

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
ANDA 206647

Name: Alosetron Hydrochloride Tablets
0.5 mg and 1 mg

Sponsor: Amneal Pharmaceuticals of New York LLC

Approval Date: December 22, 2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 206647

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 206647

APPROVAL LETTER



ANDA 206647

ANDA APPROVAL

Amneal Pharmaceuticals
50 Horseblock Road
Brookhaven, NY 11719
Attention: Alpesh Patel
Vice President, Global Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Alosetron Hydrochloride Tablets, 0.5 mg (base) and 1 mg (base).

Reference is made to your amendments dated September 10 and September 15, 2014; May 22, 2015; and February 25, April 22, September 23 and November 4, 2016.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. **Accordingly the ANDA is approved**, effective on the date of this letter. The Office of Bioequivalence has determined your Alosetron Hydrochloride Tablets, 0.5 mg (base) and 1 mg (base) to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug product (RLD), Lotronex Tablets, 0.5 mg and 1 mg, of Sebelo Ireland Limited. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Section 505-1 of the FD&C Act authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. In accordance with section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA under section 505(j) is subject to certain elements of the REMS required for the applicable listed drug.

The details of the REMS requirements were outlined in our REMS notification letter dated January 22, 2015. In that letter, you were also notified that pursuant to section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA and the listed drug it references must use a single, shared system for elements to assure safe use (ETASU), unless FDA waives that requirement.

Your final proposed REMS, submitted on November 4, 2016, and appended to this letter, is approved. The REMS consists of ETASU.

The Alosetron REMS uses a waiver-granted shared system for the ETASU. This waiver-granted shared system REMS currently includes the products listed on the FDA REMS website available at <http://www.fda.gov/remis>. Other products may be added in the future if additional NDAs or ANDAs are approved.

Under section 505-1(g)(2)(C) of the FD&C Act, FDA can require the submission of a REMS assessment if FDA determines an assessment is needed to evaluate whether the REMS should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the REMS.

Additionally, the details for what should be included in your REMS assessments and the dates of the REMS assessments are listed in Appendix 1.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**ANDA 206647 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT
METHODOLOGY**

We remind you that you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FD&C Act.

We also remind you that section 505-1(f)(8) of the FD&C Act prohibits holders of an approved covered application from using any element to assure safe use to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

ANDA 206647 REMS ASSESSMENT

**NEW SUPPLEMENT FOR ANDA 206647/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR ANDA 206647/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR ANDA 206647/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING
CHANGES SUBMITTED IN SUPPLEMENT XXX**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR ANDA 206647

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

OTHER

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

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

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at

<http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Carol A. Holquist, RPh
Acting Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

Appendix 1
REMS

Appendix 1

Dates for submission of waiver-granted REMS assessments

The Alosetron Sponsors will submit REMS Assessments to FDA 18 months following the REMS modification approval on January 7, 2016, and every 12 months thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. The Alosetron Sponsors will submit each assessment so that it will be received by the FDA on or before the due date.

REMS Assessment Plan

The REMS Assessment Plan includes, but is not limited to, the following:

1. Results of an evaluation of whether patients received counseling from the prescriber, the patients' understanding of the serious risks of ischemic colitis and serious complications of constipation associated with alosetron, and the actions patients need to take should they experience early warning signs and symptoms of these risks.
2. Results of an evaluation of prescriber understanding of the appropriate patient population, the risks of ischemic colitis and serious complications of constipation associated with alosetron, and the importance of counseling patients about these risks. The evaluation will include a comparison of prescribers who completed training and prescribers who have not reported completion of training.
3. The number of prescribers and medical specialty of prescribers who reported that they completed training in the Alosetron REMS Program, including the number and medical specialty of prescribers contacted by Roxane to become trained after prescribing alosetron and the number and medical specialty contacted who completed training, during the reporting period and cumulative.
4. The number of prescribers who have not completed training and are writing prescriptions.
5. Numbers of prescriptions, by year for the last five years and annually thereafter.
6. Number of cases of the following events reported (from any source) during the reporting period and cumulative:
 - All reports of ischemic colitis;
 - All reports involving ischemic changes, ischemia, or necrosis of the colon
 - All reports involving constipation requiring hospitalization or emergency room visit;
 - All reports involving possible complications of constipation such as obstruction, perforation, intestinal ulceration, toxic megacolon, ileus, or impaction resulting in hospitalization or emergency room visit;
 - All reports of death, regardless of causality.
7. Summary and discussion of the above cases (received during the reporting period) and the clinical significance of these events.
8. An assessment of the extent to which the elements to assure safe use are meeting the goals or whether the goals or such elements should be modified.

Initial REMS Approved: 05/2015
Most recent modification: 11/2016

Risk Evaluation and Mitigation Strategy (REMS)

Shared System for Alosetron

Selective 5-HT₃ antagonist

I. GOAL(S):

The goals and objectives of the AlosetronREMS Program are to mitigate the risks of ischemic colitis (IC) and serious complications of constipation (CoC) associated with alosetron hydrochloride (hereinafter, referred to as alosetron) by:

- Informing prescribers of alosetron about:
 - the serious risks of IC and serious CoC associated with alosetron
 - the importance of understanding that alosetron should only be used in severely affected diarrhea-predominant irritable bowel syndrome patients for whom the benefits exceed the risks.
 - the importance of counseling patients about the risks of IC and serious CoC
- Informing patients about the risks of IC and CoC and actions to take should they experience early warning signs and symptoms of these risks.

II. REMS ELEMENTS:

A. Elements to Assure Safe Use

1. Training will be provided to healthcare providers who prescribe alosetron.

- a. The Alosetron Sponsors will ensure that training provided to healthcare providers who prescribe alosetron includes information on the serious risks of IC and CoC associated with alosetron, the importance of understanding that alosetron should only be used in severely affected diarrhea-predominant irritable bowel syndrome patients for whom the benefits exceed the risks, and the importance of counseling patients about the risks of IC and serious CoC, using the Alosetron Prescribing Information and the following materials in the REMS Training Kit:
 - i. REMS letter to Healthcare Providers
 - ii. Alosetron REMS Program Prescriber Education Slide Deck
 - iii. Alosetron REMS Program Safety Information Fact Sheet for Prescribers
 - iv. Alosetron REMS Program Patient Education Sheet
 - v. Prescriber Completion of Alosetron REMS Program Training Form

- b. In order to facilitate training, the Alosetron Sponsors will:
 - i. Monitor distribution and prescription data monthly.
 - ii. Contact all prescribers identified as not having completed training and provide training within 30 days of identification by mailing or emailing the REMS Training Kit. Contact and provide training to all prescribers who do not report completion of training after the first contact up to two additional times, or until the prescriber reports completion, within 180 days of being first identified.
 - iii. Ensure that prescribers can notify the Alosetron Sponsors when they have completed training via the Alosetron REMS Program website or by faxing or mailing a Prescriber Completion of Training Form.
 - iv. Provide acknowledgement of completion of training electronically or by mail to prescribers upon receiving notification that training was completed.
 - v. Make REMS Training Materials available at professional society meetings and at medical educational venues where the Alosetron Sponsors have a presence.
 - vi. Maintain an Alosetron REMS Program website [www.AlosetronREMS.com] and contact center (1-844-267-8675) to support prescribers.
 - vii. Maintain a validated, secure database of healthcare providers who have notified the Alosetron Sponsors of completion of training, which will be defined as all training materials were reviewed independently by the healthcare provider.

- viii. Ensure that the REMS materials listed below are available on the Alosetron REMS Program website or by calling the REMS contact center.

The following materials are part of the REMS and are appended:

- REMS Training Kit
 - REMS letter for Healthcare Providers
 - Alosetron REMS Program Prescriber Education Slide Deck
 - Alosetron REMS Program Safety Information Fact Sheet for Prescribers
 - Alosetron REMS Program Patient Education Sheet
 - Prescriber Completion of Alosetron REMS Program Training Form
- Other appended REMS materials:
 - Alosetron REMS Program website Prescriber Section screenshots
 - Alosetron REMS Program website Patients Section screenshots

FDA Required REMS Safety Information for Alosetron Tablets

Important Safety Update

The FDA has required this safety update as part of the Alosetron REMS Program to inform you that the Alosetron REMS Program **has changed** from the previous program.

ENROLLED Prescriber Actions:

- You are no longer required to affix prescribing program stickers to written prescriptions for alosetron
- You may prescribe alosetron electronically

NON-ENROLLED Prescriber Actions:

- Review the Alosetron REMS Program Training Kit and complete the Alosetron REMS Program Prescriber Completion Training Form which can be found at www.AlosetronREMS.com.
- You can also submit the enclosed form by fax to 1-800-535-6805.

You will find the Alosetron REMS Program Training Kit enclosed. The Training Kit is also available online at www.AlosetronREMS.com or you can request the Training Kit by calling the Alosetron REMS Program at 1-844-267-8675.

A non-promotional factsheet, reviewed by the FDA, with more detailed safety information about the risks of alosetron is enclosed.

Summary of Changes to the REMS Program

- ❶ Prescribers are **no** longer required to affix prescribing program stickers to written prescriptions for alosetron
- ❷ Pharmacies are **no** longer required to only dispense alosetron for a paper prescription with an affixed prescribing program sticker.

Electronic prescriptions are now allowed

- ❸ Patients are no longer required to complete and submit a Patient Acknowledgment Form. Instead, a Patient Education Sheet is available for the prescriber to discuss with the patient.

Indication:

Alosetron is a selective serotonin 5-HT₃ antagonist indicated only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have chronic IBS symptoms (generally lasting 6 months or longer), had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and not responded adequately to conventional therapy.

Severe IBS includes diarrhea and 1 or more of the following:

- frequent and severe abdominal pain/discomfort
- frequent bowel urgency or fecal incontinence
- disability or restriction of daily activities due to IBS

Please visit www.AlosetronREMS.com for more information.

This letter does not contain the complete safety profile for alosetron. Please see the Prescribing Information and Medication Guide, enclosed.

Reporting Adverse Events

You are encouraged to report all suspected adverse events associated with alosetron to the FDA at www.fda.gov/medwatch, or 1-800-FDA-1088 or to the Alosetron REMS Program at 1-844-267-8675.

Sincerely,

The Alosetron REMS Program

THE ALOSETRON REMS PROGRAM

Prescriber Education Slide Deck

Understanding the Benefits and Risks of Alosetron

The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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THE ALOSETRON REMS PROGRAM

Prescriber Education Slide Deck

Understanding the Benefits and Risks of Alosetron

The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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Important Modified Alosetron REMS Program

**The modified Alosetron REMS Program has changed
from the previous program**

- ❶ Prescribers are no longer required to affix prescribing program stickers to written prescriptions for alosetron
- ❷ Pharmacies are no longer required to only dispense alosetron for a paper prescription with an affixed prescribing program sticker. **Electronic prescriptions are now allowed.**
- ❸ Patients are no longer required to complete and submit a Patient Acknowledgement Form. Instead, a Patient Education Sheet is available for the prescriber to discuss with the patient.

The Alosetron REMS Program - Please see
complete Prescribing Information for
Alosetron Tablets for full details.

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Important

Modified Alosetron REMS Program

The modified Alosetron REMS Program has changed from the previous program

- ❶ Prescribers are no longer required to affix prescribing program stickers to written prescriptions for alosetron
- ❷ Pharmacies are no longer required to only dispense alosetron for a paper prescription with an affixed prescribing program sticker. **Electronic prescriptions are now allowed.**
- ❸ Patients are no longer required to complete and submit a Patient Acknowledgement Form. Instead, a Patient Education Sheet is available for the prescriber to discuss with the patient.

Section 1:

Purpose

The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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Section 1:

Purpose

Purpose of the Prescriber Education Slide Deck for Alosetron

- By reviewing the information provided in this presentation, prescribers who prescribe alosetron hydrochloride (alosetron) will better understand the:
 - **Risks and benefits of alosetron;**
 - **Etiology of irritable bowel syndrome;**
 - **The Alosetron REMS Program**



The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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Purpose of the Prescriber Education Slide Deck for Alosetron

- By reviewing the information provided in this presentation, prescribers who prescribe alosetron hydrochloride (alosetron) will better understand the:
 - **Risks and benefits of alosetron;**
 - **Etiology of irritable bowel syndrome;**
 - **The Alosetron REMS Program**

Risk Evaluation and Mitigation Strategy (REMS)

- A REMS (Risk Evaluation and Mitigation Strategy) is a program required by the FDA to manage known or potential serious risks associated with a drug product. FDA has determined that a REMS is necessary to ensure that the benefits of alosetron tablets outweigh serious gastrointestinal adverse reactions in patients.

The Alosetron REMS Program - Please see
complete Prescribing Information for
Alosetron Tablets for full details.

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Risk Evaluation and Mitigation Strategy (REMS)

A REMS (Risk Evaluation and Mitigation Strategy) is a program required by the FDA to manage known or potential serious risks associated with a drug product. FDA has determined that a REMS is necessary to ensure that the benefits of alosetron tablets outweigh serious gastrointestinal adverse reactions in patients.

Goals and Objectives

The Alosetron REMS Program was implemented to help reduce the risks of serious gastro-intestinal (GI) adverse events.

The goals and objectives of the Alosetron REMS Program are to mitigate the risks of ischemic colitis (IC) and serious complications of constipation (CoC) associated with alosetron hydrochloride (hereinafter, referred to as alosetron) by:

- Informing prescribers of alosetron about:
 - the serious risks of IC and serious CoC associated with alosetron
 - the importance of understanding that alosetron should only be used in severely affected diarrhea-predominant irritable bowel syndrome patients for whom the benefits exceed the risks.
 - the importance of counseling patients about the risks of IC and serious CoC
- Informing patients about the risks of IC and CoC and actions to take should they experience early warning signs and symptoms of these risks.



The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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Goals and Objectives

The Alosetron REMS Program was implemented to help reduce the risks of serious gastro-intestinal (GI) adverse events.

The goals and objectives of the Alosetron REMS Program are to mitigate the risks of ischemic colitis (IC) and serious complications of constipation (CoC) associated with alosetron hydrochloride (hereinafter, referred to as alosetron) by:

- **Informing prescribers of alosetron about:**
 - **the serious risks of IC and serious CoC associated with alosetron**
 - **the importance of understanding that alosetron should only be used in severely affected diarrhea-predominant irritable bowel syndrome patients for whom the benefits exceed the risks.**
 - **the importance of counseling patients about the risks of IC and serious CoC**
- **Informing patients about the risks of IC and CoC and actions to take should they experience early warning signs and symptoms of these risks.**

Section 2:

Indication and Usage

The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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Section 2:
Indication and Usage

Indication and Usage

Alosetron is indicated **ONLY** for women with severe diarrhea-predominant IBS who have:

- **chronic IBS symptoms (generally lasting 6 months or longer),**
- **had anatomic or biochemical abnormalities of the GI tract excluded, and**
- **not responded adequately to conventional therapy.**

The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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Indication and Usage

Alosetron is indicated **ONLY** for women with severe diarrhea-predominant IBS who have:

- **chronic IBS symptoms (generally lasting 6 months or longer),**
- **had anatomic or biochemical abnormalities of the GI tract excluded, and**
- **not responded adequately to conventional therapy.**

Indication and Usage (cont'd)

- Diarrhea-predominant IBS is severe if it includes diarrhea and one or more of the following:
 - **frequent and severe abdominal pain/discomfort,**
 - **frequent bowel urgency or fecal incontinence,**
 - **disability or restriction of daily activities due to IBS.**
- Because of infrequent but serious GI adverse reactions associated with alosetron, the indication is restricted to those patients for whom the benefit-to-risk balance is most favorable.
- Clinical studies have not been performed to adequately confirm the benefits of alosetron in men.

The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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Indication and Usage (cont'd)

- Diarrhea-predominant IBS is severe if it includes diarrhea and one or more of the following:
 - **frequent and severe abdominal pain/discomfort,**
 - **frequent bowel urgency or fecal incontinence,**
 - **disability or restriction of daily activities due to IBS.**
- Because of infrequent but serious GI adverse reactions associated with alosetron, the indication is restricted to those patients for whom the benefit-to-risk balance is most favorable.
- Clinical studies have not been performed to adequately confirm the benefits of alosetron in men.

Section 3:

Important Safety Information

The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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Section 3:
Important Safety Information

Boxed Warning

WARNING: SERIOUS GASTROINTESTINAL ADVERSE REACTIONS

Infrequent but serious gastrointestinal adverse reactions have been reported with the use of alosetron. These events, including ischemic colitis and serious complications of constipation, have resulted in hospitalization, and rarely, blood transfusion, surgery, and death.

The Alosetron REMS Program - Please see
complete Prescribing Information for
Alosetron Tablets for full details.

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Boxed Warning

WARNING: SERIOUS GASTROINTESTINAL ADVERSE REACTIONS

Infrequent but serious gastrointestinal adverse reactions have been reported with the use of alosetron. These events, including ischemic colitis and serious complications of constipation, have resulted in hospitalization, and rarely, blood transfusion, surgery, and death.

Boxed Warning (cont'd)

- Alosetron is indicated only for women with severe diarrhea-predominant IBS who have not responded adequately to conventional therapy.
- Alosetron should be discontinued immediately in patients who develop constipation or symptoms of ischemic colitis. Patients should immediately report constipation or symptoms of ischemic colitis to their prescriber. Alosetron should not be resumed in patients who develop ischemic colitis. Patients who have constipation should immediately contact their prescriber if the constipation does not resolve after alosetron is discontinued. Patients with resolved constipation should resume alosetron only on the advice of their treating prescriber.

The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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Boxed Warning (cont'd)

- Alosetron is indicated only for women with severe diarrhea-predominant IBS who have not responded adequately to conventional therapy.
- Alosetron should be discontinued immediately in patients who develop constipation or symptoms of ischemic colitis. Patients should immediately report constipation or symptoms of ischemic colitis to their prescriber. Alosetron should not be resumed in patients who develop ischemic colitis. Patients who have constipation should immediately contact their prescriber if the constipation does not resolve after alosetron is discontinued. Patients with resolved constipation should resume alosetron only on the advice of their treating prescriber.

Warnings and Precautions

Serious Complications of Constipation

- Some patients have experienced serious complications of constipation without warning. Examples include:
 - **obstruction, ileus, impaction, toxic megacolon, and secondary bowel ischemia have been reported with use of alosetron during clinical trials.**
 - **in addition, rare cases of intestinal perforation and death have been reported from postmarketing clinical practice.**
 - **in some cases, complications of constipation required intestinal surgery, including colectomy.**

The Alosetron REMS Program - Please
see complete Prescribing Information for
Alosetron Tablets for full details.

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Warnings and Precautions

Serious Complications of Constipation

- Some patients have experienced serious complications of constipation without warning. Examples include:
 - **obstruction, ileus, impaction, toxic megacolon, and secondary bowel ischemia have been reported with use of alosetron during clinical trials.**
 - **in addition, rare cases of intestinal perforation and death have been reported from postmarketing clinical practice.**
 - **in some cases, complications of constipation required intestinal surgery, including colectomy.**

Warnings and Precautions (cont'd)

Serious Complications of Constipation (cont'd)

- The incidence of serious complications of constipation was ~0.1%, or 1 per 1,000 patients, in women receiving either alosetron or placebo.
- Patients who are elderly, debilitated, or taking additional medications that decrease GI motility may be at greater risk for complications of constipation.
- Alosetron should be discontinued immediately in patients who develop constipation.

The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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Warnings and Precautions (cont'd)

Serious Complications of Constipation (cont'd)

- The incidence of serious complications of constipation was ~0.1%, or 1 per 1,000 patients, in women receiving either alosetron or placebo.
- Patients who are elderly, debilitated, or taking additional medications that decrease GI motility may be at greater risk for complications of constipation.
- Alosetron should be discontinued immediately in patients who develop constipation.

