa, Pharm D., MPH, Regulatory Reviewer
Millie Wright, RN, MSN, Senior Regulatory Health Project Manager

Office of Surveillance & Epidemiology (OSE)

Office of Pharmacovigilance, Division of Epidemiology I

Sukhminder Sandhu, PhD, MPH, MS, Acting DEPI Team Leader
Eileen Wu, PharmD, Safety Evaluator Team Leader
Christian Cao, MPAS, PA-C, Safety Evaluator

Division of Risk Management

Reema Mehta, PharmD, MPH, Team Leader
Nyedra Booker, PharmD, M.P.H., Risk Management Analyst
Shelly Harris, M.P.H., REMS Assessment Analyst

Division of Medical Policy Programs

Karen Dowdy, RN, BSN, Patient Labeling Reviewer

Controlled Substance Staff

Martin Rusinowitz, M.D., Medical Officer
Katherine Bonson, PhD, Pharmacologist

Office of Manufacturing and Product Quality

Christina Capacci-Daniel, PhD, Consumer Safety Officer

Office of Translational Science - Division of Biometrics VII

Clara Kim, Ph.D., Biometrics Reviewer

EASTERN RESEARCH GROUP ATTENDEES

So Hyun Kim, Independent Assessor, Eastern Research Group

APPLICANT ATTENDEES

Lynley Thinnies, Global Regulatory Affairs Director
Mark DeSiato, VP, US Regulatory Affairs
Kathy Cantagallo, VP, Naloxegol
Mark Sostek, Medical Science Director
Tim Sullivan, Medical Director, Patient Safety
Robert LoCasale, Director Quality, Design and Analytics
Jean Surian, Global Regulatory Project Manager

Nektar Therapeutics Attendees:

Carlo Di Fonzo, Vice President, Drug Development and Regulatory Affairs

1.0 BACKGROUND

NDA 204760 was submitted on September 16, 2013 for Movantik (naloxegol) tablets.

Proposed indication: For the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.

PDUFA goal date: September 16, 2014

FDA issued a Background Package in preparation for this meeting on June 6, 2014.
AstraZeneca issued discussion points on June 16, 2014.

2.0 DISCUSSION

1. Introductory Comments

Welcome, Introductions, Ground rules, Objectives of the meeting

Discussion:

FDA stated that the purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that have been identified to date, Advisory Committee (AC) meeting plans (not planned for this application), and objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application.

2. Discussion of Advisory Committee Meeting

Discussion:

Sponsor Summary of Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC):

The AADPAC advisory panel did recommend studies be conducted to monitor for cardiovascular safety after the drugs reach the market. The panel determined that although

cardiovascular outcomes trials may be feasible, they were fraught with challenges including interpretability.

- The majority of panel members supported well-designed observational studies as the appropriate approach. Some specific design features were discussed but agreement on an overall design was not sought by FDA.*
- As stated in our presentation at the Advisory Committee, AstraZeneca feels that the best way to gather additional CV safety information for naloxegol is through conduct of a post-marketing observational study. We are ready to discuss the design of such a study at the FDA's convenience so that the study can start very shortly after market launch.*

FDA Response:

We agree that one or more post-marketing observational study or studies will be required. Please submit draft study concepts. We are interested in the capture of relevant covariates including both ≥ 65 and ≤ 65 years of age, smoking history, BMI, aspirin use, dose/type of opioid, personal/family history of cardiovascular disease, diabetes, hypertension, and dyslipidemia. We are also interested in the study's ability to ascertain sudden cardiac death. Milestone dates should be provided for your proposed studies. See the draft template of elements for you to consider when proposing a study or studies.

Discussion:

The sponsor agreed to submit study concepts to the NDA by July 8, 2014 for review. The covariates will not be limited to those listed by the FDA. FDA stated that there will be additional discussion with upper management regarding the Advisory Committee recommendations. This discussion could impact the Division's final decisions.

3. Postmarketing Requirements/Postmarketing Commitments (PMRs/PMCs)

Discussion:

At this time, we request that you conduct an in vitro study to evaluate the inhibition potential of naloxegol on hepatic CYP2C8 enzyme, as this interaction has not been assessed in this NDA submission. Please refer to the FDA Draft Guidance for Drug Interaction Studies — Study Design, Data Analysis, implications for Dosing, and Labeling Recommendations.