Warnings and Precautions (cont'd)

Ischemic Colitis

- Some patients have experienced symptoms of ischemic colitis without warning.
- Ischemic colitis has been reported in patients receiving alosetron in clinical trials as well as during marketed use of the drug.
- In IBS clinical trials:
 - **cumulative incidence of ischemic colitis in women receiving alosetron was:**
0.2%, or 2 per 1,000 patients (95% CI 1 to 3), over 3 months
0.3%, or 3 per 1,000 patients (95% CI 1 to 4), over 6 months
 - **patient experience in controlled clinical trials is insufficient to estimate the incidence of ischemic colitis in patients taking alosetron for longer than 6 months**

The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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Warnings and Precautions (cont'd)

Ischemic Colitis

- Some patients have experienced symptoms of ischemic colitis without warning.
- Ischemic colitis has been reported in patients receiving alosetron in clinical trials as well as during marketed use of the drug.
- In IBS clinical trials:
 - **cumulative incidence of ischemic colitis in women receiving alosetron was:**
0.2%, or 2 per 1,000 patients (95% CI 1 to 3), over 3 months
0.3%, or 3 per 1,000 patients (95% CI 1 to 4), over 6 months
 - **patient experience in controlled clinical trials is insufficient to estimate the incidence of ischemic colitis in patients taking alosetron for longer than 6 months**

Warnings and Precautions (cont'd)

Ischemic Colitis (cont'd)

- Alosetron should be discontinued immediately in patients with signs of ischemic colitis, e.g., rectal bleeding, bloody diarrhea, or new or worsening abdominal pain.
- Because ischemic colitis can be life threatening, patients with signs or symptoms of ischemic colitis should be evaluated promptly and have appropriate diagnostic testing performed.
- Treatment with alosetron should not be resumed in patients who develop ischemic colitis.

The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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Warnings and Precautions (cont'd)

Ischemic Colitis (cont'd)

- Alosetron should be discontinued immediately in patients with signs of ischemic colitis, e.g., rectal bleeding, bloody diarrhea, or new or worsening abdominal pain.
- Because ischemic colitis can be life threatening, patients with signs or symptoms of ischemic colitis should be evaluated promptly and have appropriate diagnostic testing performed.
- Treatment with alosetron should not be resumed in patients who develop ischemic colitis.

Contraindications

- Alosetron should not be initiated in patients with constipation.
- Alosetron is contraindicated in patients with a history of:
 - **chronic or severe constipation or sequelae from constipation;**
 - **intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforation, and/or adhesions;**
 - **ischemic colitis, impaired intestinal circulation, thrombophlebitis, or hypercoagulable state;**
 - **Crohn's disease or ulcerative colitis;**
 - **diverticulitis;**
 - **severe hepatic impairment.**

The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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Contraindications

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 - **Crohn's disease or ulcerative colitis;**
 - **diverticulitis;**
 - **severe hepatic impairment.**

Contraindications (cont'd)

- Concomitant administration of alosetron with fluvoxamine is contraindicated.



The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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Contraindications (cont'd)

- Concomitant administration of alosetron with fluvoxamine is contraindicated.

Drug Interactions

In vivo data suggest that alosetron is primarily metabolized by cytochrome P450 (CYP) 1A2, with minor contributions from CYP3A4 and CYP2C9. Therefore, inducers or inhibitors of these enzymes may change the clearance of alosetron.

- Concomitant administration of alosetron and fluvoxamine is contraindicated.
- Concomitant administration of alosetron and moderate CYP1A2 inhibitors, including quinolone antibiotics and cimetidine, has not been evaluated, but should be avoided unless clinically necessary because of similar potential drug interactions.

The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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Drug Interactions

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Drug Interactions (cont'd)

- Caution should be used when alosetron and ketoconazole are administered concomitantly.
- Coadministration of alosetron and strong CYP3A4 inhibitors, such as clarithromycin, telithromycin, protease inhibitors, voriconazole, and itraconazole has not been evaluated but should be undertaken with caution because of similar potential drug interactions.
- The effect of induction or inhibition of other pathways on exposure to alosetron and its metabolites is not known.

The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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Drug Interactions (cont'd)

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- The effect of induction or inhibition of other pathways on exposure to alosetron and its metabolites is not known.

Use in Specific populations

- Pregnancy Category B.
- It is not known whether alosetron is excreted in human milk; caution should be exercised when alosetron is administered to a nursing woman.
- Safety and effectiveness in pediatric patients have not been established.
- Postmarketing experience suggests that elderly patients may be at greater risk for complications of constipation; therefore, appropriate caution and follow-up should be exercised if alosetron is prescribed for these patients.

The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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Use in Specific populations

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- It is not known whether alosetron is excreted in human milk; caution should be exercised when alosetron is administered to a nursing woman.
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- Postmarketing experience suggests that elderly patients may be at greater risk for complications of constipation; therefore, appropriate caution and follow-up should be exercised if alosetron is prescribed for these patients.

Use in Specific populations (cont'd)

- Increased exposure to alosetron and/or its metabolites is likely to occur in patients with hepatic impairment. Alosetron should not be used in patients with severe hepatic impairment and should be used with caution in patients with mild or moderate hepatic impairment.

Use in Specific populations (cont'd)

- Increased exposure to alosetron and/or its metabolites is likely to occur in patients with hepatic impairment. Alosetron should not be used in patients with severe hepatic impairment and should be used with caution in patients with mild or moderate hepatic impairment.

Adverse Reactions Reported in ≥ 1% of IBS Patients^a

Gastrointestinal Adverse Reactions	Alosetron 1 mg BID (n=8,328 ^b)	Placebo (n=2,363)
Constipation ^c	29%	6%
Abdominal discomfort and pain	7%	4%
Nausea	6%	5%
GI discomfort and pain	5%	3%
Abdominal distention	2%	1%
Regurgitation and reflux	2%	2%
Hemorrhoids	2%	1%

^a Reported in ≥1% of alosetron patients and occurring more frequently on alosetron 1 mg twice-a-day than on placebo.

^b Data reported from 22 repeat-dose studies in patients with IBS treated for 8 to 24 weeks.

^c P<0.0001 vs placebo.

The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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^b Data reported from 22 repeat-dose studies in patients with IBS treated for 8 to 24 weeks.

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Adverse Reactions

Constipation is a frequent and dose-related side effect of treatment with alosetron.

- In clinical studies constipation was reported in ~29% of patients with IBS treated with alosetron 1 mg twice daily (n=9,316).
 - The effect was statistically significant compared with placebo ($P<0.0001$);
 - 11% of patients treated with alosetron 1 mg twice daily withdrew from the studies due to constipation.
- Although the number of IBS patients treated with alosetron 0.5 mg twice daily is relatively small (n=243), 11% of patients reported constipation and 4% of patients withdrew from clinical studies due to constipation.

The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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Overdosage

- No specific antidote available for overdose of alosetron.
- Patients should be managed with appropriate supportive therapy.

The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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Overdosage

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Section 4:

How to Prescribe Alosetron

Tablets

The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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Section 4:
How to Prescribe Alosetron Tablets

Dosage and Administration

- Usual Dose in Adults
 - To lower the risk of constipation, alosetron should be started at 0.5 mg twice-a-day.
 - Patients well controlled on 0.5 mg twice-a-day may be maintained on this regimen.
 - If, after 4 weeks, the 0.5 mg twice-a-day dosage is tolerated but does not adequately control IBS symptoms, increase dose to 1 mg twice-a-day, the dose used in controlled clinical trials.



The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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Dosage and Administration (cont'd)

- Usual Dose in Adults
 - **Alosetron should be started at a dosage of 0.5 mg twice-a-day. Patients controlled on this dose may be maintained on this regimen.**
 - If after 4 weeks, the 0.5 mg twice-a-day dosage is well tolerated but does not adequately control the IBS symptoms, then the dosage can be increased up to 1 mg twice-a-day.
 - **Alosetron should be discontinued in patients who have not had adequate control of IBS symptoms after 4 weeks of treatment with 1 mg twice-a-day.**
 - Alosetron should be discontinued immediately in patients who develop constipation or signs of ischemic colitis.
 - Alosetron should not be restarted in patients who develop ischemic colitis.



The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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Dosage and Administration (cont'd)

- Usual Dose in Adults
 - **Alosetron should be started at a dosage of 0.5 mg twice-a-day. Patients controlled on this dose may be maintained on this regimen.**
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 - Alosetron should be discontinued immediately in patients who develop constipation or signs of ischemic colitis.
 - Alosetron should not be restarted in patients who develop ischemic colitis.

Dosage and Administration (cont'd)

- Clinical trial and postmarketing experience suggest that debilitated patients or patients taking additional medications that decrease GI motility may be at greater risk of serious complications of constipation.
- Therefore, appropriate caution and follow-up should be exercised if alosetron is prescribed for these patients.
- Alosetron can be taken with or without food.

The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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Dosage and Administration (cont'd)

- Clinical trial and postmarketing experience suggest that debilitated patients or patients taking additional medications that decrease GI motility may be at greater risk of serious complications of constipation.
- Therefore, appropriate caution and follow-up should be exercised if alosetron is prescribed for these patients.
- Alosetron can be taken with or without food.

Section 5:

Alosetron

REMS Program

The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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Section 5:
Alosetron REMS Program

Training in the Alosetron REMS Program

- Prescribers should read the Prescribing Information (PI) and other training materials to understand the benefits and risks of treatment with alosetron for severe diarrhea-predominant IBS.
- Prescribers can communicate the completion of training by filling out the Prescriber Completion of Alosetron REMS Program Training Form at www.AlosetronREMS.com or return it by mail or by fax.
- **The form must be completed and returned to the Alosetron REMS Program before a prescriber can be considered trained in the program.**

The Alosetron REMS Program - Please see
complete Prescribing Information for
Alosetron Tablets for full details.

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Training in the Alosetron REMS Program

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- **The form must be completed and returned to the Alosetron REMS Program before a prescriber can be considered trained in the Alosetron REMS Program.**

Training in the Alosetron REMS Program (cont'd)

- Alosetron REMS Training Kit includes the following:
 - REMS letter for Healthcare Providers
 - Alosetron REMS Program Prescriber Education Slide Deck
 - Alosetron REMS Program Safety Information Fact Sheet for Prescribers
 - Alosetron REMS Program Patient Education Sheet
 - Prescriber Completion of Alosetron REMS Program Training Form

The Alosetron REMS Program - Please see
complete Prescribing Information for
Alosetron Tablets for full details.

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Training in the Alosetron REMS Program (cont'd)

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 - REMS letter for Healthcare Providers
 - Alosetron REMS Program Prescriber Education Slide Deck
 - Alosetron REMS Program Safety Information Fact Sheet for Prescribers
 - Alosetron REMS Program Patient Education Sheet
 - Prescriber Completion of Alosetron REMS Program Training Form

Patient Education

- Once you have selected an appropriate patient for therapy:
 - provide the patient with the Alosetron Patient Education Sheet
 - review it together with the patient and explain the risks of therapy
 - answer any questions the patient may have.
- Instruct the patient to read the Medication Guide supplied with the product

The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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 - provide the patient with the Alosetron Patient Education Sheet
 - review it together with the patient and explain the risks of therapy
 - answer any questions the patient may have.
- Instruct the patient to read the Medication Guide supplied with the product

Patient Responsibilities

Patients should be instructed to:

- read the Alosetron Patient Education Sheet before starting alosetron.
- read the Medication Guide before starting alosetron and each time they refill their prescription.
- not take alosetron if they are constipated.
- immediately discontinue alosetron and contact their prescriber if they become constipated or have symptoms of ischemic colitis such as new or worsening abdominal pain, bloody diarrhea, or blood in the stool.
- immediately contact their prescriber again if their constipation does not resolve after discontinuation of alosetron.

The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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Patient Responsibilities

Patients should be instructed to:

- read the Alosetron Patient Education Sheet before starting alosetron.
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- not take alosetron if they are constipated.
- immediately discontinue alosetron and contact their prescriber if they become constipated or have symptoms of ischemic colitis such as new or worsening abdominal pain, bloody diarrhea, or blood in the stool.
- immediately contact their prescriber again if their constipation does not resolve after discontinuation of alosetron.

Patient Responsibilities(cont'd)

Patients should be instructed to:

- resume alosetron only if their constipation has resolved and after discussion with and the agreement of their treating prescriber.
- stop taking alosetron and contact their prescriber if alosetron does not adequately control IBS symptoms after 4 weeks of taking 1 mg twice-a-day.

The Alosetron REMS Program - Please see
complete Prescribing Information for
Alosetron Tablets for full details.

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Patient Responsibilities(cont'd)

Patients should be instructed to:

- resume alosetron only if their constipation has resolved and after discussion with and the agreement of their treating prescriber.
- stop taking alosetron and contact their prescriber if alosetron does not adequately control IBS symptoms after 4 weeks of taking 1 mg twice-a-day.

- You have now reached the end of this Education Slide Deck.
- If you have questions about the Alosetron REMS Program, please call 1-844-267-8675 or visit www.AlosetronREMS.com.

The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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- You have now reached the end of this Education Slide Deck.
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Alosetron REMS Program

Safety Information Fact Sheet for Prescribers

FDA Required REMS* Safety Information

- **RISK OF SERIOUS GASTROINTESTINAL ADVERSE REACTIONS**
 - Infrequent but serious gastrointestinal adverse reactions have been reported with the use of alosetron hydrochloride tablets (alosetron). These events, including ischemic colitis and serious complications of constipation, have resulted in hospitalization and, rarely, blood transfusion, surgery, and death.
- **INDICATED ONLY** for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have not responded adequately to conventional therapy
- **DISCONTINUE** alosetron immediately in patients who develop constipation or symptoms of ischemic colitis. Do not resume alosetron in patients who develop ischemic colitis
- **Contraindicated in patients with:**
 - Constipation
 - History of chronic or severe constipation or sequelae from constipation; intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforation, and/or adhesions; ischemic colitis; impaired intestinal circulation, thrombophlebitis, or hypercoagulable state; Crohn's disease or ulcerative colitis; diverticulitis; severe hepatic impairment
 - Concomitant use of fluvoxamine (LUVOX®)

Risk of Serious Gastrointestinal Adverse Reactions

- **Counsel** patients to discontinue alosetron immediately and contact you right away if they develop constipation or symptoms of ischemic colitis
- **Evaluate** patients with signs of ischemic colitis (e.g., rectal bleeding, bloody diarrhea, new or worsening abdominal pain)
- **Discontinue** alosetron immediately if signs of ischemic colitis occur, such as rectal bleeding, bloody diarrhea, or new or worsening abdominal pain.

Appropriate Patient Selection

Prescribers should select the appropriate patients to receive alosetron in accordance with the approved indication. Alosetron is contraindicated in patients with constipation, history of chronic or severe constipation or sequelae from constipation; intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforation, and/or adhesions; ischemic colitis; impaired intestinal circulation, thrombophlebitis, or hypercoagulable state; Crohn's disease or ulcerative colitis; diverticulitis; severe hepatic impairment; and patients on fluvoxamine (LUVOX®).

*What is the Alosetron REMS Program?

A REMS (Risk Evaluation and Mitigation Strategy) is a program required by the FDA to manage known or potential serious risks associated with a drug product. FDA has determined that a REMS is necessary to ensure that the benefits of alosetron tablets outweigh serious gastrointestinal adverse reactions in patients. This factsheet is required by the FDA as part of the Alosetron REMS Program. Please visit www.AlosetronREMS.com for further information.

Indication

Alosetron is a selective serotonin 5-HT₃ antagonist indicated only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have chronic IBS symptoms (generally lasting 6 months or longer), had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and not responded adequately to conventional therapy.

Severe IBS includes diarrhea and 1 or more of the following:

- frequent and severe abdominal pain/discomfort
- frequent bowel urgency or fecal incontinence
- disability or restriction of daily activities due to IBS

Reporting Adverse Events:

You are encouraged to report all suspected adverse events associated with alosetron to the FDA at www.fda.gov/medwatch, or 1-800-FDA-1088 or to the Alosetron REMS Program at 1-844-267-8675.

This factsheet does not contain the complete safety profile for alosetron. Please refer to the Alosetron Prescribing Information, including Boxed Warning, for further information.

Alosetron REMS Program Patient Education Sheet

FDA Required Alosetron Safety Information

What is alosetron?

- Alosetron is a prescription medicine only for women with severe irritable bowel syndrome (IBS) whose main problem is diarrhea and who did not get the relief needed from other treatments. Alosetron has not been shown to help men with irritable bowel syndrome (IBS) or patients under age 18.

What is the most serious risk information about alosetron treatment?

- About 1 out of every 1,000 women who take alosetron may get serious complications of constipation. About 3 out of every 1,000 women who take alosetron over a 6-month period may get a serious problem where blood flow to parts of the large bowel is reduced (ischemic colitis).
- The serious condition of ischemic colitis, and other serious complications of constipation, can happen suddenly. These complications may lead to a hospital stay, and in rare cases, blood transfusions, surgery, and death.
- Certain patients may be more likely to develop a serious bowel condition while taking alosetron. These include older patients, those who have other health problems and those who take other medicines that may cause constipation.

What should I tell my doctor before I start taking alosetron?

- Tell your doctor about any illnesses you have, or other medicines you are taking or planning to take.

How do I take alosetron?

- Take alosetron exactly as your doctor prescribes it.

When should I stop taking alosetron and call my doctor?

- Stop taking alosetron and call your doctor right away if you get constipated, if you have new or worse pain in your stomach area (abdomen), or if you see blood in your bowel movements.
- Call your doctor again if the constipation you called about before has not gotten better.
- Do not start taking alosetron again unless your doctor tells you to do so, if you stopped taking it because you got constipated.

- Talk with your doctor 4 weeks after starting alosetron to recheck your IBS symptoms.
- Stop taking alosetron and call your doctor if your IBS symptoms have not improved after 4 weeks of taking 1 mg of alosetron 2 times a day.
- If you see other doctors about your IBS or possible side effects from alosetron, tell the doctor who prescribed alosetron.

This education sheet only discusses the most serious risk information of alosetron. For more safety information about alosetron please see the alosetron medication guides available at www.AlosetronREMS.com

Please visit www.AlosetronREMS.com for further information.

Prescriber Completion of Alosetron REMS Program Training Form

Thank you for completing the Alosetron REMS Program training. As a confirmation that you independently reviewed the provided training materials, please provide your details in the form below. Upon receipt you will be sent an acknowledgment notice.

*Indicates Required Field

Name of Prescriber (print)*

(First)

(Last)

Signature*

Date*

NPI Number* _____

Specialty*

☐ Gastroenterology

☐ General Surgery

☐ Internal Medicine

☐ Colon & Rectal Surgery

☐ Nurse Practitioner

☐ Nuclear Medicine

☐ Family Medicine

☐ Cardiovascular Diseases

☐ Physician Assistant

☐ Obstetrics/Gynecology

☐ Other (Please specify) _____

Office Name _____

Office Address* _____

Office City* _____

State* _____

Zip Code* _____

Office Phone Number* _____

Office Fax Number* _____

Email* _____

Confirmation Correspondence Preference (please select one): ☐ Fax ☐ Email

If you have any questions regarding the Alosetron REMS Program, please call 1-844-267-8675.

To complete training, visit www.AlosetronREMS.com or complete this form in its entirety and mail or fax it to the Alosetron REMS Program to the following address:

Alosetron REMS

PO Box 29292, Phoenix, AZ 85038

Fax Number: 1-800-535-6805

Alosetron REMS Program

Risk Evaluation and Mitigation Strategy

Web Mockups

V19

FOOTER

Footer is included on every web page. To reduce the length of the document, the screenshot is included once.

Please consult the [Prescribing Information](#).

[Resources](#) | [Terms of Use](#) | [Privacy Policy](#) | [Contact Us](#)



For Patients

For Prescribers

Alosetron REMS (Risk Evaluation and Mitigation Strategy)

What is the Alosetron REMS Program?

A REMS (Risk Evaluation and Mitigation Strategy) is a program required by the Food and Drug Administration (FDA) to manage known or potential serious risks associated with a drug product. The FDA has determined that a REMS is necessary for alosetron to ensure the benefits of the drug outweigh the risk of serious gastrointestinal (GI) adverse reactions.

The Alosetron REMS Program was implemented to help reduce the risks of a serious GI adverse event.