Please provide dates for the following milestones: final protocol submission, study completion and final report submission.

Additional PMRs/PMCs may be considered in light of discussion at the AADPAC Meeting and upon finalization of reviews.

Sponsor Question: Potential Post-Marketing Commitments/Requirements: Provide progress on the in-vitro study with CYP2C8

As part of the Late Cycle communication, the Division requested the conduct of an in vitro

study to evaluate the inhibition potential of naloxegol on hepatic CYP2C8 enzyme, as this interaction has not been assessed in this NDA submission.

Upon receipt of the late communication AstraZeneca has performed the study in anticipation of the Post marketing requirement. A brief summary of the results can be found below. A full report will be available by the end of July. AstraZeneca is happy to submit this report as soon as it is available provided this submission would not affect the review clock. If it is in agreement with the Division that the final report should be submitted by the end of July, then can we assume that this would no longer be a Post Marketing Commitment/Requirement?

In-vitro study with CYP2C8 results

The potential of naloxegol to inhibit CYP2C8 was assessed by measuring the rate of formation of isoform specific metabolites derived from a marker substrate when incubated with metabolically competent pooled human liver microsomes in the presence of NADPH. These activities were measured under linear conditions for time and protein concentration using the following marker substrate Amodiaquine (CYP2C8) at or below the Km concentration.

The metabolism of marker substrate was determined by HPLC-MS/MS methods. Relevant control incubations were performed and CYP isoform-selective reversible inhibitors were used as positive controls.

The potential for reversible inhibition of CYP enzymes was investigated by co-incubation of naloxegol at six concentrations (0.1, 0.3, 1.0, 3.0, 10 and 30 μ M) with human liver microsomes in the presence of the CYP enzyme marker substrates and NADPH, and then monitoring the rate of formation of CYP isoform-specific metabolites. If appropriate, the IC50 value (concentration of inhibitor required to produce 50% inhibition of metabolite formation) was determined for each test occasion.

The results of assays performed in triplicate showed that the IC50 was greater than the highest inhibitor concentration used (30 μ M). When this is compared to the naloxegol peak concentration in patients (0.12 μ M) this indicates a very low potential for meaningful inhibition. A full report will be available by the end of July.

FDA Response:

If the in vitro study evaluates both reversible and time-dependent inhibition of CYP2C8 and the report is submitted by the end of July 2014, we will review within the review cycle without an extension of the review clock. The need for a PMR/PMC will be made after the review of the study report.

Discussion:

The sponsor agreed to submit the final study report by the end of July 2014. The Division requests the sponsor submit the report to the NDA with cross-reference to the IND.

Sponsor Question

(b) (4)

(b) (4)

FDA Response:

(b) (4)

Discussion:

(b) (4)

4. Major Labeling Issues

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. 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.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions (summarized by section of the label):

Section 2: Dosage and Administration

1. Your proposed 25 mg once daily dose appears to be an adequate starting dose for the overall population. Specific dosing recommendations for patients unable to tolerate the 25 mg once daily starting dose, patients with renal impairment, and patients receiving concomitant moderate CYP3A4 inhibitors were provided in the May 30, 2014 draft label and are re-iterated below.
 - a. [REDACTED] (b) (4)
 - b. The starting dosage for patients with creatinine clearance (CL_{cr}) < 60 mL/min (i.e., patients with moderate, severe or end-stage renal impairment) is 12.5 mg once daily. If this (b) (4) is well tolerated but OIC symptoms continue, the dosage may be increased to 25 mg once daily taking into consideration the potential for markedly increased exposures in some patients with renal impairment and the increased risk of adverse reactions with higher exposures [see *Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].
 - c. Avoid concomitant use of TRADENAME with moderate CYP3A4 inhibitor drugs (e.g., diltiazem, erythromycin, verapamil). If concurrent use is unavoidable, reduce the TRADENAME (b) (4) to 12.5 mg once daily and monitor (b) (4) for adverse reactions. [REDACTED] (b) (4)
[see *Drug Interactions (7) and Clinical Pharmacology (12.3)*].
2. Also, in the Dosage and Administration section, you have proposed that if patients discontinue their opioid pain medication [REDACTED] (b) (4) they should discontinue TRADENAME. Please state if there are any additional recommendations directed to the prescriber; if there are additional recommendations, please propose language for this section.

Section 4: Contraindications

3. We are considering (in consultation with reviewers from the Division of Neurology Products) if the statement about [REDACTED] (b) (4) is appropriate for the labeling; and if so, whether it should be included in Contraindications or Warnings and Precautions.

Sponsor Question:

AstraZeneca is in agreement with most of the changes, but requests clarification/discussion regarding the text concerning blood-brain barrier disruption, the removal of section 9 on abuse potential, the timing that FDA is planning to communicate their evaluation of the tool described in the clinical trials section of the label, and inconsistency [REDACTED] (b) (4)

- i. *Blood-Brain barrier disruption – AstraZeneca does not believe that that a warning that is based on theoretical risk should be elevated to the level of a contraindication. It is more appropriate for the warnings and precautions. Can the Division provide clarity around this?*

FDA Response:

There is a pending consult with the Division of Neurology Products. We are considering each of these options (Contraindication vs. Warning and Precaution). The anticipated completion date of the consult review is approximately one month from now. The final outcome of the review will be communicated to you as part of labeling negotiations.

Discussion:

The sponsor requested that if the Division's decision is to include the information in the Warnings & Precautions or Contraindication section of the prescribing information, it should also be considered for other drugs in the same class. The sponsor noted that Relistor does not have a Warning or Contraindication for this issue in their prescribing information.

Sponsor Question:

- ii. *Removal of Section 9: Can the Division clarify why Section 9 was removed? At the time of the Mid Cycle meeting the Division explained that we could expect at approval a label indicating reflecting scheduled product status until DEA accepted a recommendation to decontrol naloxegol. AstraZeneca would then have to submit for a label change to remove the scheduling. Can the agency confirm if this applies to packaging as well? Can the Division share what areas will be changed in a decontrolled label and packaging, does it just relate to the scheduling classification or are there other areas of the label/packing affected? Can the Division provide the decontrolled language ahead of the final schedule*

determination adoption by DEA? Can the label change from scheduled to a non-controlled be handled as a CBE 30?

FDA Response:

If the sponsor wishes to market naloxegol as soon as the NDA is approved, Section 9.1 of the label will need state that naloxegol is a Schedule II substance under the CSA.

We are considering the CSS recommendation to accept the sponsor's proposed wording for Sections 9.2 (Abuse) and 9.3 (Dependence).

We cannot convey any information about scheduling, since this is still in a predecisional status.

Discussion:

The sponsor inquired whether the CSS review had been completed. CSS replied that both the review and the Eight Factor Analysis, which is responsive to the legal requirements of the CSA have been completed. The sponsor inquired whether the scheduling action would be finalized by the PDUFA goal date.

(b) (4)

The Division clarified that the schedule of naloxegol will be represented accurately on the label and carton and container labels.

The Division will provide guidance

(b) (4)

Post Meeting Comment:

(b) (4)

Section 14: Clinical Studies

4. We have the following comments about the labeling language for your first-ranked secondary endpoint (assessed in a subgroup identified using an investigator-administered questionnaire):
 - a) We are currently reviewing the qualitative study report/protocol (for the investigator-administered questionnaire), and will determine if it is acceptable to report results in the subgroup identified using this instrument in the labeling.

- b) Even if the instrument is acceptable, we do not agree with the term (b) (4).
(b) (4)
We propose describing the subgroup as follows: "(b) (4) patients (identified using an investigator-administered questionnaire) (b) (4) prior to enrollment, had (b) (4) reported (b) (4) these laxatives at least 4 out of the past 14 (b) (4)."

Sponsor Question:

- iii. *"We are currently reviewing the qualitative study report and protocol for this instrument and will determine if it is acceptable to report results in the subgroups identified using this instrument in the labeling". Can the Division indicate the timing for the conclusion of this review and when we might have the outcome communicated to AstraZeneca?*

FDA Response:

This review will be completed within approximately one month. The final outcome of the review will be communicated to you as part of labeling negotiations.