The goals and objectives of the Alosetron REMS Program are to mitigate the risks of ischemic colitis (IC) and serious complications of constipation (CoC) associated with alosetron hydrochloride (hereinafter, referred to as alosetron) by:

- Informing prescribers of alosetron about:
 - the serious risks of IC and serious CoC associated with alosetron
 - the importance of understanding that alosetron should only be used in severely affected diarrhea-predominant irritable bowel syndrome patients for whom the benefits exceed the risks
 - the importance of counseling patients about the risks of IC and serious CoC
- Informing patients about the risks of IC and CoC and actions to take should they experience early warning signs and symptoms of these risks.

Alosetron is indicated ONLY for women with severe diarrhea-predominant IBS who have:

- Chronic irritable bowel syndrome symptoms (generally lasting for 6 months or longer),
- had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and
- not responded adequately to conventional therapy.



For Patients

For Prescribers

Patient Role in the Alosetron REMS Program

Only patients who are counseled on the safe use of alosetron by their prescriber should be prescribed alosetron. Patients will be counseled on the Alosetron REMS Program by trained prescribers. Patients will have the opportunity to discuss any questions or concerns they have with their prescriber. The prescriber will provide and review the Alosetron REMS Program Patient Education Sheet with the patient at the beginning of treatment. Please use the links below to review the Alosetron REMS Program Patient Education Sheet and Medication Guide.



[Alosetron REMS Program Patient Education Sheet](#)

Medication Guide



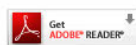
[Alosetron Medication Guide \(Amneal Pharmaceuticals LLC\)](#)



[Alosetron Medication Guide \(Par Pharmaceutical, Inc.\)](#)



[Alosetron Medication Guide \(Roxane Laboratories, Inc.\)](#)



PRESCRIBERS



For Patients

For Prescribers

Prescriber Role in the Alosetron REMS Program

Only prescribers who train in the Alosetron REMS Program, based on their understanding of the benefits and risks, should prescribe alosetron. The Alosetron REMS Program facilitates patients safety. The program requires patients and prescribers to understand the appropriate use of alosetron and its potential risks, as well as potential adverse events and how to handle them.

Prescribers should comply with the following requirements of the Alosetron REMS Program:

- Review the Alosetron REMS Program Prescriber Education Slide Deck
- Fill out and submit the Prescriber Completion of Alosetron REMS Program Training Form.

Prescriber Training

Prescribers should train in the Alosetron REMS Program prior to prescribing alosetron.

To train in the Alosetron REMS Program via web:

1. Review the Alosetron REMS Program Prescriber Education Slide Deck located in the Resources section below.
2. Press **Next** to begin the completion of training process.

To train in the Alosetron REMS Program via fax:

1. Review the Alosetron REMS Program Prescriber Education Slide Deck located in the Resources section below.
2. Complete the Prescriber Completion of Alosetron REMS Program Training Form located in the Resources section below.
3. Fax the completed Prescriber Completion of Alosetron REMS Program Training Form to the Alosetron REMS Program at 1-800-535-6805.

Resources

- [Prescriber Completion of Alosetron REMS Program Training Form](#)
- [Alosetron REMS Program Patient Education Sheet](#)
- [Alosetron REMS Program Prescriber Education Slide Deck](#)
- [Alosetron REMS Program Safety Information Fact Sheet for Prescribers](#)
- [REMS Letter to Healthcare Providers](#)

Prescribing Information and Medication Guide

- [Alosetron Prescribing Information \(Amneal Pharmaceuticals LLC\)](#)
- [Alosetron Medication Guide \(Amneal Pharmaceuticals LLC\)](#)
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PRESCRIBER AGREEMENT



For Patients

For Prescribers

The Alosetron REMS Program — Prescriber Completion of Training

Thank you for completing the Alosetron REMS Program training. As a confirmation that you independently reviewed the program training materials, please press the **Complete Training** button and provide your details on the following form.

Complete Training

PRESCRIBER ONLINE TRAINING FORM



For Patients

For Prescribers

Please complete the fields below and press **Submit** to complete training in the Alosetron REMS Program. All fields below are required unless otherwise indicated.

Prescriber Information

First Name	
Last Name	
Specialty	-- Please Select --
National Provider Identifier (NPI)	
Office Name	
Address 1	
Address 2	(Optional)
City	
State	-- Please Select --
Zip Code	
Phone	
Fax	
Email	
Correspondence Confirmation Preference	☐ Email ☐ Fax

Your signature and date are required to complete your training. Please type your exact first and last name along with today's date in the spaces provided below. This will serve as your electronic signature and will certify that you have read and agreed to the terms provided for the program.

Signature (First and Last Name as typed above)	Date MM/DD/YYYY	☐ I'm not a robot	 reCAPTCHA Privacy - Terms
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PRESCRIBER ONLINE TRAINING FORM – OTHER SPECIALTY SELECTED



For Patients

For Prescribers

Please complete the fields below and press **Submit** to complete training in the Alosetron REMS Program. All fields below are required unless otherwise indicated.

Prescriber Information

First Name	
Last Name	
Specialty	Other -- Please Specify --
National Provider Identifier (NPI)	
Office Name	
Address 1	
Address 2	(Optional)
City	
State	-- Please Select --
Zip Code	
Phone	
Fax	
Email	
Correspondence Confirmation Preference	☐ Email ☐ Fax

Your signature and date are required to complete your training. Please type your exact first and last name along with today's date in the spaces provided below. This will serve as your electronic signature and will certify that you have read and agreed to the terms provided for the program.

Signature (First and Last Name as typed above)	Date MM/DD/YYYY	☐ I'm not a robot	 reCAPTCHA Privacy - Terms
			Submit

PREScriBER TRAINING CONFIRMATION



For Patients

For Prescribers

Congratulations!

You have successfully trained in the Alosetron REMS Program!

Below is your Alosetron REMS Program Training Confirmation. Please note, you will receive acknowledgement of completion of training via your correspondence confirmation preference. Please retain this information for your records.

Training Confirmation: <Confirmation ID>

RESOURCES



For Patients

For Prescribers

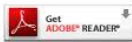
Resources

Prescriber

- [Alosetron REMS Program Prescriber Education Slide Deck](#)
- [Prescriber Completion of Alosetron REMS Program Training Form](#)
- [Alosetron REMS Program Patient Education Sheet](#)
- [Alosetron REMS Program Safety Information Fact Sheet for Prescribers](#)
- [REMS Letter to Healthcare Providers](#)

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CONTACT US



For Patients

For Prescribers

Contact Us

If you have any questions or require additional information, please contact the Alosetron REMS Program utilizing the information provided below.

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PHOENIX AZ 85038-9292



Carol
Holquist

Digitally signed by Carol Holquist
Date: 12/22/2016 09:03:06AM
GUID: 508da712000293e0f6d8acfd3c5e67fe



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 206647

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **ALOSETRON HYDROCHLORIDE TABLETS** safely and effectively. See full prescribing information for **ALOSETRON HYDROCHLORIDE TABLETS**, for oral use

Initial U.S. Approval: 2008

WARNING: SERIOUS GASTROINTESTINAL ADVERSE REACTIONS

See full prescribing information for complete boxed warning.

Inrequent but serious gastrointestinal adverse reactions have been reported with the use of alosetron hydrochloride tablets. These events, including ischemic colitis and serious complications of constipation, have resulted in hospitalization and, rarely, blood transfusion, surgery and death.

- **Alosetron hydrochloride is indicated only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have not responded adequately to conventional therapy. (1)**
- **Discontinue alosetron hydrochloride immediately in patients who develop constipation or symptoms of ischemic colitis. Do not resume alosetron hydrochloride in patients who develop ischemic colitis (1, 2.1, 5.1, 5.2)**

INDICATIONS AND USAGE

Alosetron hydrochloride tablets are a selective serotonin 5-HT₂ antagonist indicated only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have:

- chronic IBS symptoms (generally lasting 6 months or longer),
- had anatomic or biochemical abnormalities of the gastrointestinal tract excluded and
- not responded adequately to conventional therapy. (1)

Severe IBS includes diarrhea and 1 or more of the following:

- frequent and severe abdominal pain/discomfort,
- frequent bowel urgency or fecal incontinence,
- frequent bloody urgency or fecal incontinence,
- disability or restriction of daily activities due to IBS (1).

DOSEAGE AND ADMINISTRATION

- Starting dose is 0.5 mg twice a day (2.1)
- May increase dose to 1 mg twice a day after 4 weeks if starting dose is well tolerated but does not adequately control IBS symptoms (2.1)
- Discontinue alosetron hydrochloride tablets in patients who have not had adequate control of IBS symptoms a ter 4 weeks of treatment w 1 mg twice a day (2.1)

DOSEAGE FORMS AND STRENGTHS

Tablets: 0.5 and 1 mg (3)

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS GASTROINTESTINAL ADVERSE REACTIONS

Inrequent but serious gastrointestinal adverse reactions have been reported with the use of alosetron hydrochloride tablets. These events, including ischemic colitis and serious complications of constipation, have resulted in hospitalization and, rarely, blood transfusion, surgery and death.

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FULL PRESCRIBING INFORMATION

WARNING: SERIOUS GASTROINTESTINAL ADVERSE REACTIONS

Inrequent but serious gastrointestinal adverse reactions have been reported with the use of alosetron hydrochloride tablets. These events, including ischemic colitis and serious complications of constipation, have resulted in hospitalization and, rarely, blood transfusion, surgery and death.

- **Alosetron hydrochloride is indicated only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have not responded adequately to conventional therapy (see Indications and Usage (1)).**
- **Alosetron hydrochloride should be discontinued immediately in patients who develop constipation or symptoms of ischemic colitis. Patients should immediately report constipation or symptoms of ischemic colitis to their prescriber. Alosetron hydrochloride should not be resumed in patients who develop ischemic colitis. Patients who have constipation should immediately contact their prescriber. If the constipation does not respond after alosetron hydrochloride is discontinued, Patients with resolved constipation should resume alosetron hydrochloride only on the advice of their treating prescriber (see Dosage and Administration (2.1), Warnings and Precautions (5.1), (5.2)).**

1 INDICATIONS AND USAGE

Alosetron hydrochloride tablets are indicated only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have:

- chronic IBS symptoms (generally lasting 6 months or longer),
- had anatomic or biochemical abnormalities of the gastrointestinal tract excluded and
- not responded adequately to conventional therapy.

Diarrhea-predominant IBS is severe if it includes diarrhea and one or more of the following:

- frequent and severe abdominal pain/discomfort,
- frequent bowel urgency or fecal incontinence,
- disability or restriction of daily activities due to IBS.

Because of infrequent but serious gastrointestinal adverse reactions associated with alosetron hydrochloride tablets, the indication is restricted to those patients for whom the benefit-to-risk balance is most favorable.

Clinical studies have not been performed to adequately confirm the benefits of alosetron hydrochloride tablets in men.

2 DOSEAGE AND ADMINISTRATION

2.1 Adult Patients

To lower the risk of constipation, alosetron hydrochloride tablets should be started at a dosage of 0.5 mg twice a day. Patients who become constipated at this dosage should stop taking alosetron hydrochloride tablets until the constipation resolves. They may be restarted at 0.5 mg once a day. If constipation occurs at the lower dose, alosetron hydrochloride tablets should be discontinued immediately.

Patients well controlled on 0.5 mg once or twice a day may be maintained on this regimen. After 4 weeks the dosage is well tolerated but does not adequately control IBS symptoms, then the dosage can be increased to up to 1 mg twice a day. **Alosetron hydrochloride tablets should be discontinued in patients who have not had adequate control of IBS symptoms after 4 weeks of treatment w 1 mg twice a day.**

Alosetron hydrochloride tablets can be taken with or without food (see Clinical Pharmacology (12.3)).

Alosetron hydrochloride tablets should be discontinued immediately in patients who develop constipation or signs of ischemic colitis. Alosetron hydrochloride tablets should be restarted in patients who have resolved constipation or symptoms of ischemic colitis only on the advice of their treating prescriber. Clinical trial and postmarketing experience suggest that debilitated patients or patients taking additional medications that decrease gastrointestinal motility may be at greater risk of serious complications of constipation. Therefore, appropriate caution and follow-up should be exercised if alosetron hydrochloride tablets are prescribed for these patients.

Postmarketing experience suggests that elderly patients may be at greater risk for complications of constipation; therefore, appropriate caution and follow-up should be exercised if alosetron hydrochloride tablets are prescribed for these patients (see Warnings and Precautions (5.1)).

2.2 Patients With Hepatic Impairment

Alosetron hydrochloride tablets are extensively metabolized by the liver and increased exposure to alosetron hydrochloride tablets may be expected in patients with hepatic impairment. Increased drug exposure may increase the risk of serious adverse reactions. Alosetron hydrochloride tablets should be used with caution in patients with mild or moderate hepatic impairment and is contraindicated in patients with severe hepatic impairment (see Contraindications (4.3), Use in Specific Populations (8.3)).

3 DOSEAGE FORMS AND STRENGTHS

0.5 mg and 1 mg tablets

Alosetron hydrochloride tablets, 0.5 mg/0.562 mg alosetron hydrochloride equivalent to 0.5 mg alosetron, are white, oval, film-coated tablets debossed w/ "A4249" on one side and plain on the other side.

Alosetron hydrochloride tablets, 1 mg/1.124 mg alosetron hydrochloride equivalent to 1 mg alosetron, are light blue, oval shaped, film-coated tablets debossed with "A4249" on one side and plain on the other side.

4 CONTRAINDICATIONS

4.1 Constipation

Alosetron hydrochloride should not be initiated in patients with constipation (see Warnings and Precautions (5.1)).

4.2 History of Severe Bowel or Hepatic Disorders

Alosetron hydrochloride is contraindicated in patients with a history of the following:

- chronic or severe constipation or sequelae from constipation,
- intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforation and/or adhesions,
- ischemic colitis, impaired intestinal circulation, thrombophlebitis, or hypercoagulable state,
- Crohn's disease or ulcerative colitis,
- diverticulitis,
- severe hepatic impairment.

4.3 Concomitant Use of Fluvoxamine

Concomitant administration of alosetron hydrochloride w/ fluvoxamine is contraindicated. Fluvoxamine, a known strong inhibitor for CYP4A2, has been shown to

CONTRAINDICATIONS

- Do not initiate in patients with:
 - History of chronic or severe constipation or sequelae from constipation; intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforation and/or adhesions; ischemic colitis; impaired intestinal circulation, thrombophlebitis, or hypercoagulable state; Crohn's disease or ulcerative colitis; diverticulitis; severe hepatic impairment (4.2)
- Concomitant use of fluvoxamine (4.3)

WARNINGS AND PRECAUTIONS

- **Serious Complications of Constipation** May occur in some patients without warning. Include obstruction of, ileus, impaction, toxic megacolon and secondary bowel ischemia and in rare cases perforation and death have been reported. Risk is increased in patients who are elderly, debilitated, or taking medications that decrease bowel motility (5.1).
- Discontinue alosetron hydrochloride immediately if constipation occurs. (5.1)
- Ischemic colitis may occur in some patients without warning. Promptly evaluate patients with signs of ischemic colitis (e.g., rectal bleeding, bloody diarrhea, new or worsening abdominal pain). (5.2)
- Discontinue alosetron hydrochloride immediately if signs of ischemic colitis occur, such as rectal bleeding, bloody diarrhea, or new or worsening abdominal pain. (5.2)

ADVERSE REACTIONS

Most common adverse reactions (incidence >2% and -placebo) in clinical studies were constipation, abdominal discomfort and pain, nausea and gastrointestinal discomfort and pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Annual Pharmaceutical at 1-877-835-5472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

- CYP4A2 Inhibitors: Avoid concomitant use because of increased exposure and ha-tile of alosetron. Use with fluvoxamine is contraindicated. (4.3, 7.1)
- CYP3A4 Inhibitors: Use with caution in combination due to increased exposure of alosetron. (7.2)

USE IN SPECIFIC POPULATIONS

- **Hepatic Impairment:** Discontinue in severe hepatic impairment. Use with caution in patients with mild or moderate hepatic impairment. (4.2, 8.3)

- **Geriatric Use:** Elderly patients may be at greater risk for complications of constipation. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2016

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8.6 Hepatic Impairment	8.7 Renal Impairment
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12 CLINICAL PHARMACOLOGY	12.1 Mechanism of Action
12.2 Pharmacokinetics	12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY	13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES	14.1 Dose-Ranging Study
14.2 Efficacy Studies	14.3 Long-Term Use
15 REFERENCES	16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION	17.1 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

increase mean alosetron plasma concentrations (AUC) approximately 6-fold and prolong the half-life by approximately 3-fold (see Drug Interactions (7.1)).

5 WARNINGS AND PRECAUTIONS

5.1 Serious Complications of Constipation

Some patients have experienced serious complications of constipation without warning.

Serious complications of constipation, including obstruction, ileus, impaction, toxic megacolon and secondary bowel ischemia, have been reported with use of alosetron hydrochloride during clinical trials. Complications of constipation have been reported with use of 1 mg twice daily and with lower doses. A dose response relationship has not been established for serious complications of constipation. The incidence of serious adverse response relationship has not been established. Ischemic colitis has been reported in women receiving either alosetron hydrochloride or placebo. In addition, rare cases of perforation and death have been reported from postmarketing clinical practice. In some cases, complications of constipation required intestinal surgery, including colectomy. Patients who are elderly, debilitated, or taking additional medications that decrease gastrointestinal motility may be at greater risk for complications of constipation.

Alosetron hydrochloride should be discontinued immediately in patients who develop constipation (see Boxed Warning).

5.2 Ischemic Colitis

Some patients have experienced ischemic colitis without warning.

Ischemic colitis has been reported in patients receiving alosetron hydrochloride in clinical trials as well as during marketing use of the drug. In IBS clinical trials, the cumulative incidence of ischemic colitis in women receiving alosetron hydrochloride was 0.2% (2 per 1,000 patients), 95% confidence interval 1 to 3) through 3 months and was 0.3% (3 per 1,000 patients), 95% confidence interval 1 to 4) through 6 months. Ischemic colitis has been reported with use of 1 mg twice daily and with lower doses. A dose-response relationship has not been established. Ischemic colitis has been reported in one patient receiving placebo. The patient experience in controlled clinical trials is insufficient to estimate the incidence of ischemic colitis in patients taking alosetron hydrochloride for longer than 6 months.

Alosetron hydrochloride should be discontinued immediately in patients with signs of ischemic colitis such as rectal bleeding, bloody diarrhea, or new or worsening abdominal pain. Because ischemic colitis can be life-threatening, patients with signs or symptoms of ischemic colitis should be evaluated promptly and have appropriate diagnostic testing performed. Treatment with alosetron hydrochloride should not be resumed in patients who develop ischemic colitis.

6 ADVERSE REACTIONS

The following adverse reactions are described in more detail in other sections of the label.

- Complications of constipation (see Boxed Warning, Warnings and Precautions (5.1))
- Ischemic colitis (see Boxed Warning, Warnings and Precautions (5.2))

6.1 Clinical Trials Experience

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

Patients With Irritable Bowel Syndrome. Table 1 summarizes adverse reactions from 22 repeat-dose studies in patients with IBS who were treated with 1 mg of alosetron hydrochloride twice daily for 8 to 24 weeks. The adverse reactions in Table 1 were reported in 1% or more of patients who received alosetron hydrochloride and occurred more frequently on alosetron hydrochloride than on placebo. A statistically significant difference was observed for constipation in patients treated with alosetron hydrochloride compared to placebo.

Table 1. Adverse Reactions Reported in >1% of Patients With Irritable Bowel Syndrome and More Frequently on Alosetron Hydrochloride 1 mg Twice Daily Than Placebo

Adverse Reaction	Placebo (n = 2,363)	Alosetron Hydrochloride (n = 8,328)
Constipation	0%	29%
Abdominal discomfort and pain	4%	7%
Nausea	5%	6%
Diarrhea	3%	5%
Abdominal distention	1%	2%
Regurgita on and reflux	2%	2%
Hemorrhoids	1%	2%

Gastrointestinal Constipation is a frequent and dose-related side effect of treatment with alosetron hydrochloride (see Warnings and Precautions (5.1)). In clinical studies constipation was reported in approximately 29% of patients with IBS treated with alosetron hydrochloride 1 mg twice daily (n = 8,316). This effect was statistically significant compared to placebo (p<0.0001). Events were reported in 1% or more of patients who received alosetron hydrochloride and occurred more frequently on alosetron hydrochloride than on placebo. A statistically significant difference was observed for constipation in patients treated with alosetron hydrochloride compared to placebo.