Sponsor Question:

- iv. *Can the Division clarify the inconsistency (b) (4) (b) (4) We want to understand what is required so we can make the necessary changes for the June 20, 2014 submission.*

FDA Response:

(b) (4)

We request that you change (b) (4) to "TRADENAME (naloxegol)" throughout the label.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by June 20, 2014. The resubmitted labeling will be used for further labeling discussions. At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Discussion:

Sponsor agreed to submit the label by June 20, 2014.

5. Review Plans

Discussion:

The Pediatric Review Committee will convene on July 16, 2014 [REDACTED] (b) (4)

[REDACTED].

The Pediatric Review Committee will convene on August 6, 2014 [REDACTED] (b) (4)

[REDACTED]

6. Wrap-up and Action Items

Discussion:

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

Study Concept Table

Data Source	• Please delineate the databases/data sources that will be available, including Outpatient data, Electronic Medical record, Inpatient diagnosis and Claims data, Pharmacy data, Lab data, , and any other data that will be linked. • Please indicate linkage to Social Security Administration Master Death File or other death databases. • Please indicate whether primary data will be collected, especially for CV risk factors that may not be available in an electronic database.
Study Population	• Please establish a minimum number of patients to be enrolled in each arm. • Please indicate the comparator arm(s).
Entry Criteria	• Please add additional enrollment criterion, both inclusion and exclusion criteria.
Follow-up	• Please define the follow-up period, including any patient censoring. state follow-up censoring criteria. • Please describe plans to minimize missing data, especially for patients who are lost to follow-up. • Please describe recruitment plans to offset the impact of patients lost to follow-up on statistical power.
Validation of Exposure/Outcome	• Please indicate whether exposures/outcomes will be validated. • Please indicate the ability to capture AMI, stroke and sudden cardiac death. • If they will be validated, please indicate whether medical record reviewers will be blinded to the study objective and to the exposure of interest. In addition, please incorporate a case adjudication plan into the final study protocol.
Covariates	• Please indicate the ability of the proposed study to capture data and adjust for potential confounders, including but not limited to: age, sex, OTC aspirin use, smoking, BMI, family history, personal history, diabetes, hypertension, and dyslipidemia
Sample Size	• The sample size should be calculated for the primary analysis
Analysis Plan	• Please specify the hypothesis that will be tested in the primary analysis. • Please indicate what statistical methods will be used for the primary analysis. Also indicate the ability of the proposed analyses to control for potential confounders, including but not limited to age, sex, smoking, OTC aspirin use, BMI, family history, personal history, diabetes, hypertension, and dyslipidemia. • Please indicate any sensitivity analyses that will be conducted.

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/s/

MAUREEN D DEWEY
07/10/2014

JOYCE A KORVICK
07/10/2014



NDA 204760

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

AstraZeneca Pharmaceuticals LP
Attention: Lynley K. Thinnes
Director, Regulatory Affairs
1800 Concord Pike, P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Thinnes:

Please refer to your New Drug Application (NDA) dated and received September 16, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for MOVANTIK (naloxegol) tablets, 12.5 mg and 25 mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for June 18, 2014. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Deputy Director for Safety
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:

Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: June 18, 2014, 11:00 AM – 12:30 P.M.
Meeting Location: White Oak Building 22, Room 1419
10903 New Hampshire Avenue
Silver Spring, MD 20993

Application Number: NDA 204760

Product Name: Movantik (naloxegol oxalate)

Indication: For the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain

Sponsor/Applicant Name: AstraZeneca Pharmaceuticals LP

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

There are no substantive review issues at this time. However, we will need to further assess the recommendations regarding safety discussed at the June 11-12, 2014 Anesthetic and Analgesic Drug Products Advisory Committee Meeting (AADPAC).