The following adverse reactions were reported in approximately 29% of patients with IBS treated with alosetron hydrochloride 1 mg twice daily for 8 days. Occurrences of constipation in clinical trials were generally mild to moderate in intensity, transient in nature and resolved either spontaneously with continued treatment or with the use of laxatives. However, at least one case of constipation requiring surgery has been reported in clinical studies and in postmarketing experience (see Boxed Warning and Warnings and Precautions (5.1)). In Studies 1 and 2, 9% and 2% of patients treated with alosetron hydrochloride reported constipation and a consecutive days with no bowel movement, respectively (see Clinical Studies (14.2)). Following interruption of treatment, 73% of the affected patients resumed bowel movements within a 2-day period and were able to re-initiate treatment with alosetron hydrochloride.

Hepatic: A similar incidence in elevated levels of ALT (>2.5-fold) was seen in patients receiving alosetron hydrochloride or placebo (1% vs. 1.2%). A single case of hepatitis (elevated ALT, AST, alkaline phosphatase and bilirubin) without jaundice in a patient receiving alosetron hydrochloride was reported in a 12-week study. A causal association with alosetron hydrochloride has not been established.

Long-Term Safety: Patient experience in controlled clinical trials is insufficient to estimate the incidence of ischemic colitis in patients taking alosetron hydrochloride for longer than 6 months.

Women With Severe Diarrhea-Predominant Irritable Bowel Syndrome: Table 2 summarizes the gastrointestinal adverse reactions from a repeat-dose study in female patients with severe diarrhea-predominant IBS who were treated for 12 weeks. The adverse reactions in Table 2 were reported in 3% or more of patients who received alosetron hydrochloride and occurred more frequently with alosetron hydrochloride than with placebo. Other events reported in 3% or more of patients who received alosetron hydrochloride and occurred more frequently with alosetron hydrochloride than w/ placebo included upper respiratory tract infection, viral gastroenteritis, muscle spasms, headaches and fatigue.

Table 2. Gastrointestinal Adverse Reactions Reported in ≥3% of Women W/ Severe Diarrhea-Predominant Irritable Bowel Syndrome and More Frequently on Alosetron Hydrochloride Than Placebo.

Adverse Reaction	Placebo (n = 176)	Alosetron Hydrochloride (n = 175)	Alosetron Hydrochloride (n = 172)	Alosetron Hydrochloride (n = 176)
Constipation	5%	9%	16%	19%
Abdominal pain	3%	5%	6%	7%
Diarrhea	2%	3%	2%	2%
Hemorrhoid hemorrhage	2%	3%	2%	2%
Fatulence	2%	2%	1%	3%
Hemorrhoids	2%	1%	1%	3%
Abdominal pain upper	1%	3%	1%	1%

Adverse reactions reported in another study of 701 women with severe diarrhea-predominant IBS were similar to those shown in Table 2. Gastrointestinal adverse reactions reported in 3% or more of patients who received alosetron hydrochloride during the study were similar to those reported in Table 2. Gastrointestinal adverse reactions reported in 3% or more of patients who received alosetron hydrochloride during the study were similar to those reported in Table 2. Gastrointestinal adverse reactions reported in 3% or more of patients who received alosetron hydrochloride during the study were similar to those reported in Table 2.

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Medication Guide
Alosetron (a-L0-ze-tron) Hydrochloride Tablets

Before using alosetron hydrochloride tablets for the first time, you should:

- Understand that alosetron hydrochloride tablets have serious risks for some people.
- Read and follow the directions in this Medication Guide.

Carefully read the Medication Guide you get with each refill for alosetron hydrochloride tablets. There may be new information. This Medication Guide does not take the place of talking with your doctor.

1. What is the most important information I should know about alosetron hydrochloride tablets?

A. Alosetron hydrochloride tablets are a medicine only for some women with severe chronic irritable bowel syndrome (IBS) whose:

- main problem is diarrhea and
- IBS symptoms have not been helped enough by other treatments.

B. Some patients have developed serious bowel side effects while taking alosetron hydrochloride tablets. Serious bowel (intestine) side effects can happen suddenly, including the following:

1. Serious complications of constipation: About 1 out of every 1,000 women who take alosetron hydrochloride tablets may get serious complications of constipation. These complications **may lead to a hospital stay and, in rare cases, blood transfusions, surgery and death.** People who are older, who are weak from illness, or who take other constipating medicines may be more likely to have serious complications of constipation with alosetron hydrochloride tablets.

To lower your chances of getting serious complications of constipation, do the following:

- **If you are constipated,** do not start taking alosetron hydrochloride tablets.
- **If you get constipated while taking alosetron hydrochloride tablets,** stop taking it right away and call your doctor.
- **If your constipation does not get better after stopping alosetron hydrochloride tablets,** call your doctor again.
- **If you stopped taking alosetron hydrochloride tablets, do not start taking alosetron hydrochloride tablets again** unless your doctor tells you to do so.

2. Ischemic colitis (reduced blood flow to the bowel): About 3 out of every 1,000 women who take alosetron hydrochloride tablets over a 6-month period may get a serious problem where blood flow to parts of the large bowel is reduced. This is called ischemic colitis. The chance of getting ischemic colitis when you take alosetron hydrochloride tablets for more than 6 months is not known. **Ischemic colitis may lead to a hospital stay and, in rare cases, blood transfusions, surgery and death.**

To lower your chances of getting serious complications of ischemic colitis, stop taking alosetron hydrochloride tablets and call your doctor right away if you get:

- new or worse pain in your stomach area (abdomen) or
- blood in your bowel movements.

C. Are alosetron hydrochloride tablets right for you?

Alosetron hydrochloride tablets may be right for you if all of these things are true about you:

- Your doctor has told you that your symptoms are due to IBS.
- Your IBS bowel problem is diarrhea.
- Your IBS has lasted for 6 months or longer.
- You tried other IBS treatments and they did not give you the relief you need.
- Your IBS is severe.

You can tell if your IBS is severe if **at least 1** of the following is true for you:

- You have lots of painful stomach cramps or bloating.
- You often cannot control the need to have a bowel movement, or you have “accidents” where your underwear gets dirty from diarrhea or bowel movements.
- You cannot lead a normal home or work life because you need to be near a bathroom.

Enough testing has not been done to confirm if alosetron hydrochloride tablets works in men or children under age 18.

2. What are alosetron hydrochloride tablets?

Alosetron hydrochloride tablets are a medicine only for some women with severe chronic IBS whose:

- main problem is diarrhea and
- IBS symptoms have not been helped enough by other treatments.

Alosetron hydrochloride tablets do not cure IBS and it may not help every person who takes it. For those who are helped, alosetron hydrochloride tablets reduces lower stomach area (abdominal) pain and discomfort, the sudden need to have a bowel movement (bowel urgency) and diarrhea from IBS. If you stop taking alosetron hydrochloride tablets, your IBS symptoms may return within 1 or 2 weeks to what they were before you started taking alosetron hydrochloride tablets.

Alosetron hydrochloride tablets are not recommended for children.

3. Who should not take alosetron hydrochloride tablets?

Alosetron hydrochloride tablets are not right for everyone. **Do not take alosetron hydrochloride tablets if any of the following apply to you:**

- Your main IBS problem is constipation or you are constipated most of the time.
- You have had a serious problem from constipation. **If you are constipated now, do not start taking alosetron hydrochloride tablets.**
- You have had serious bowel blockages.
- You have had blood flow problems to your bowels, such as ischemic colitis.
- You have had blood clots.
- You have had Crohn's disease, ulcerative colitis, diverticulitis, or severe liver disease.
- You do not understand this Medication Guide or you are not willing to follow it.
- You are taking fluvoxamine (LUVOX®).

4. What should I talk about with my doctor before taking alosetron hydrochloride tablets?

Talk with your doctor:

- about the possible benefits and risks of alosetron hydrochloride tablets.
- about how much of a problem IBS is in your life and what treatments you have tried.
- about any other illnesses you have and medicines you take or plan to take. These include prescription and non-prescription medicines, supplements and herbal remedies. Certain illnesses and medicines can increase your chance of getting serious side effects while taking alosetron hydrochloride tablets. Other medicines may interact with how the body handles alosetron hydrochloride tablets.
- about any allergies that you have. See the end of the Medication Guide for a complete list of ingredients in alosetron hydrochloride tablets.
- if you are pregnant, planning to get pregnant, or breastfeeding.

5. How should I take alosetron hydrochloride tablets?

- Take alosetron hydrochloride tablets exactly as your doctor prescribes it. You can take alosetron hydrochloride tablets with or without food.
- Begin with 0.5 mg two times a day for 4 weeks to see how alosetron hydrochloride tablets affects you. You and your doctor may decide that you should keep taking this dose if you are doing well.
- Check with your doctor 4 weeks after starting alosetron hydrochloride tablets:
 - If you try 0.5 mg two times a day for 4 weeks, it may not control your symptoms. If you do not get constipation or other side effects from alosetron hydrochloride tablets, your doctor may increase your dose up to 1 mg two times a day.
 - If 1 mg two times a day does not work after 4 weeks, alosetron hydrochloride tablets is not likely to help you. You should stop taking it and call your doctor.
- **If you miss a dose of alosetron hydrochloride tablets**, just skip that dose. Do **not** take 2 doses the next time. Wait until the next time you are supposed to take it and then take your normal dose.
- **Follow the important instructions in the section “What is the most important information I should know about alosetron hydrochloride tablets?”** about when you must stop taking the medicine and when you should call your doctor.
- **If you see other doctors** about your IBS or side effects from alosetron hydrochloride tablets, tell the doctor who prescribed alosetron hydrochloride tablets.

6. What are the possible side effects of alosetron hydrochloride tablets?

Constipation is the most common side effect among women with IBS who take alosetron hydrochloride tablets. **Some patients have developed serious bowel side effects while taking alosetron hydrochloride tablets.** Read the section “**What is the most important information I should know about alosetron hydrochloride tablets?**” at the beginning of this Medication Guide for information about the serious side effects you may get with alosetron hydrochloride tablets.

This Medication Guide does not tell you about all the possible side effects of alosetron hydrochloride tablets. Your doctor or pharmacist can give you a more complete list.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

7. How should I store alosetron hydrochloride tablets?

- Store alosetron hydrochloride tablets between 59°F to 86°F (15°C to 30°C).
- Protect alosetron hydrochloride tablets from light and getting wet (moisture).

Keep alosetron hydrochloride tablets and all medicines out of the reach of children.

8. General information about the safe and effective use of alosetron hydrochloride tablets

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you have any questions or concerns about alosetron hydrochloride tablets, ask your doctor. Do not use alosetron hydrochloride tablets for a condition for which it was not prescribed. Do not share your medicine with other people. It may harm them.

Your doctor or pharmacist can give you more information about alosetron hydrochloride tablets that was written for healthcare professionals. You can also contact the company that makes alosetron hydrochloride tablets (toll free) at 1-877-835-5472 or at www.amneal.com.

9. What are the ingredients of alosetron hydrochloride tablets?

Active Ingredient: alosetron hydrochloride.

Inactive Ingredients: lactose anhydrous, magnesium stearate, microcrystalline cellulose and pregelatinized starch (maize). The white film-coat for the 0.5 mg tablet contains hypromellose, polyethylene glycol, polysorbate 80 and titanium dioxide. The light blue film-coat for the 1 mg tablet contains FD&C blue #2, hypromellose, macrogol, polysorbate 80 and titanium dioxide.

*Trademarks are the property of their respective owners.

Distributed by:

Amneal Pharmaceuticals

Bridgewater, NJ 08807

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Rev. 04-2016-00

NDC 65162-248-03

Alosetron

Hydrochloride

Tablets

0.5 mg

PHARMACIST: PLEASE
DISPENSE WITH ATTACHED
MEDICATION GUIDE

 Rx only
30 Tablets



*Each film-coated tablet contains alosetron hydrochloride equivalent to 0.5 mg alosetron.

See prescribing information for Dosage and Administration.

Store at 20° to 25°C (68° to 77°F); (see USP Controlled Room Temperature). Protect from light and moisture.

Dispense in a tight, light-resistant container as defined in the USP.

Distributed by: **Amneal Pharmaceuticals**
Bridgewater, NJ 08807

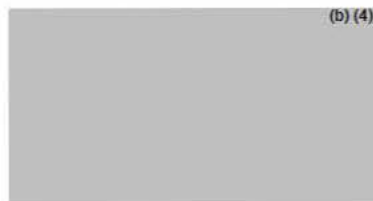
Rev. 04-2016-00



65162 24803 6

Non-Varnish Area

Label Size 1.5" x 4.625"



NDC 65162-248-50

Alosetron Hydrochloride Tablets

0.5 mg*

PHARMACIST: PLEASE
DISPENSE WITH ATTACHED
MEDICATION GUIDE



Rx only
500 Tablets



*Each film-coated tablet contains alosetron hydrochloride equivalent to 0.5 mg alosetron.

See prescribing information for Dosage and Administration.

Store at 20° to 25°C (68° to 77°F); [see USP Controlled Room Temperature]. Protect from light and moisture.

Dispense in a tight, light-resistant container as defined in the USP.

Distributed by: **Amneal Pharmaceuticals**
Bridgewater, NJ 08807

Rev. 04-2016-00



Non-Varnish Area

Label Size 2.125" x 6.5"



NDC 65162-249-03

Alosetron

Hydrochloride

Tablets

1 mg *

PHARMACIST: PLEASE
DISPENSE WITH ATTACHED
MEDICATION GUIDE


Rx only
30 Tablets



*Each film-coated tablet contains alosetron hydrochloride equivalent to 1 mg alosetron.

See prescribing information for Dosage and Administration.

Store at 20° to 25°C (68° to 77°F); [see USP Controlled Room Temperature]. Protect from light and moisture.

Dispense in a tight, light-resistant container as defined in the USP.

Distributed by: **Amneal Pharmaceuticals**
Bridgewater, NJ 08807

Rev. 04-2016-00

65162 24903 3

Non-Varnish Area

Label Size 1.5" x 4.625"



NDC 65162-249-50

Alosetron Hydrochloride Tablets

1 mg*

PHARMACIST: PLEASE
DISPENSE WITH ATTACHED
MEDICATION GUIDE



Rx only
500 Tablets



*Each film-coated tablet contains alosetron hydrochloride equivalent to 1 mg alosetron.

See prescribing information for Dosage and Administration.

Store at 20° to 25°C (68° to 77°F); [see USP Controlled Room Temperature]. Protect from light and moisture.

Dispense in a tight, light-resistant container as defined in the USP.

Distributed by: **Amneal Pharmaceuticals**
Bridgewater, NJ 08807

Rev. 04-2016-00



N 3 65162 24950 7

Non-Varnish Area

Label Size 2.125" x 6.5"



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 206647

LABELING REVIEWS

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	04/28/2016
ANDA Number(s)	206647
Review Number	2
Applicant Name	Amneal Pharmaceuticals
Established Name & Strength(s)	Alosetron Hydrochloride Tablets, 0.5 mg (base) and 1 mg (base)
Proposed Proprietary Name	None
Submission Received Date	04/22/2016
Labeling Reviewer	Dinaxi Jetton, Pharm. D
Labeling Team Leader	Ellen Hwang, Pharm. D
Review Conclusion ☒ ACCEPTABLE – No Comments. ☐ ACCEPTABLE – Include Post Approval Comments ☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant. *Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant. ☐ On Policy Alert List	

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

NA

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission dated 04/22/2016.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

1.3 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.

These comments will be addressed post approval (in the first labeling supplement review).

Click here to enter text.

NA

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

Reviewer Comments:

Cycle 2 Review: Labeling Deficiencies determined on 03/20/2016 based on submission dated 12/24/2013. Deficiencies were issued with an ECD dated 04/11/2016 and Firm submitted a response on 04/22/2016.

1. GENERAL COMMENT

In your quality submission, the drug product manufacturer is listed as Amneal Pharmaceuticals
50 Horseblock Road Brookhaven, NY 11719. (b) (4)

Amneal's Response:

Amneal acknowledges the Agency's comment. Amneal would like to clarify here that, as per 21 CFR 201.1(j), even though Amneal's Generic Drug Product (i.e. Alosetron Hydrochloride Tablets, 0.5 mg and 1 mg) was manufactured in Brookhaven, NY, (b) (4)

(b) (4) of Alosetron Hydrochloride Tablets, 0.5 mg and 1 mg. Additionally, Amneal would like to inform to the agency that, due to business reasons; Amneal has (b) (4)
(b) (4) updated the Distributor's address (b) (4) to

"Amneal Pharmaceuticals, Bridgewater, NJ 08807", in all the relevant sections of Labeling of Alosetron Hydrochloride Tablets, 0.5 mg and 1 mg.

2. CONTAINER LABEL [All Strengths/All Sizes]

- a. (b) (4) so it does not compete with the established name and strength. We refer you to Section C (pg. 4) of the Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm349009.pdf>
- b. We note that there is a pictorial representation of the drug product. Ensure image of the tablet represent the actual tablet and reflect the true size, color and imprint. Refer to "[Guidance for Industry, Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors](#)", section III (D) (4) (page 6).
- c. Please add an asterisk (*) after the expression of strength of Alosetron (PDP) and before the "Each tablet contains..." statement on the side panel. Refer to Naming of Drug Products Containing Salt Drug Substances, Guidance for Industry, sections II (A) and (B) (page 3).

3. PRESCRIBING INFORMATION

- a. Revise your insert labeling to be in accordance with the most recently approved insert labeling for the reference listed drug (RLD), LOTRONEX[®], NDA 021107/S-027 approved 01/07/2016.
- b. HIGHLIGHTS OF PRESCRIBING INFORMATION – To be in accordance with the Guidance for Industry: Labeling for Human Prescription Drug and Biological Products - Implementing the PLR Content and Format Requirements, revise the Limitation statement and Title line to read:

These highlights do not include all the information needed to use ALOSETRON HYDROCHLORIDE TABLETS safely and effectively. See full prescribing information for ALOSETRON HYDROCHLORIDE TABLETS.

ALOSETRON HYDROCHLORIDE tablets, for oral use
Initial U.S. Approval: 2000

- c. When referring to the drug product, use "aloseptron hydrochloride tablets" (b) (4) as the established name.
- d. DESCRIPTION section – Revise (b) (4) to read "polysorbate 80" to be consistent with your quality submission and the SPL Data Elements.

4. MEDICATION GUIDE

- Revise your Medication Guide to be in accordance with the most recently approved Medication Guide for the reference listed drug (RLD), LOTRONEX®, NDA 021107/S-027 approved 01/07/2016.
- Add the phonetic spelling of the established name (or proprietary name if one is proposed) in the Title in accordance with 21 CFR 208.20(b) (1).
- Ensure a sufficient number of Medication Guides is available for dispensing and distribution to patients receiving a prescription for your drug product, per 21 CFR 208.24.

Amneal's Response to 4c:

Additionally, Amneal would like to inform to the Agency that "Each bottle will be affix with the package insert, which includes the Medication Guide. The Medication Guide will also be printed in pads of 25 counts and provided to distributors in each shipper box."

Reviewer's Assessment: Firm has adequately revised the container labels, package insert and medication guide as per Agency request. Firm's response to the GENERAL COMMENT and MEDICATION GUIDE (4C) is acceptable, as are the revisions to labeling pieces.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were NOT requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments: Firm has adequately revised the container labels as per Agency request and revision of Distributor information is acknowledged and acceptable.

Below are previously and currently submitted labels for comparison:



Cycle 1 Labels (Orig.
12-24-2013).pdf



Cycle 2 Labels
(Amend. 04-22-2016).

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

NA

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in [DLR's SharePoint Drug Facts](#)? **NO**

If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

Is the drug product listed in the Policy Alert Tracker on [OGD's SharePoint](#)? **NO**

If Yes, please explain.