ADVISORY COMMITTEE MEETING

A specific matters Advisory Committee meeting is not planned. However, we may devote a portion of this meeting to discussion of items that were raised in the June 11 -12, 2014 AADPAC Meeting to assess cardiovascular risk.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

Potential Post-Marketing Commitments/Requirements (PMRs/PMCs)

At this time, we request that you conduct an in vitro study to evaluate the inhibition potential of naloxegol on hepatic CYP2C8 enzyme, as this interaction has not been assessed in this NDA submission. Please refer to the FDA Draft Guidance for Drug Interaction Studies —Study Design, Data Analysis, implications for Dosing, and Labeling Recommendations.

Please provide dates for the following milestones: final protocol submission, study completion and final report submission.

Additional PMRs/PMCs may be considered in light of discussion at the AADPAC Meeting and upon finalization of reviews.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. 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.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions (summarized by section of the label):

Section 2: Dosage and Administration

1. Your proposed 25 mg once daily dose appears to be an adequate starting dose for the overall population. Specific dosing recommendations for patients unable to tolerate the 25 mg once daily starting dose, patients with renal impairment, and patients receiving concomitant

moderate CYP3A4 inhibitors were provided in the May 30, 2014 draft label and are reiterated below.

- a. [REDACTED] (b) (4)
 - b. The starting dosage for patients with creatinine clearance (CLcr) < 60 mL/min (i.e., patients with moderate, severe or end-stage renal impairment) is 12.5 mg once daily. If this (b) (4) is well tolerated but OIC symptoms continue, the dosage may be increased to 25 mg once daily taking into consideration the potential for markedly increased exposures in some patients with renal impairment and the increased risk of adverse reactions with higher exposures [see *Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)*].
 - c. Avoid concomitant use of TRADENAME with moderate CYP3A4 inhibitor drugs (e.g., diltiazem, erythromycin, verapamil). If concurrent use is unavoidable, reduce the TRADENAME (b) (4) to 12.5 mg once daily and monitor closely for adverse reactions. [REDACTED] (b) (4)
[see *Drug Interactions (7)* and *Clinical Pharmacology (12.3)*].
2. Also, in the Dosage and Administration section, you have proposed that if patients discontinue their opioid pain medication [REDACTED] (b) (4), they should discontinue TRADENAME. Please state if there are any additional recommendations directed to the prescriber; if there are additional recommendations, please propose language for this section.

Section 4: Contraindications

3. We are considering (in consultation with reviewers from the Division of Neurology Products) if the statement about [REDACTED] (b) (4) is appropriate for the labeling; and if so, whether it should be included in Contraindications or Warnings and Precautions.

Section 14: Clinical Studies

4. We have the following comments about the labeling language for your first-ranked secondary endpoint (assessed in a subgroup identified using an investigator-administered questionnaire):
- a) We are currently reviewing the qualitative study report/protocol (for the investigator-administered questionnaire), and will determine if it is acceptable to report results in the subgroup identified using this instrument in the labeling.
 - b) Even if the instrument is acceptable, we do not agree with the term [REDACTED] (b) (4). We propose describing the subgroup as follows: "[REDACTED] (b) (4) patients (identified using an investigator-administered questionnaire) [REDACTED] (b) (4) prior to enrollment, had [REDACTED] (b) (4) reported [REDACTED] (b) (4) these laxatives at least 4 out of the past 14 days [REDACTED] (b) (4)." (u) (4)

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by June 20, 2014. The resubmitted labeling will be used for further labeling discussions. At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

LCM AGENDA

1. Introductory Comments – 2 minutes (Maureen Dewey, M.P.H./Anil Rajpal, M.D.)
Welcome, Introductions, Ground rules, Objectives of the meeting
2. Discussion of Advisory Committee Meeting – 10 minutes
3. Postmarketing Requirements/Postmarketing Commitments – 5 minutes (Anil Rajpal, M.D./Sandhya Apparaju, Ph.D.)
4. Major labeling issues – 20 minutes (Anil Rajpal, M.D./Sandhya Apparaju, Ph.D.)

5. Review Plans – 5 minutes (Anil Rajpal, M.D.)

The Pediatric Review Committee will convene on July 16, 2014 [REDACTED] (b) (4)

The Pediatric Review Committee will convene on August 6, 2014 [REDACTED] (b) (4)

6. Wrap-up and Action Items – 5 minutes (Maureen Dewey, M.P.H.)

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/s/

JOYCE A KORVICK
06/06/2014