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling
(Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA RLD information.)

NDA#/Supplement# (S-000 if original): 021107/S-027

Supplement Approval Date: 01/07/2016

Proprietary Name: LOTRONEX®

Established Name: Alosetron Hydrochloride Tablets

Description of Supplement:

This Prior Approval supplemental new drug application provides for the following labeling changes to be in alignment with the risk evaluation and mitigation strategy (REMS) modification for Lotronex:

1. Package Insert: Box Warning, Dosage and Administration (2.3), Contraindications (4.3), Warnings and Precautions (5.3), Patient Counseling Information (17).
2. Medication Guide

Your approved Medication Guide will no longer be part of the risk evaluation and mitigation strategy (REMS), but is now approved under 21 CFR 208.

For the Record:

- **NDA 021107/S-026 (approved 01/07/2016)**

Re: NDA 21-107; LOTRONEX® (alosecron hydrochloride) Tablets
Prior Approval Supplement-026
Proposed REMS Modification

Dear Dr. Korvick:

Reference is made to the Agency REMS Modification Notification dated 20 May 2015. Reference is also made to the approval of S-025 providing for a REMS revision dated 24 July 2015. Enclosed for your review is the proposed REMS modification.

The present modification of the LOTRONEX REMS is primarily based on FDA's request to modify the approved LOTRONEX REMS, dated 20 May 2015 and the REMS revision Supplement 025 approved on 24 July 2015. To provide a continuum of nomenclature for the Prescribers and Patients, the proposed modified LOTRONEX REMS accounts for a harmonization of nomenclature. Such harmonization includes recently approved terms as LOTRONEX/alosecron hydrochloride, LOTRONEX and its authorized generic.

The most significant departure from the requested changes is the description of the Brand LOTRONEX with the generic leaving out the word 'authorized'. Prometheus has plans to share this program with other generic alosecron hydrochloride manufacturers and would like to employ the most inclusive terminology.

In addition the following minor name changes are proposed with rationale:

- LOTRONEX/alosecron hydrochloride Patient Education Sheet - Since the document will not require the patient or prescriber to fill out any information or collect a signature, rather than identify it as a (b) (4) it will be considered an 'Education Sheet'
- LOTRONEX REMS Program Prescriber Education Slide Deck -The word 'Program' is utilized to encompass all the components of the LOTRONEX REMS Program, therefore this single element is better identified as the Prescriber Education Slide Deck.

- **NDA 021107/S-028 (received 03/18/2016)** is a CMC supplemental application currently "Pending" which provides for alternate sites for the alosecron hydrochloride (b) (4) **It does not affect labeling.**

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling
(Check the box used as the Model Labeling)

☐ MOST RECENTLY APPROVED ANDA RLD LABELING ANDA#/Supplement# (S-000 if original): Click here to enter text. Supplement Approval Date: Click here to enter text. Proprietary Name: Click here to enter text. Established Name: Click here to enter text. Description of Supplement: Click here to enter text.
☐ TEMPLATE (e.g., BPCA, PREA, and Carve-out): Click here to enter text.
☒ OTHER (Describe): <u>There are currently 3 ANDAs in-house that were referenced for consistency:</u> ANDA 200652 - approved 05/04/2015 ANDA 206113 – currently in “Complete Response” as of 02/24/2016 ANDA 209180 – currently in “Pending” status

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under [21 CFR 314.94\(a\)\(8\)](#)? **YES**
 Are the specific requirements for format met under [21 CFR 201.57\(new\)](#) or [201.80\(old\)](#)? **YES**
 Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

Insert labeling has been revised to be in accordance with the most recently approved labeling for the reference listed drug (RLD), LOTRONEX®, NDA 021107/S-027 approved 01/07/2016.

Insert labeling is Acceptable.

The following is noted: Macrogol is the International Nonproprietary Name (INN) for polyethylene glycol and are synonymous.

In the SPL Data Elements section, 1 mg tablet - The Firm has listed the this ingredient as “polyethylene glycol”. In the DESCRIPTION section of the package insert, the ingredient is listed “macrogol”. The difference will be allowed. SPL is Acceptable.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels (Source: Annual Report – 15, dated 04/08/2015)

Annual Reportable Changes

The following Annual Reportable labeling changes were made during this reporting period:

- “Made in CANADA” was added to the PI, Cartons and bottle labels.
- Storage temperature was updated to follow USP and
- Part numbers/revision dates were updated.



N 3

65483-894-03

NDC 65483-894-03

30 Tablets



LOTIRONEX[®]
(alose tron hydrochloride) Tablets

Each film-coated tablet contains alose tron hydrochloride equivalent to 0.5 mg alose tron.

R_x only

See prescribing information for Dosage and Administration.

Store at 20-25°C (68-77°F)
(USP Controlled Room Temperature).



0.5 mg

Federal Law requires the dispensing of LOTIRONEX[®] with the Medication Guide attached.

Dispense in a tight, light-resistant container as defined in the USP.

PROMETHEUS[®]
Therapeutics & Diagnostics

Prometheus Laboratories Inc.
San Diego, CA 92121 Made in Canada
LX003D Rev. 03/14

Exp

Lot

LX003D



N 3

65483-895-03

NDC 65483-895-03

30 Tablets



LOTIRONEX[®]
(alose tron hydrochloride) Tablets

Each film-coated tablet contains alose tron hydrochloride equivalent to 1 mg alose tron.

R_x only

See prescribing information for Dosage and Administration.

Store at 20-25°C (68-77°F)
(USP Controlled Room Temperature).



1 mg

Federal Law requires the dispensing of LOTIRONEX[®] with the Medication Guide attached.

Dispense in a tight, light-resistant container as defined in the USP.

PROMETHEUS[®]
Therapeutics & Diagnostics

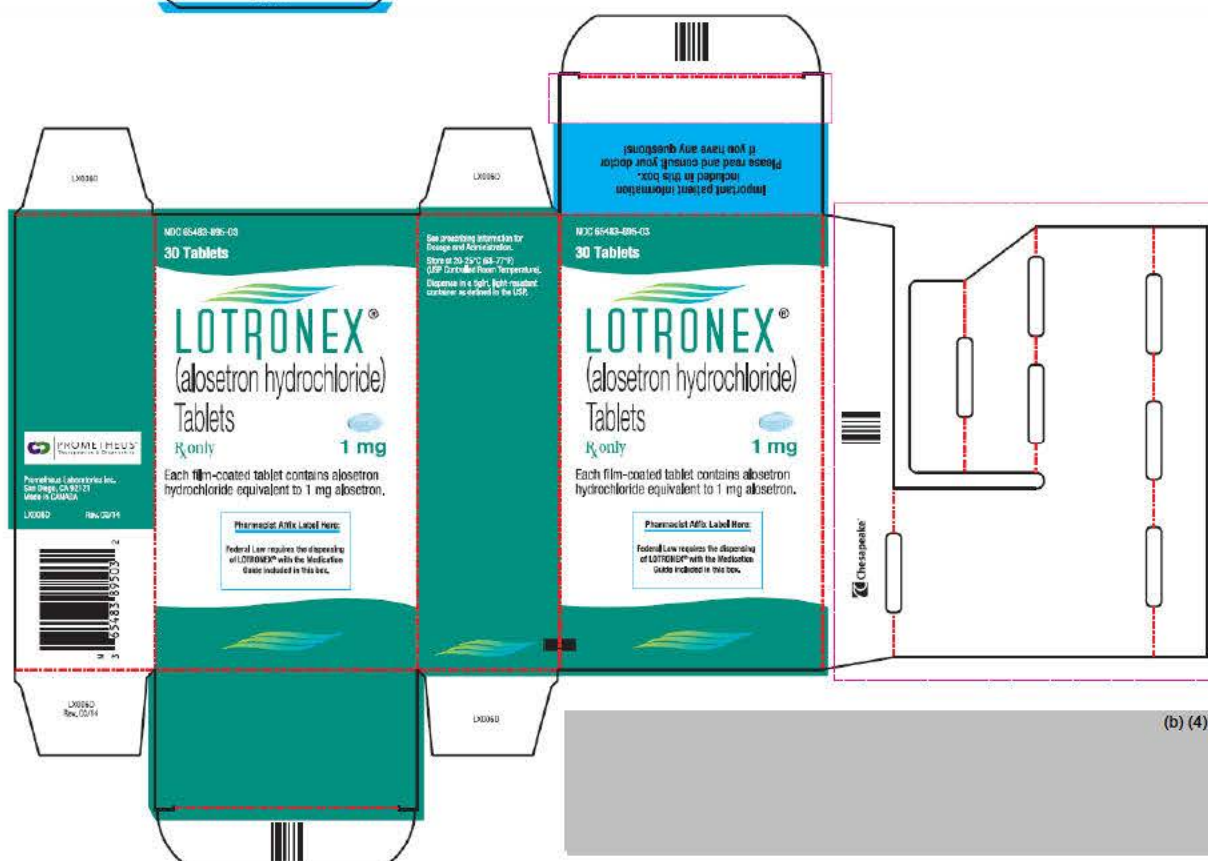
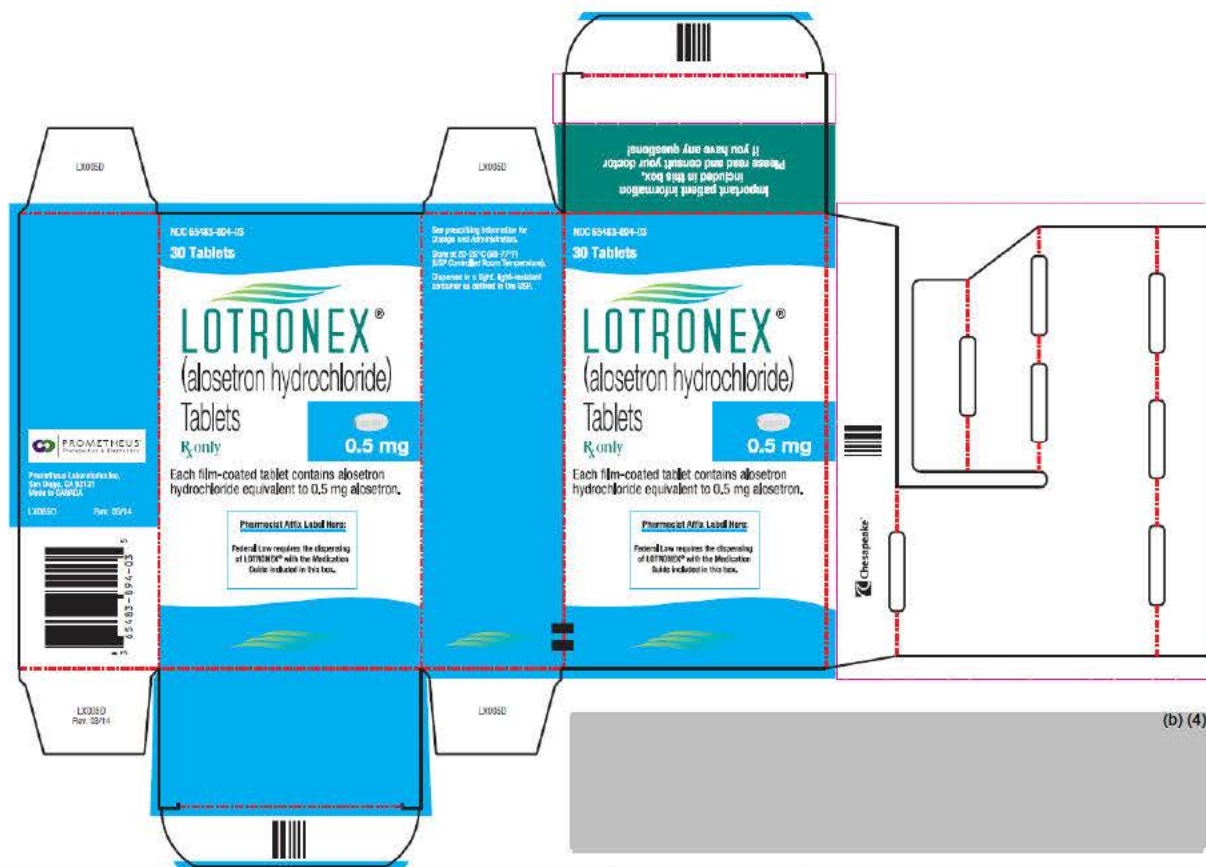
Prometheus Laboratories Inc.
San Diego, CA 92121 Made in Canada
LX004D Rev. 03/14

Exp

Lot

LX004D

7 | Page



3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	04/28/2016	NO	NA	NA
PF	04/28/2016	NO	NA	NA

Reviewer Comments: NA

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 4/28/2016.

Table 3 provides Orange Book patents for the Model Labeling and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
6284770	October 5, 2018	U-405	FOR WOMEN WITH SEVERE DIARRHEA-PREDOMINANT IRRITABLE BOWEL SYNDROME (IBS)	PIV	12/24/2013	None

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

On 11/19/2015 Firm submitted Patent Amendment: Notice of Termination and Dismissal of Patent Litigation to notify the Agency of the termination and dismissal of the patent infringement litigation between Prometheus Laboratories, Inc. ("Prometheus") and Amneal involving Amneal's Abbreviated New Drug Application ("ANDA") # 206647 for Alosetron Hydrochloride Tablets, 0.5 mg and 1mg.

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
NA					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments:

NA

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
Are there changes to the manufacturer/distributor/packer statements? **YES**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)

Previous Labeling Review (Original 12/24/2013)	Currently Proposed Amendment (04/22/2016)	Assessment
(b) (4)	Each tablet also contains the inactive ingredients lactose anhydrous, magnesium stearate, microcrystalline cellulose and pregelatinized starch (maize). The white film coat for the 0.5 mg tablet contains hypromellose, polyethylene glycol, polysorbate 80 and titanium dioxide. The light blue film coat for the 1 mg tablet contains FD&C blue #2, hypromellose, macrogol, polysorbate 80 and titanium dioxide.	No changes to the inactive ingredients. However, to be consistent with the quality submission, Agency requested (b) (4) to be revised to read "polysorbate 80". It is Acceptable.

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products

Previous Labeling Review	Currently Proposed	Assessment
--------------------------	--------------------	------------

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products

(b) (4)	16 HOW SUPPLIED/STORAGE AND HANDLING Alosetron hydrochloride tablets, 0.5 mg (0.562 mg alosetron hydrochloride equivalent to 0.5 mg alosetron), are supplied as white, oval shaped, film-coated tablets debossed with “AN248” on one side and plain on the other side. They are available as follows: Bottles of 30: NDC 65162-248-03 with child-resistant closures. Bottles of 500: NDC 65162-248-50 with child-resistant closures. Alosetron hydrochloride tablets, 1 mg (1.124 mg alosetron hydrochloride equivalent to 1 mg alosetron), are supplied as light blue, oval shaped, film-coated tablets debossed with “AN249” on one side and plain on the other side. They are available as follows: Bottles of 30: NDC 65162-249-03 with child-resistant closures. Bottles of 500: NDC 65162-249-50 with child-resistant closures. Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Protect from light and moisture.	HOW SUPPLIED section reflects Agency requested revision to the established name (to use hydrochloride instead of (b) (4) throughout the labeling). Firm also revised the storage statement to be same as RLD. It is Acceptable.
---------	---	--

Table 7: Manufacturer/Distributor/Packer Statements

Previous Labeling Review	Currently Proposed	Assessment
(b) (4)	Distributed by: Amneal Pharmaceuticals Bridgewater, NJ 08807	Firm provided rational (see ECD Response in Section 2) to revise the MANUFACTURER STATEMENT. Firm revised to their company specific information. It is Acceptable.

5. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments:

NA

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline reviewer(s):

Reviewer Comments:

NA

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item “Final, Draft, or “NA”. If you enter “NA” under the second column, you do NOT need to enter “NA” for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling

	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Final	30s and 500s (0.5 mg and 1 mg)	04/22/2016	Satisfactory
Blister	NA			
Carton	NA			
(Other – specify)	NA			

Table 9: Review Summary of Prescribing Information and Patient Labeling

	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Final	Revised: 04/2016	04/22/2016	Satisfactory
Medication Guide	Final	Rev. 04-2016-00	04/22/2016	Satisfactory
Patient Information	NA			
SPL Data Elements	Submitted	Revised: 4/2016	04/22/2016	Satisfactory



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 04/11/2016 02:10:14 PM

To: alpesh@amneal.com

CC: Juliette.Larmie-Gyamfi@fda.hhs.gov

BCC: scott.dallas@fda.hhs.gov

Subject: EASILY CORRECTABLE DEFICIENCY Original ANDA 206647

ANDA 206647

Dear Alpesh Patel,

Please find attached Easily Correctable Labeling Deficiencies for pending ANDA 206647.

Provide a complete response to these deficiencies by April 25, 2016. We will not process or review a partial response. Facsimile or e-mail responses will not be accepted.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
LABELING
REFERENCE # 7394556

If you do not submit a complete response by April 25, 2016, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence. For more information, please refer to the guidance for industry, ANDA Submissions – Amendments and Easily Correctable Deficiencies Under GDUFA, available on FDA's website.

If you have questions, please contact Juliette Larmie-Gyamfi via email at Juliette.Larmie-Gyamfi@fda.hhs.gov.

Sincerely,

Juliette Larmie-Gyamfi

Labeling Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

EASILY CORRECTABLE DEFICIENCY

ANDA 206647

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855



APPLICANT: Amneal Pharmaceuticals

TEL: [REDACTED]

(b) (6)

ATTN: Alpesh Patel

Email: alpesh@amneal.com

FROM: Juliette Larmie-Gyamfi

Dear Alpesh Patel:

This communication is in reference to your abbreviated new drug application (ANDA) dated December 24, 2013, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Alosetron Hydrochloride Tablets, 0.5 mg (base) and 1 mg (base).

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCIES* identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies within ten (10) U.S. business days.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**EASILY CORRECTABLE DEFICIENCY
LABELING
REFERENCE # 7394556**

If you do not submit a complete response within ten (10) U.S. business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments.

If you are unable to submit a complete response within ten (10) U.S. business days, please contact the Labeling Project Manager immediately so a complete response may be issued if appropriate.

Please submit official archival copies of your response to the ANDA, facsimile or e-mail responses will not be accepted. A partial response to this communication will not be processed as an amendment and will not start a review.

We have completed our review and have the following comments:

LABELING DEFICIENCIES:

1. GENERAL COMMENT

In your quality submission, the drug product manufacturer is listed as Amneal Pharmaceuticals

50 Horseblock Road Brookhaven, NY 11719. (b) (4)

(b) (4)

(b) (4)

2. CONTAINER LABEL [All Strengths/All Sizes]

- a. (b) (4) so it does not compete with the established name and strength. We refer you to Section C (pg. 4) of the Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm349009.pdf>
- b. We note that there is a pictorial representation of the drug product. Ensure image of the tablet represent the actual tablet and reflect the true size, color and imprint. Refer to "[Guidance for Industry, Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors](#)", section III (D) (4) (page 6).
- c. Please add an asterisk (*) after the expression of strength of (b) (4) (PDP) and before the "Each tablet contains..." statement on the side panel. Refer to Naming of Drug Products Containing Salt Drug Substances, Guidance for Industry, sections II (A) and (B) (page 3).

3. PRESCRIBING INFORMATION

- a. Revise your insert labeling to be in accordance with the most recently approved insert labeling for the reference listed drug (RLD), LOTRONEX[®], NDA 021107/S-027 approved 01/07/2016.
- b. HIGHLIGHTS OF PRESCRIBING INFORMATION – To be in accordance with the Guidance for Industry: Labeling for Human Prescription Drug and Biological Products - Implementing the PLR Content and Format Requirements, revise the Limitation statement and Title line to read:

These highlights do not include all the information needed to use ALOSETRON HYDROCHLORIDE TABLETS safely and effectively. See full prescribing information for ALOSETRON HYDROCHLORIDE TABLETS.

**ALOSETRON HYDROCHLORIDE tablets, for oral use
Initial U.S. Approval: 2000**

- c. When referring to the drug product, use "aloseptron hydrochloride tablets" (b) (4) as the established name.
- d. DESCRIPTION section – Revise (b) (4) to read "polysorbate 80" to be consistent with your quality submission and the SPL Data Elements.

4. MEDICATION GUIDE

- a. Revise your Medication Guide to be in accordance with the most recently approved Medication Guide for the reference listed drug (RLD), LOTRONEX®, NDA 021107/S-027 approved 01/07/2016.
- b. Add the phonetic spelling of the established name (or proprietary name if one is proposed) in the Title in accordance with 21 CFR 208.20(b) (1).
- c. Ensure a sufficient number of Medication Guides is available for dispensing and distribution to patients receiving a prescription for your drug product, per 21 CFR 208.24.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

If you have questions regarding these deficiencies or would like acknowledgement of receipt of your amendment upon submission, please contact the Labeling Project Manager, Juliette Larmie-Gyamfi, at Juliette.Larmie-Gyamfi@fda.hhs.gov.

Sincerely yours,

Juliette N.

Larmie-

gyamfi -S

Juliette Larmie-Gyamfi

Labeling Project Manager

Division of Labeling Review

Office of Regulatory Operations

Office of Generic Drugs

Center for Drug Evaluation and Research

Digitally signed by Juliette N
Larmie gyamfi. S
DN: c=US, o=U.S. Government
ou=HHS, ou=FDA, ou=People
092342.19200300.100.1.1=20016
.95466, cn=Juliette N Larmie
gyamfi. S
Date: 2016.04.11 14:08:35 -0400

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	03/30/2016
ANDA Number(s)	206647
Review Number	1
Applicant Name	Amneal Pharmaceuticals
Established Name & Strength(s)	Alosetron Hydrochloride Tablets, 0.5 mg (base) and 1 mg (base)
Proposed Proprietary Name	None
Submission Received Date	12/24/2013
Labeling Reviewer	Dinaxi Jetton
Labeling Team Leader	Ellen Hwang
Review Conclusion ☐ ACCEPTABLE – No Comments ☐ ACCEPTABLE – Include Post Approval Comments ☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant. *Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.	
☐ On Policy Alert List	

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1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on 03/20/2016 based on your submission dated 12/24/2013:

1. GENERAL COMMENT

In your quality submission, the drug product manufacturer is listed as Amneal Pharmaceuticals
50 Horseblock Road Brookhaven, NY 11719. (b) (4)

2. CONTAINER LABEL [All Strengths/All Sizes]

- a. (b) (4) so it does not compete with the established name and strength. We refer you to Section C (pg. 4) of the Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm349009.pdf>
- b. We note that there is a pictorial representation of the drug product. Ensure image of the tablet represent the actual tablet and reflect the true size, color and imprint. Refer to "[Guidance for Industry, Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors](#)", section III (D) (4) (page 6).
- c. Please add an asterisk (*) after the expression of strength of (b) (4) (PDP) and before the "Each tablet contains..." statement on the side panel. Refer to Naming of Drug Products Containing Salt Drug Substances, Guidance for Industry, sections II (A) and (B) (page 3).

3. PRESCRIBING INFORMATION

- a. Revise your insert labeling to be in accordance with the most recently approved insert labeling for the reference listed drug (RLD), LOTRONEX®, NDA 021107/S-027 approved 01/07/2016.
- b. HIGHLIGHTS OF PRESCRIBING INFORMATION – To be in accordance with the Guidance for Industry: Labeling for Human Prescription Drug and Biological Products - Implementing the PLR Content and Format Requirements, revise the Limitation statement and Title line to read:

These highlights do not include all the information needed to use ALOSETRON HYDROCHLORIDE TABLETS safely and effectively. See full prescribing information for ALOSETRON HYDROCHLORIDE TABLETS.

ALOSETRON HYDROCHLORIDE tablets, for oral use
Initial U.S. Approval: 2000

- c. When referring to the drug product, use "alosetron hydrochloride tablets" (b) (4) as the established name.
- d. DESCRIPTION section – Revise (b) (4) to read "polysorbate 80" to be consistent with your quality submission and the SPL Data Elements.

4. MEDICATION GUIDE

- a. Revise your Medication Guide to be in accordance with the most recently approved Medication Guide for the reference listed drug (RLD), LOTRONEX®, NDA 021107/S-027 approved 01/07/2016.

- b. Add the phonetic spelling of the established name (or proprietary name if one is proposed) in the Title in accordance with 21 CFR 208.20(b) (1).
- c. Ensure a sufficient number of Medication Guides is available for dispensing and distribution to patients receiving a prescription for your drug product, per 21 CFR 208.24.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission(s) dated (add date).

1.3 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.

These comments will be addressed post approval (in the first labeling supplement review).

[Click here to enter text.](#)

2. LABELING REVIEW INFORMATION

2.1 REGULATORY INFORMATION

Has the ANDA been accepted for filing? YES (10/02/2014)
Are there any pending issues in <u>DLR's SharePoint Drug Facts</u>? NO If Yes, please explain.
Is the drug product listed in the Policy Alert Tracker on <u>OGD's SharePoint</u>? NO If Yes, please explain.

2.2 MODEL LABELING

2.2.1 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling
(Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA RLD information.)

NDA#/Supplement# (S-000 if original): 021107/S-027

Supplement Approval Date: 01/07/2016

Proprietary Name: LOTRONEX®

Established Name: Alosetron Hydrochloride Tablets

Description of Supplement:

This Prior Approval supplemental new drug application provides for the following labeling changes to be in alignment with the risk evaluation and mitigation strategy (REMS) modification for Lotronex:

1. Package Insert: Box Warning, Dosage and Administration (2.3), Contraindications (4.3), Warnings and Precautions (5.3), Patient Counseling Information (17).
2. Medication Guide

Your approved Medication Guide will no longer be part of the risk evaluation and mitigation strategy (REMS), but is now approved under 21 CFR 208.

For the Record:

- **NDA 021107/S-026 (approved 01/07/2016)**

Re: NDA 21-107; LOTRONEX® (alose tron hydrochloride) Tablets
Prior Approval Supplement-026
Proposed REMS Modification

Dear Dr. Korvick:

Reference is made to the Agency REMS Modification Notification dated 20 May 2015. Reference is also made to the approval of S-025 providing for a REMS revision dated 24 July 2015. Enclosed for your review is the proposed REMS modification.

The present modification of the LOTRONEX REMS is primarily based on FDA's request to modify the approved LOTRONEX REMS, dated 20 May 2015 and the REMS revision Supplement 025 approved on 24 July 2015. To provide a continuum of nomenclature for the Prescribers and Patients, the proposed modified LOTRONEX REMS accounts for a harmonization of nomenclature. Such harmonization includes recently approved terms as LOTRONEX/alose tron hydrochloride, LOTRONEX and its authorized generic.

The most significant departure from the requested changes is the description of the Brand LOTRONEX with the generic leaving out the word 'authorized'. Prometheus has plans to share this program with other generic alose tron hydrochloride manufacturers and would like to employ the most inclusive terminology.

In addition the following minor name changes are proposed with rationale:

- LOTRONEX/alose tron hydrochloride Patient Education Sheet - Since the document will not require the patient or prescriber to fill out any information or collect a signature, rather than identify it as a (b) (4) it will be considered an 'Education Sheet'
- LOTRONEX REMS Program Prescriber Education Slide Deck -The word 'Program' is utilized to encompass all the components of the LOTRONEX REMS Program, therefore this single element is better identified as the Prescriber Education Slide Deck.

- **NDA 021107/S-028 (received 03/18/2016)** is a CMC supplemental application currently "Pending" which provides for alternate sites for the alose tron hydrochloride (b) (4) It does not affect labeling.

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling
(Check the box used as the Model Labeling)

- ☐ **MOST RECENTLY APPROVED ANDA RLD LABELING**
 ANDA#/Supplement# (S-000 if original): Click here to enter text.
 Supplement Approval Date: Click here to enter text.
 Proprietary Name: Click here to enter text.
 Established Name: Click here to enter text.
 Description of Supplement: Click here to enter text.
- ☐ **TEMPLATE (e.g., BPCA, PREA, and Carve-out):** Click here to enter text.
- ☒ **OTHER (Describe):**

There are currently 3 ANDAs in-house that were referenced for consistency:

ANDA 200652 - approved 05/04/2015

ANDA 206113 – currently in “Complete Response” as of 02/24/2016

ANDA 209180 – currently in “Pending” status

2.2.2 MODEL CONTAINER LABELS

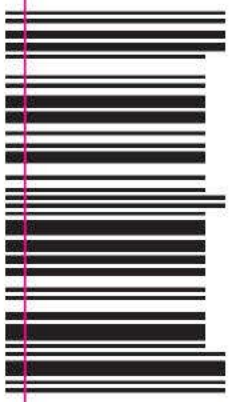
Model container/carton/blister labels (Source: Annual Report – 15, dated 04/08/2015)

Annual Reportable Changes

The following Annual Reportable labeling changes were made during this reporting period:

- “Made in CANADA” was added to the PI, Cartons and bottle labels.
- Storage temperature was updated to follow USP and
- Part numbers/revision dates were updated.





65483-895-03

NDC 65483-895-03

30 Tablets

Federal Law requires the dispensing of LOTRONEX® with the Medication Guide attached.



LOT RONEX®

(alose tron hydrochloride) Tablets



1 mg

Each film-coated tablet contains alose tron hydrochloride equivalent to 1 mg alose tron.

R_x only

See prescribing information for Dosage and Administration.

Store at 20-25°C (68-77°F) (USP Controlled Room Temperature).

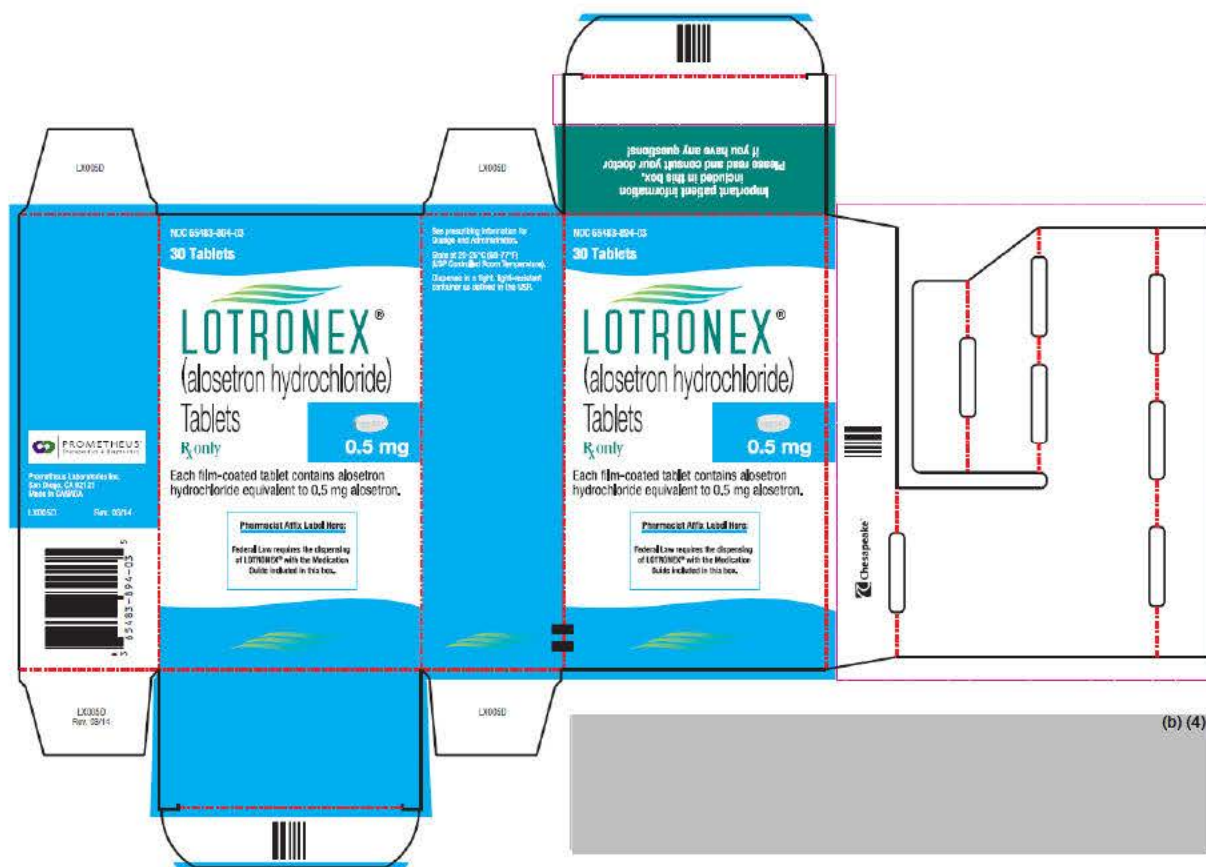
Lot
Exp
LX004D

Dispense in a tight, light-resistant container as defined in the USP.



PROMETHEUS®
Therapeutics & Diagnostics

Prometheus Laboratories Inc.
San Diego, CA 92121 Made in Canada
LX004D Rev. 03/14



(b) (4)



2.3 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	3/30/2016	NO	NA	NA
PF	3/30/2016	NO	NA	NA

2.4 PATENTS AND EXCLUSIVITIES

The [Orange Book](#) was searched on 3/30/2016.

Table 3 provides Orange Book patents for the Model Labeling and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
6284770	October 5, 2018	U-450	FOR WOMEN WITH SEVERE DIARRHEA-PREDOMINANT IRRITABLE BOWEL SYNDROME (IBS)	PIV	12/24/2013	None

On 07/29/2014 Firm submitted Patent Amendment to provide Agency with a copy of the complaint served on Amneal by Prometheus Laboratories, Inc. ("Prometheus"), holder of the Reference Listed Drug, LOTRONEX® (alosetron hydrochloride) Tablets, 0.5 mg and 1 mg (NDA #021107), and owner of U.S. Patent 6,284,770, listed in the Orange Book for LOTRONEX® (alosetron hydrochloride) Tablets, 0.5 mg and 1 mg.

On 11/19/2015 Firm submitted Patent Amendment: Notice of Termination and Dismissal of Patent Litigation to notify the Agency of the termination and dismissal of the patent infringement litigation between Prometheus Laboratories, Inc. ("Prometheus") and Amneal involving Amneal's Abbreviated New Drug Application ("ANDA") # 206647 for Alosetron Hydrochloride Tablets, 0.5 mg and 1mg.

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
NA					

2.5 **MANUFACTURING FACILITY**

Table 5 provides a description of the drug product manufacturing facility.

Table 5: Comparison of Manufacturer/Distributor/Packer Labeling Statements		
Name and Address of Facility ANDA Manufactured (Module 3.2.P.3.1 of Original submission 12/24/2013)	Name and Address on ANDA Container (Original Submission, 12/24/2013)	Name and Address on ANDA Prescribing Information (Package Insert and Medication Guide from Original submission, 12/24/2013)
<u>Drug Product Manufacturing & Packaging site:</u> Amneal Pharmaceuticals 50 Horseblock Road Brookhaven, NY 11719		(b) (4)
(b) (4)		

3. **ASSESSMENT OF ANDA LABELING AND LABELS**

The results for each material reviewed in this section provide the basis for the labeling comments to the applicant.

Is this product Rx or OTC? Please check one.

- ☒ Rx Product (If Rx, skip 3.2 OTC DRUG PRODUCT and go to 3.3 CONTAINER/CLOSURE.)
☐ OTC Product (If OTC, skip 3.1 RX DRUG PRODUCT and go to 3.3 CONTAINER/CLOSURE)

3.1 **RX (PRESCRIPTION) DRUG PRODUCT**

3.1.1 **RX: PRESCRIBING INFORMATION**

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under [21 CFR 314.94\(a\)\(8\)](#)? **NO**

Are the specific requirements for format met under [21 CFR 201.57\(new\)](#) or [201.80\(old\)](#)? **NO**

Is the established name for this ANDA acceptable? **YES**

Does the Model Labeling have combined insert labeling for multiple NDAs or dosage forms? **NO**

Are the required USP recommendations reflected in the labeling? **NA**

Is the applicant's "patent carve out" acceptable? **NA**

Is the applicant's "exclusivity carve out" acceptable? **NA**

Is the Manufacturer statement acceptable? **NO**

Reviewer Comments:

Firm will be asked to make the following revisions:

1. Revise insert labeling to be in accord with the most recently approved labeling of the RLD, LOTRONEX® NDA 021107/S-027 approved 01/07/2016.
2. Revise limitation paragraph and title to be in accord with PLR guidance.
3. When referring to the drug product, use "alose tron hydrochloride tablets" as the established name.

(b) (4)

3.1.1.1 RX: DESCRIPTION

We reviewed the DESCRIPTION section for accuracy (with input from the chemistry review, if appropriate) and acceptability from labeling perspective. We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling.

Table 6: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section

Model Labeling Inactive Ingredients	ANDA Labeling Inactive Ingredients
Each tablet also contains the inactive ingredients lactose (anhydrous), magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The white film coat for the 0.5 mg tablet contains hypromellose, titanium dioxide, and triacetin. The blue film coat for the 1 mg tablet contains hypromellose, titanium dioxide, triacetin, and indigo carmine.	(b) (4)

Reviewer Assessment:

Does the chemistry review follow the [Chemistry/Labeling Memorandum of Understanding](#) (MOU)? **YES, chemistry review complete**

(Note: The MOU became effective on November 1, 2014. MOU does not apply to amendment reviews for ANDAs originally reviewed before November 1, 2014.)

If the chemistry review follows the MOU, labeling reviewer is not responsible for reviewing for accuracy of the DESCRIPTION section for chemical properties, system components of the drug product, etc. Please refer to the MOU, Appendix A, and DESCRIPTION section for delineation of responsibilities. If chemistry review does NOT follow the MOU, labeling reviewer will follow the traditional review approach of reviewing the entire DESCRIPTION section.)

Are the inactive ingredients information consistent with "Components and Composition" information as provided in Module 3.2.P.1? (If Chemistry follows the MOU, refer to the Labeling section of Chemistry review.) **YES**

For products required to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **NA**

Does any inactive ingredient require special warnings, precautions, or labeling statements? **NA**

If the labeling includes a “Does not contain...” statement, is it acceptable/allowed? **NA** Has the statement been verified by chemistry? **NA**

Reviewer Comments:

Firm will be asked to make the following revisions:

1. Revise the IA (b) (4) to read “polysorbate 80” as it is presented in Module 3.2.P.1 (Components and Composition) and SPL and quality submission.

Below is taken from Module 3.2.P.1 of Original submission 12/24/2016:

(b) (4)

(b) (4)

(b) (4)

3.1.1.2 RX: HOW SUPPLIED/STORAGE AND HANDLING

We compared the descriptions of the model product to the ANDA finished product. Product differences, such as scoring configuration and storage conditions, are highlighted in Table 7 and will be referred to the appropriate review discipline for evaluation.

Table 7: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	16 HOW SUPPLIED/STORAGE AND HANDLING LOTRONEX Tablets, 0.5 mg (0.562 mg alosetron HCl equivalent to 0.5 mg alosetron) are white, oval, film-coated tablets debossed with GX EX1 on one face. Bottles of 30 (NDC 65483-894-03) with child-resistant closures. LOTRONEX Tablets, 1 mg (1.124 mg alosetron HCl equivalent to 1 mg alosetron), are blue, oval, film-coated tablets debossed with GX CT1 on one face. Bottles of 30 (NDC 65483-895-03) with child-resistant closures. Store at 20-25°C (68-77°F) (USP Controlled Room Temperature).Protect from light and moisture.
ANDA Labeling	16 HOW SUPPLIED/STORAGE AND HANDLING (b) (4)

Reviewer Assessment:

Does the chemistry review follow the Chemistry/Labeling MOU? YES, chemistry review complete If the chemistry review does NOT follow the MOU, is the description (scoring, color and imprint) of the finished product in the HOW SUPPLIED section consistent with the information in Module 3.2.P.5.1 for Drug Product Specification? YES Does the ANDA require the same color coding as the Model Labeling? NO Is there any difference in scoring configuration between the ANDA and the Model Labeling? NO Are the packaging sizes and configurations acceptable as compared to the Model Labeling? YES If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? NO Is the storage or dispensing statement acceptable as compared to the Model Labeling? YES Is the storage or dispensing statement acceptable as compared to the USP? NA

Reviewer Comments:

(b) (4)
--

Amneal apologizes for the inconvenience caused to the Agency due to this typographical error.

Reviewer's Assessment: *Satisfactory*
It is acceptable.

3.1.2 RX: MEDICATION GUIDE

Is Medication Guide required? **YES**

If YES go to Reviewer Assessment below, if NO go to section 3.1.3.

Reviewer Assessment:

Was Medication Guide submitted? **YES**

Is the Medication Guide same as the model labeling, except for allowable differences? **NO**

Does the Medication Guide meet the requirements of [21 CFR 208.20](#)? **YES**

Has the Applicant committed to provide a sufficient number of medication guides? **NO**

Is the phonetic spelling of the proprietary or established name present? **NO**

Is FDA 1-800-FDA-1088 phone number included? **YES**

Reviewer Comments:

Firm will be asked to make the following revisions:

1. Revise your MG to be in accordance with the most recently approved MG for the reference listed drug (RLD), LOTRONEX®, NDA 021107/S-027 approved 01/07/2016.
2. Add the phonetic spelling of the established name (or proprietary name if one is proposed) in the Title in accordance with 21 CFR 208.20(b)(1).
3. Ensure a sufficient number of Medication Guides is available for dispensing and distribution to patients receiving a prescription for your drug product, per 21 CFR 208.24.

3.1.3 RX: OTHER PATIENT LABELING

Are other patient labeling required? **NO**

If YES go to Reviewer Assessment below, if NO go to section 3.1.4.

Reviewer Assessment:

Was other patient labeling submitted? **CLICK HERE**

Is the patient labeling the same as the model labeling, except for allowable differences? **CLICK HERE**

Reviewer Comments:

3.1.4 RX: CONTAINER LABEL

Was container label (other than Blisters) submitted? **YES**

(For BLISTER labels, go to section 3.1.5.)

We evaluated the container labels for the inclusion of all required statements and safety considerations.

Reviewer Assessment:

Is the established name acceptable? **YES**

Is title case used in expressing the established name? **YES**

Does labeling comply with Tall Man lettering recommendations found on [FDA webpage](#)? **NA**

Is container label too small to contain all required information? **NO** If yes, does the container meet the “too small” exemption found in [21 CFR 201.10\(i\)](#)? **NA**

Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **YES**

Is the following information properly displayed?

Net quantity statement: **YES**

Route(s) of administration (other than oral): **NA**

Warnings (if any) or cautionary statements (if any): **NA**

Medication Guide Pharmacist instructions per [21 CFR 208.24\(d\)](#): **YES**

[Controlled substance symbol](#): **NA**

Usual Dosage statement: **YES**

Product strength equivalency statement: **NO**

NDC: **YES**

Bar code per [21 CFR 201.25\(c\)\(2\)](#): **YES**

Is the Manufacturer/Distributor/Packager statement acceptable? **NO**

For foreign manufacturers, does the labeling have the country of origin? **NA**

Are the required USP recommendations reflected on the label(s)? **NA**

Is the storage or dispensing statement consistent with the How Supplied section of the insert? **YES**

Does any inactive ingredient require special warnings, precautions, or labeling statements? **NA**

Are multiple strengths differentiated by use of different color or other acceptable means? **YES**

Are the labels of related products differentiated to avoid selection errors? **NA**

Does the ANDA require the same color coding as the Model Labeling? **NO**

Are the requirements of [21 CFR 201.15](#) met for all required label statements? **YES**

Are the requirements of [21 CFR 201.100](#) met for all required label statements? **YES**

Reviewer Comments:

The following revisions will be requested:

1. (b) (4)
2. (b) (4)
3. Revise the MG dispensing instructions to be same as RLD – (b) (4)
4. Ensure tablet depiction is actual a picture of an actual tablet and not an image. (b) (4)
5. (b) (4)
6. (b) (4)

3.1.4.1 RX: CONTAINER LABEL FOR PARENTERAL SOLUTIONS

Is container for parenteral solution? **NO**

If YES go to Reviewer Assessment below, if NO go to section 3.1.4.2.

Reviewer Assessment:

Is the product strength expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP, General Chapter <1> Injection? **CLICK HERE**

If volume is less than 1 mL, is strength per fraction of a milliliter the only expression of strength? **CLICK HERE**

Is the quantity or proportion of all inactive ingredients listed on label as required under [21 CFR 201.100\(b\)\(5\)\(iii\)](#)? **CLICK HERE**

Reviewer Comments:

Click here to enter text.

3.1.4.2 RX: CONTAINER LABEL FOR SOLID INJECTABLE

Is container for solid injectable? **NO**

If YES go to Reviewer Assessment below, if NO go to section 3.1.4.3.

Reviewer Assessment:

Is the strength in terms of the total amount of drug per vial? **CLICK HERE**

Are instructions for reconstitution and resultant concentration provided, if space permits? **CLICK HERE**

Is the quantity or proportion of all inactive ingredients listed on label as required under [21 CFR 201.100\(b\)\(5\)\(iii\)](#)? **CLICK HERE**

Reviewer Comments:

Click here to enter text.

3.1.4.3 RX: CONTAINER LABEL FOR PHARMACY BULK PACKAGE

Is container a Pharmacy Bulk Package (parenteral preparations for admixtures)? **NO**

If YES go to Reviewer Assessment below, if NO go to section 3.1.5.

Reviewer Assessment:

Is there a prominent, boxed declaration reading “Pharmacy Bulk Package – Not for Direct Infusion” on the principal display panel following the expression of strength? **CLICK HERE**

Does the container label include graduation marks? **CLICK HERE**

Does label contain the required information on proper aseptic technique including time frame in which the container may be used once it has been entered? **CLICK HERE**

Is the quantity or proportion of all inactive ingredients listed on label as required under [21 CFR 201.100\(b\)\(5\)\(iii\)](#)? **CLICK HERE**

Reviewer Comments:

Click here to enter text.

3.1.5 RX: UNIT DOSE BLISTER LABEL

Is container a Unit Dose Blister Pack? **NO**

If YES go to Reviewer Assessment below, if NO go to section 3.1.6.

Reviewer Assessment:

Does each blister include only one dosage unit (e.g., one tablet, one capsule)? **CLICK HERE**

Do proprietary name, established name, strength, bar code, and manufacturer appear accurately on each blister cell? **CLICK HERE**

Reviewer Comments:

Click here to enter text.

3.1.6 RX: CARTON (OUTER OR SECONDARY PACKAGING) LABELING

Was carton labeling submitted? **NO**

If YES go to Reviewer Assessment below, if NO go to section 3.3.

Reviewer Assessment:

Are the answers to the Container Label questions the same for the Carton Labeling? **CLICK HERE** If no, please explain the differences in the Reviewer Comments section.

If container is too small or otherwise unable to accommodate a label with enough space to include all required information, is all required information present on the carton labeling? **CLICK HERE**

If country of origin is not on Container, does it appear on outer packaging labeling? **CLICK HERE**

Reviewer Comments:

Click here to enter text.

3.2 OTC (OVER THE COUNTER) DRUG PRODUCT

3.2.1 OTC: LABELING THAT INCLUDES DRUGS FACTS INFORMATION

Reviewer Assessment:

Is the patient labeling the same as the model labeling, except for allowable differences? [CLICK HERE](#)

Is Drug Facts Labeling format acceptable per [21 CFR 201.66](#)? [CLICK HERE](#)

Does “Questions?” have a toll-free number no less than 6 pt. font size per [21 CFR 201.66\(c\)\(9\)](#) or “1-800-FDA-1088” per [21 CFR 201.66 \(c\)\(5\)\(vii\)](#)? [CLICK HERE](#)

Did firm submit a Labeling Format Information Table to evaluate the font size? [CLICK HERE](#)

Is the applicant’s “patent carve out” acceptable? [CLICK HERE](#)

Is the applicant’s “exclusivity carve out” acceptable? [CLICK HERE](#)

Is the established name for this ANDA acceptable? [CLICK HERE](#)

Is title case used in expressing the established name? [CLICK HERE](#)

Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? [CLICK HERE](#)

Is the following information properly displayed?

Pharmacological category: [CLICK HERE](#)

Net quantity statement: [CLICK HERE](#)

Route(s) of administration (other than oral): [CLICK HERE](#)

Warnings (if any) or cautionary statements (if any): [CLICK HERE](#)

NDC: [CLICK HERE](#)

Bar code per [21 CFR 201.25\(c\)\(2\)](#): [CLICK HERE](#)

Is the Manufacturer/Distributor/Packager statement acceptable? [CLICK HERE](#)

For foreign manufacturers, does the labeling have the country of origin? [CLICK HERE](#)

Are the required USP recommendations reflected in the labeling? [CLICK HERE](#)

Is the storage statement acceptable? [CLICK HERE](#)

Does any inactive ingredient require special warnings, precautions, or labeling statements? [CLICK HERE](#)

Are multiple strengths differentiated by use of different color or other acceptable means? [CLICK HERE](#)

Are the labels of related products differentiated to avoid selection errors? [CLICK HERE](#)

Reviewer Comments:

[Click here to enter text](#)

3.2.1.1 OTC: INACTIVE INGREDIENTS COMPARISON

We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling.

Table 8: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section

Model Labeling Inactive Ingredients	ANDA Inactive Ingredients
Click here to enter text	Click here to enter text

Reviewer Assessment:

Are the inactive ingredients information consistent with “Components and Composition” information as provided in Module 3.2.P.1? [CLICK HERE](#)

Are the inactive ingredients listed in alphabetical order? [CLICK HERE](#)

For products required/recommended to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? [CLICK HERE](#)

Does any inactive ingredient require special warnings, precautions, or labeling statements? [CLICK HERE](#)

If the labeling includes a “Does not contain...” statement, is it acceptable/allowed? [CLICK HERE](#) Has the statement been verified by chemistry? [CLICK HERE](#)

Reviewer Comments:

[Click here to enter text](#)

3.2.1.2 OTC: HOW SUPPLIED AND STORAGE INFORMATION

We compared the descriptions of the model product to the ANDA finished product. Product differences, such as scoring configuration and storage conditions, are highlighted in Table 9 and will be referred to the appropriate review discipline for evaluation.

Table 9: Comparison of Model Labeling to ANDA finished product	
Model Labeling	Click here to enter text
ANDA (enter source of information of product description on the right hand column; e.g., chemistry Review & date, Module 3.2.P.5.1)	Click here to enter text

Reviewer Assessment:

Is the description ([scoring](#), color and [imprint](#)) of the finished product consistent with the Drug Product Quality submission? **CLICK HERE**

Is there any difference in scoring configuration between the ANDA and the Model Labeling? **CLICK HERE**

Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **CLICK HERE**

If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **CLICK HERE**

Is the storage or dispensing statement acceptable as compared to the Model Labeling? **CLICK HERE**

Reviewer Comments:

[Click here to enter text](#)

3.2.2 OTC: OTHER PATIENT LABELING

Are other patient labeling required? **CLICK HERE**

If YES go to Reviewer Assessment below, if NO go to section 3.3.

Reviewer Assessment:

Was other patient labeling submitted? **CLICK HERE**

Is the patient labeling the same as the model labeling, except for allowable differences? **CLICK HERE**

Reviewer Comments:

[Click here to enter text](#)

3.3 CONTAINER/CLOSURE

We evaluated the container/closure system of this product to determine if special child-resistant packaging is required based on packaging configuration. Additionally, we evaluated other aspects of the container closure that relate to the dosage form, product formulation, and product class. Below is a description of the container/closure for the ANDA product.

Reviewer Assessment:

Describe container closure (e.g., 30s CRC, 100s non-CRC) and cite source of information in **Reviewer Comments** text box.

Does the container require a child-resistant closure (CRC) as described in the [Poison Prevention Act and regulations](#)? **YES**

Are the tamper evident requirements met for [OTC](#) and [Controlled Substances](#)? (If quality review follows the chemistry-labeling MOU, obtain answer from Appendix D of chemistry review; if quality review does not follow the MOU, labeling reviewer is responsible for assessing for tamper evidence.) **NA**

For ophthalmic products:

Does this ophthalmic product cap color match [the American Academy of Ophthalmology \(AAO\) packaging color-coding](#) scheme? **NA**

For parenteral products:

Is there text on the cap/ferrule overseal of this injectable product? **NA**

If YES, does text comply with the recommendations in USP General Chapter <1>? **NA**

What is the cap and ferrule color? **NA**

NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.

Reviewer Comments: [30s and 500s are CRC]

1.4 Packaging Configuration and Sizes for Bottle Packaging
Table 2 Packaging Configuration & Sizes for Alosetron HCl Tablet, 0.5 mg

(b) (4)

Table 3 Packaging Configuration & Sizes for Alosetron HCl Tablet, 1 mg

(b) (4)

3.4 CALCULATIONS FOR CONTENTS IN LABELING

Is calculation of ingredient(s) required? **NO**

If YES, go to Table 10 and Reviewer Assessment below, if NO go to section 3.5.

We verified the calculation on the following content.

Table 10: Ingredients		
Ingredient	Stated Content	Location of the Information
(b) (4)	(b) (4)	CMC Review dated 01/07/2016

(Note: For Rx products, if chemistry review follows the MOU, chemistry reviewer will verify the accuracy of the active and inactive ingredient amount(s) if information is in the DESCRIPTION and HOW SUPPLIED sections for all products, and additionally, DOSAGE AND ADMINISTRATION section for parenteral products. See Chemistry-Labeling MOU, Appendix A, Miscellaneous section for discussion on calculations.)

Reviewer Assessment:

Does the chemistry review follow the Chemistry/Labeling MOU? **CLICK HERE**

Are the stated contents in the table above acceptable? **CLICK HERE**

Aluminum content in small volume parenterals, large volume parenterals, and pharmacy bulk packages, which are used in TPNs, need to be in the labeling per [21 CFR 201.323](#).

Did the chemistry reviewer verify the aluminum content? **CLICK HERE**

Are the labeling requirements met per [21 CFR 201.323](#)? **CLICK HERE**

Reviewer Comments:

NA

3.5 STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS

We evaluated the [SPL data elements](#) to ensure they are consistent with the information submitted in the ANDA.

Table 11: ANDA Tablet/Capsule Size and Imprint

Tablet/Capsule Strength	ANDA Tablet/Capsule Size (mm) and imprint code from SPL	ANDA Tablet/Capsule Size (mm) and imprint code (Regional Information – Module 3.2.R for tablet size and Product Specification - Module 3.2.P.5.1 of Amendment submission received 05/22/2015)
0.5 mg	(b) (4) AN248	Tablet size = (b) (4) Oval shaped White, oval shaped, film coated tablets debossed with “AN248” on one side and plain on the other side.
1 mg	(b) (4) AN249	Tablet size = (b) (4) Oval shaped Light blue, oval shaped, film coated tablets debossed with “AN249” on one side and plain on the other side.

Reviewer Assessment:

For solid oral dosage forms: Do size and imprint code from the SPL data elements match the information provided in the quality submission? **YES**

Are all the other data elements (strength, inactive ingredients, product characteristics, packaging etc.) consistent with the information submitted in the ANDA labeling? **YES**

Reviewer Comments:

All data elements (strength, inactive ingredients, product characteristics, packaging etc.) are consistent with the information submitted in the ANDA labeling.

CMC Review (dated 01/07/2016, page 100) provides **tablet length** and imprint code:

ANDA Strength	Length (mm)	Imprint Code
0.5 mg	(b) (4)	AN248
1 mg	(b) (4)	AN249

4. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments:

NA

5. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other review discipline reviewer(s):

Reviewer Comments:

NA

6. SPECIAL CONSIDERATIONS

NA

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 12 and 13 provide a summary of recommendations for each labeling piece analyzed in this review.

Table 12: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Draft	30s and 500s (0.5 mg and 1 mg)	12/24/2013	Revise
Blister	NA			
Carton	NA			
(Other – specify)	NA			
Table 13 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Draft	Revised: 09/2010	12/24/2013	Revise
Medication Guide	Draft	Rev. 09-2013	12/24/2013	Revise
Patient Information	NA			
SPL Data Elements	Submitted	Revised: 9/2010	12/23/2013	Satisfactory

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 206647

REMS REVIEWS

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

OSE RCM #	2016-2313	
Reviewer Name	Jacqueline Sheppard, Pharm.D. Anahita Tavakoli, M.A.	
Acting Deputy Division Director	Jamie Wilkins Parker, Pharm.D.	
Review Completion Date	November 17, 2016	
Subject	Evaluation of Proposed REMS	
Established Name	Alosetron hydrochloride	
Applicant/Application No.	Amneal Pharmaceuticals Par Pharmaceuticals	ANDA 206647 ANDA 206113
Therapeutic Class	Selective serotonin 5-HT3 antagonist	
Formulation(s)	0.5 mg and 1 mg oral tablets	
Dosing Regimen	One tablet twice a day	
Proposed Indication(s)	Treatment of severe diarrhea-predominant irritable bowel syndrome in women with chronic IBS	

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates the proposed risk evaluation and mitigation strategy (REMS) submitted on September 23, 2016 and amended on November 4, 2016 by Amneal Pharmaceuticals and Roxane Pharmaceuticals. The proposed REMS developed jointly by members of the Alosetron REMS Group (ARG) comprised of Roxane Laboratories, Amneal Pharmaceuticals and Par Pharmaceuticals provides an updated REMS document, REMS supporting document and REMS materials from that of the currently approved waiver-granted REMS for Alosetron. The submission will also constitute a REMS modification for Roxane Laboratories, ANDA 200652.

2 Background

2.1 PRODUCT BACKGROUND

Alosetron is an approved generic of the Reference Listed Drug (RLD) Lotronex (NDA 21107). The Lotronex REMS was approved with elements to assure safe use on September 2, 2010, to address the risk of ischemic colitis and serious complications of constipation. Alosetron was approved on May 4, 2015, with a REMS comparable to the Lotronex REMS, after the Agency granted Roxane a waiver for the requirement to form a single, shared system REMS with Lotronex. (b) (4)

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for the proposed REMS modification relevant to this review:

- 9/23/16: ANDA 206647 received from Amneal. The proposal provides the proposed shared waiver-granted REMS, REMS supporting document and REMS materials in response to the inclusion of the first additional ANDA into the alosetron shared system.
- 9/23/16: ANDA 206113 received from Par. The proposal provides the proposed shared waiver-granted REMS, REMS supporting document and REMS materials in response to the inclusion of the first additional ANDA into the alosetron shared system.
- 10/27/16: Interim comments sent to ARG including edits to REMS document and website (b) (4)
- 11/04/16: ANDA 206647 received from Amneal. The submission updated the REMS document and appended materials based upon interim comments sent on 10/27/16.
- 11/04/16: ANDA 206113 received from Par. The submission updated the REMS document and appended materials based upon interim comments sent on 10/27/16.

3 Proposed REMS Modifications

3.1 REMS DOCUMENT

The ARG incorporated and responded appropriately to all of the Agency's comments and revisions requested in the October 26, 2016 DRISK review regarding the REMS document.

3.2 REMS APPENDED MATERIALS

The ARG incorporated and responded appropriately to all of the Agency's comments and revisions requested in the October 26, 2016 DRISK review regarding the (b) (4) Website, Dear Healthcare Provider Letter and all other appended materials.

3.3 REMS SUPPORTING DOCUMENT AND ASSESSMENT PLAN

The Supporting Document is consistent with REMS and appended REMS materials. The ARG incorporated and responded appropriately to all of the Agency's comments and revisions requested in the October 26, 2016 DRISK review regarding the REMS Supporting Document.

4 Conclusion & Recommendations

DRISK finds the proposed modification for the alosetron shared system REMS, appended materials (attached), and supporting document, as submitted by members of the ARG on November 4, 2016 acceptable. DRISK recommends approval of the REMS appended to this review.

(b) (4)

5 Appendices

REMS Document

REMS Letter to Healthcare Providers

Alosetron REMS Program Prescriber Education Slide Deck

Alosetron REMS Program Safety Information Fact Sheet for Prescribers

Alosetron REMS Program Patient Education Sheet

Prescriber Completion of Alosetron REMS Program Training Form

Alosetron REMS Program website Prescriber Section screenshots

Alosetron REMS Program website Patients Section screenshots

5.1 REFERENCES

Amneal. Proposed REMS for Alosetron, <eCTD Sequence 0012>, dated November 4, 2016.

Par. Proposed REMS for Alosetron, <eCTD Sequence 0011>, dated November 4, 2016.

Amneal. Proposed REMS for Alosetron, <eCTD Sequence 0011>, dated September 23, 2016.

Par. Proposed REMS for Alosetron, <eCTD Sequence 0010>, dated September 23, 2016.

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

/s/

JACQUELINE E SHEPPARD
11/17/2016

JAMIE C WILKINS PARKER
11/18/2016

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

OSE RCM #	2016-2313		
Reviewer Name	Jacqueline Sheppard, Pharm.D. Anahita Tavakoli, M.A.		
DRISK Acting Team Leader	Robert Pratt, Pharm.D.		
Division Director	Cynthia LaCivita, Pharm.D.		
Review Completion Date	October 26, 2016		
Subject	Evaluation of Proposed REMS modification		
Established Name	Alosetron hydrochloride		
Applicant/Application No.	Amneal Pharmaceuticals	ANDA 206647	
	Par Pharmaceuticals	ANDA 206113	
Therapeutic Class	Selective serotonin 5-HT ₃ antagonist		
Formulation(s)	0.5 mg and 1 mg oral tablets		
Dosing Regimen	One tablet twice a day		
Proposed Indication(s)	Treatment of severe diarrhea-predominant irritable bowel syndrome in women with chronic IBS		

*** This document contains proprietary information that cannot be released to the public***

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates the proposed shared waiver-granted REMS, REMS supporting document and REMS materials that were developed jointly by members of the Alosetron REMS Group (ARG) comprised of Roxane Laboratories, Amneal Pharmaceuticals and Par Pharmaceuticals. The submission will also constitute a REMS modification for Roxane Laboratories, ANDA 200652.

The modification was submitted in response to the inclusion of the first additional ANDAs, Amneal and Par (ANDAs 206447 and 206113), into the alosetron shared system. (b) (4)

(b) (4)

(b) (4) Finally, the modification allows for the addition of a CAPTCHA¹ as a new level of security under the Prescriber online Training Form of the alosetron REMS website. The ARG's proposed shared system (SS) REMS consists of elements to assure safe use (ETASU).

2 Background

2.1 PRODUCT BACKGROUND

Alosetron is an approved generic of the Reference Listed Drug (RLD) Lotronex (NDA 21107). The Lotronex REMS was approved with elements to assure safe use on September 2, 2010, to address the risk of ischemic colitis and serious complications of constipation. Alosetron was approved on May 4, 2015, with a REMS comparable to the Lotronex REMS, after the Agency granted Roxane a waiver for the requirement to form a single, shared system REMS with Lotronex (b) (4)

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for the proposed REMS modification relevant to this review:

¹ A CAPTCHA is a type of challenge-response test used in computing to determine whether or not the user is human.

- 5/04/15: ANDA 200652 approved after the requirement for a single, shared system REMS program for alosetron hydrochloride products waived. The new program is named the Alosetron REMS Program.
- 5/11/15: REMS Modification Notification letter issued which stated that the approved REMS for alosetron must be modified to minimize the burden on the healthcare delivery system of complying with the REMS. Roxane was instructed to submit a REMS modification to remove the Medication Guide and safe use conditions (ETASU D) from the REMS, and to change prescriber certification to a prescriber training program not linked to distribution. The correspondence provided the Agency's version of the modified REMS document.
- 7/10/15: ANDA 200652 Suppl-02 received from Roxane. The proposal includes modified REMS goals, removal of the Medication Guide from the REMS elements, and modifications to the ETASU.
- 1/07/16: ANDA 200652 Suppl-02 approved. The supplement provided for modified goals, removal of the Medication Guide, and modifications to the ETASU.
- 2/03/16: ANDA 200652 Suppl-03 received from Roxane. The proposal includes a modification to the Website interface.
- 9/23/16: ANDA 200652 Suppl-04 received from Roxane. The proposal provides the proposed shared waiver-granted REMS, REMS supporting document and REMS materials in response to the inclusion of the first additional ANDA into the alosetron shared system.
- 9/23/16: ANDA 206647 received from Amneal. The proposal provides the proposed shared waiver-granted REMS, REMS supporting document and REMS materials in response to the inclusion of the first additional ANDA into the alosetron shared system.
- 9/23/16: ANDA 206113 received from Par. The proposal provides the proposed shared waiver-granted REMS, REMS supporting document and REMS materials in response to the inclusion of the first additional ANDA into the alosetron shared system.

3 Proposed REMS Modifications

(b) (4)

(b) (4) the name of the stakeholders should be Alosetron Sponsors (b) (4)

(b) (4) This is in line with the Agency's current thinking on the naming of REMS program Sponsors. The sponsor name should be changed throughout all the materials. This will not affect the name of the REMS program (Alosetron REMS Program) but used only when referring to the Sponsors (Alosetron Sponsors).

3.1 REMS DOCUMENT

The Alosetron REMS group modified the REMS document in response to the inclusion of the first additional ANDA into the alosetron shared system.

Goals

There are no proposed changes to the Alosetron goals.

Elements to Assure Safe Use

The following changes to have been proposed to the ETASU of the REMS document:

- The requirement to distribute the REMS training kit (b) (4)

Reviewer Comment: We agree with this proposal. The REMS training kit was distributed by Roxane on March 7, 2016 and the requirements for a mass distribution are now complete. The REMS training kit is still required to be distributed to prescribers who have prescribed alosetron and have not been identified as having completed training. See comments in Section 4.

3.2 REMS APPENDED MATERIALS

REMS Letter to Healthcare Providers

Reviewer Comment: DRISK agrees with this modification. See comments in Section 4.

Reviewer Comment: We agree with this modification. See comments in Section 4.

Alosetron REMS Program Patient Education Sheet

Review Comment: We agree with this modification.

Alosetron REMS Website

Reviewer Comment: We agree with this modification.

- The single sponsor “Prescribing Information and Medication Guide” PDF link (b) (4) new sections were added entitled (b) (4) Prescribing Information and Medication Guide” with PDF links to each sponsors’ alosetron (b) (4) Prescribing Information and Medication Guides.

Reviewer Comment: We agree with this modification, however, the use of the term (b) (4) when describing the Prescribing Information is not necessary. The section should be entitled “Prescribing Information and Medication Guide.”

- A CAPTCHA was added as a new level of security under the Prescriber online Training Form on the alosetron REMS website. This will require users to check a box stating they are not a robot prior to submission.

Reviewer Comment: We agree with this modification.



3.3 REMS SUPPORTING DOCUMENT AND ASSESSMENT PLAN

The REMS Supporting Document was updated to reflect the inclusion of additional ANDAs into the shared system. Additionally, the communication section was updated to reflect the completion of the communication requirements by Roxane, the sole sponsor of the waived Alosetron REMS program at that time. We find these changes acceptable. However, additional changes are required to the supporting document to align with the comments on the REMS Document that are provided with this review.

4 Discussion

The ARG modified the REMS document in response to the inclusion of the first additional ANDAs, Par and Amneal, into the alosetron shared system REMS (b) (4)

(b) (4)

(b) (4)

The name of the stakeholders should be “Alosetron Sponsors (b) (4)”. This is in line with the Agency’s current thinking on the naming of REMS program Sponsors. The sponsor name should be changed throughout all the materials. This will not affect the name of the REMS program (Alosetron REMS Program) but only when referring to the Sponsors (Alosetron Sponsors). For example in the REMS document, the term Alosetron REMS Program was added (b) (4) when referring to the program. This is appropriate usage and we agree with this change.



(b) (4)

(b) (4) However, while the REMS training kit no longer has to be distributed in bulk mailing, the REMS training kit is still required to be distributed to prescribers who have prescribed alosetron and have not been identified as having completed training. (b) (4)

(b) (4)

(b) (4)

(b) (4) The section should be entitled “Prescribing Information and Medication Guide.” Furthermore, we agree with the addition of the added CAPTCHA as a new level of security under the Prescriber online Training Form to require users to check a box stating they are not a robot prior to submission.

Additionally, the communication section of the REMS Supporting Document was updated to reflect the completion of the communication requirements by Roxane, the sole sponsor of the waived Alosetron REMS program at that time. We find these changes acceptable.

Finally, DRISK agrees with all other previously mentioned revisions, additions, and deletions made to the REMS Document, appended materials, and REMS Supporting Document unless otherwise noted above.

5 Conclusion & Recommendations

(b) (4)

Comments for Par and Amneal are provided in Section 6.

6 Comments for the Sponsors

The comment (b) (4) are based on the Agency's review of the proposed REMS for alosetron submitted under ANDAs 206647 and 206113 submitted on September 23, 2016. In order to facilitate further review, we ask that you respond to these comments within 7 business days.

A. General Comments

1. We have provided a revised REMS document for the Alosetron REMS Program. A complete REMS including all appended materials and REMS Supporting Document should be submitted to each application. Submit both in Word documents with tracked changes version and clean Word versions of each document, as well as a pdf version of each previously mentioned document and appended materials. We ask that you respond to these comments and re-submit all documents by November 4, 2016.
2. Revise the name of the stakeholders to Alosetron Sponsors (b) (4)
(b) (4) The sponsor name should be changed throughout all the materials. This is in line with the Agency's current thinking on the naming of REMS program Sponsors. This will not affect the name of the REMS program (Alosetron REMS Program) but should be used only when referring to the Sponsors (Alosetron Sponsors). For example, the "Alosetron Sponsors will ensure training..." and "Alosetron REMS Program Patient Education Sheet" are correct usages.

(b) (4)

C. Website

1. (b) (4) the new sections encompassing PDF links to each sponsors' alosetron Prescribing Information and Medication Guides should be entitled "Prescribing Information and Medication Guide." (b) (4)

7 Appendices

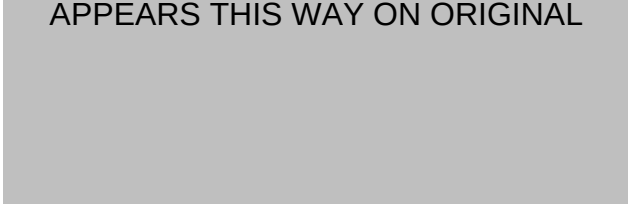
REMS Document

7.1 REFERENCES

Amneal. Proposed REMS for Alosetron, <eCTD Sequence 0011>, dated September 23, 2016.

Par. Proposed REMS for Alosetron, <eCTD Sequence 0010>, dated September 23, 2016.

APPEARS THIS WAY ON ORIGINAL



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

/s/

JACQUELINE E SHEPPARD
10/26/2016

CYNTHIA L LACIVITA
10/26/2016
Concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 206647

CHEMISTRY REVIEWS

CHECKLIST FOR THE CHEMISTRY REVIEW:**ANDA 206647 Alosetron Hydrochloride Tablets, 0.5mg and 1mg**

Function	Performed By (Initial and Date)	Check appropriate box
Is this package for new strength PAS?	RBPM (NT 12/20/2016)	☐ Yes ☒ No
DMF adequate?	RBPM (NT 12/20/2016)	☒ Yes ☐ No *(see comments)
Any outstanding consults?	RBPM (NT 12/20/2016)	☐ Yes *(see comments) ☒ No
Final recommended dissolution method/specification acknowledged by Firm?	LN 12/20/2016	☒ Yes ☐ No ☐ N/A
Are all facility inspections acceptable?	RBPM (NT 12/20/2016)	☒ Yes ☐ No
Is microbiology recommendation adequate for sterile products?	RBPM (NT 11/09/2016)	☐ Yes ☐ No ☒ N/A
Are there comparability protocols provided? If yes, how many?	LN 12/20/2016	☐ Yes How many: _____ ☒ No
If USP monograph exists, do the specifications conform to the current USP?	LN 12/20/2016	☐ Yes ☐ No *(see comments) ☒ N/A
Is the final review uploaded into the current IT platform?	RBPM (NT 12/20/2016)	☒ Yes ☐ No
http://panorama.fda.gov/task/view?ID=5420fal1c000bede14d60918a39761b1a		
No official USP monographs exist for DS or DP.		
Note to RBPM: Please confirm DMF adequate status prior to finalizing the document.		
Division	Signature	Date
DIRP 1/Branch 3	Laxma R Nagavelli, PhD	12/20/2016



Laxma
Nagavelli

Digitally signed by Laxma Nagavelli
Date: 12/20/2016 01:14:07PM
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Nuri
Tawwab

Digitally signed by Nuri Tawwab
Date: 12/20/2016 11:28:22AM
GUID: 555c967c00129c34451d9208238b1dcf

Approvability: –CMC *Approvable*

DMF: (b) (4) is currently Adequate and no new information has been submitted since 5/1/2015. Both DS and DP are not official in USP.

Dissolution: Dissolution method was revised in Amendment dated 9/10/2014 and accepted based on DBE review dated 9/28/2014

ANDA 206647

**Alosetron Hydrochloride Tablets,
0.5 mg and 1 mg**

Amneal Pharmaceuticals

**Solmaz Dehghan, PharmD, PhD
OLDP/DIRP-I**

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III. List of Deficiencies To Be Communicated.....		Error! Bookmark not defined.

- A. Deficiencies.....**Error! Bookmark not defined.**
- B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response: **Error! Bookmark not defined.**

Chemistry Review Data Sheet

1. ANDA #: 206647

2. REVIEW #: 1

3. REVIEW DATE: 2nd IR reviewed on 31-Mar-2016

4. REVIEWER: Solmaz Dehghan, PharmD, PhD

5. PREVIOUS DOCUMENTS:

<u>Previous Document(s)</u>	<u>Document Date</u>
N/A	

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	23-Dec-2013
Patent & Exclusivity/Patent Certification/Information	02-Jul-2014
Patent & Exclusivity/Patent Certification	29-Jul-2014
Bioequivalence/Response to Information Request; Bioequivalence/Dissolution Acknowledgement; Quality/Quality Information	10-Sep-2014
Quality/Controls Information; Quality/Dissolution Data	15-Sep-2014
Quality Response to Information Request	22-May-2015
REMS Correspondence ¹	23-Jul-2015
Patent amendment	19-Nov-2015
Quality/Response to Information Request	25-Feb-2016

1. This submission is not quality related.

7. NAME & ADDRESS OF APPLICANT:

Name:	Amneal Pharmaceuticals
Address:	85 Adams Avenue, Hauppauge, NY 11788, USA
Representative:	Alpesh Patel
Telephone:	(b) (6)
Fax:	631-529-3523

(b) (4)

8. DRUG PRODUCT NAME/CODE/TYPE:

Chemistry Review Data Sheet

Proprietary Name: LOTRONEX[®]

Non-Proprietary Name (USAN): Alosetron Hydrochloride Tablets

9. LEGAL BASIS FOR SUBMISSION:

Reference Listed Drug	LOTRONEX [®]
Dosage Form	IR Tablet
Active Ingredient(s)	Alosetron Hydrochloride
Strengths	0.5 mg and 1 mg
NDA Holder	PROMETEUS LABS
NDA #	N021107

Unexpired Patents and Exclusivities

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021107	001	5360800	Jan 13, 2013	Y	Y	U - 405	
N021107	001	6284770	Oct 5, 2018			U - 405	

10. PHARMACOL. CATEGORY:

Selective serotonin 5-HT₃ antagonist (anti-IBS chronic symptoms)

11. DOSAGE FORM: IR Tablets

12. STRENGTH/POTENCY: 0.5 mg and 1 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ☒ Rx ☐ OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

- ☐ SPOTS product – Form Completed
☒ Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

- ☐ NANO product – Form Completed (See Appendix A.4)
☒ Not a NANO product

15c. PRECEDENT:

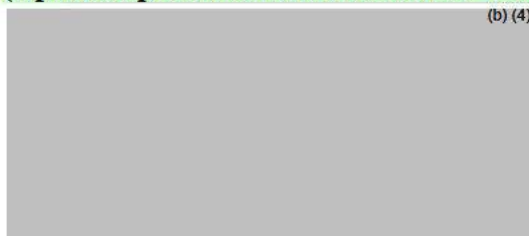
- ☐ The review of this ANDA establishes a precedent – TL concurrence
☒ Not a Precedent

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one, Mono hydrochloride

Structural Formula (Updated per amendment dated 25-Feb-2016):



(b) (4)

Molecular Formula: $C_{17}H_{18}N_4O \cdot HCl$

Molecular Weight: 330.81 g/mol

CAS Number: 122852-69-1

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMF(s):

DMF #	HOLDER	ITEM REFERENCED	STATUS ¹	DATE REVIEW COMPLETED	Reviewer
(b) (4)	(b) (4)	Alosetron Hydrochloride	<i>Adequate</i>	01-May-2015	Bapu Gaddam
		(b) (4)	N/A	N/A	N/A
			N/A	N/A	N/A
			N/A	N/A	N/A
			N/A	N/A	N/A
			N/A	N/A	N/A
			N/A	N/A	N/A
			N/A	N/A	N/A
			N/A	N/A	N/A



CHEMISTRY REVIEW



Chemistry Review Data Sheet

	(b) (4)	N/A	N/A	N/A
		N/A	N/A	N/A

¹ Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
RLD	NDA 021107	0.5 mg and 1 mg Oral Tablets

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A	N/A	N/A
Methods Validation	N/A	N/A	N/A
Labeling	<i>Pending</i>	N/A	N/A
Bioequivalence	Dissolution (<i>Adequate</i>) BE (<i>Adequate</i>)	28-Sep-2014 23-Dec-2014	Kimberly Raines Surendra Shrivastava
Toxicology/Clinical	N/A	N/A	N/A
EA	Categorical Exclusion Claim	02-Apr-2013	N/A
Radiopharmaceutical	N/A	N/A	N/A
Samples Requested	N/A	N/A	N/A

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ☒ Yes ☐ No If no, explain reason(s) below:

20. EES INFORMATION

Drug Substance			
Function	Site Information	FEI/CFN#	Status
API Manufacturer	(b) (4)		Approved (11-Nov-2014)
Drug Product			
Function	Site Information	FEI/CFN#	Status
(b) (4)	@Amneal Pharmaceuticals 50 Horseblock Road Brookhaven, NY 11719	3005263655	Approved (11-Nov-2014)
	(b) (4)		Approved (19-Oct-2015)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

(b) (4)			
	(b) (4)		N/A
			N/A

Provided Information:

(b) (4)

Executive Summary Section

Executive Summary

*I. Recommendations**1. A. Recommendation and Conclusion on Approvability**CMC Approvable**2. B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable*

N/A

*II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)**I Drug Substance*

Currently, there is no USP monograph available for Alosetron Hydrochloride.

Alosetron Hydrochloride is chemically designated as 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one, mono hydrochloride and its empirical formula is $C_{17}H_{18}N_4O \cdot HCl$. Alosetron Hydrochloride is described as a white to (b) (4) which is soluble in water and 0.1 M hydrochloric acid. (b) (4)

II Drug Product

No USP monograph exists for this drug product.

(b) (4)

Executive Summary Section

Dissolution was revised in Amendment dated 9/10/2014 and accepted based on DBE review dated 9/28/2014

USP Apparatus:	II (paddle)
Rotational Speed:	50 rpm (1.0 mg) 75 rpm (0.5 mg)
Temperature:	37 ± 0.5 °C
Media:	Water (deaerated)
Volume:	500 mL
Specifications:	NLT (b) (4) (Q) in 20 minutes

Maximum Daily Dose (MDD): 2 mg

	Identification Threshold (IT)	Qualification Threshold (QT)
Drug Substance	0.10%	0.15%
Drug Product	0.5%	1.0%

B. Description of How the Drug Product is Intended to be Used

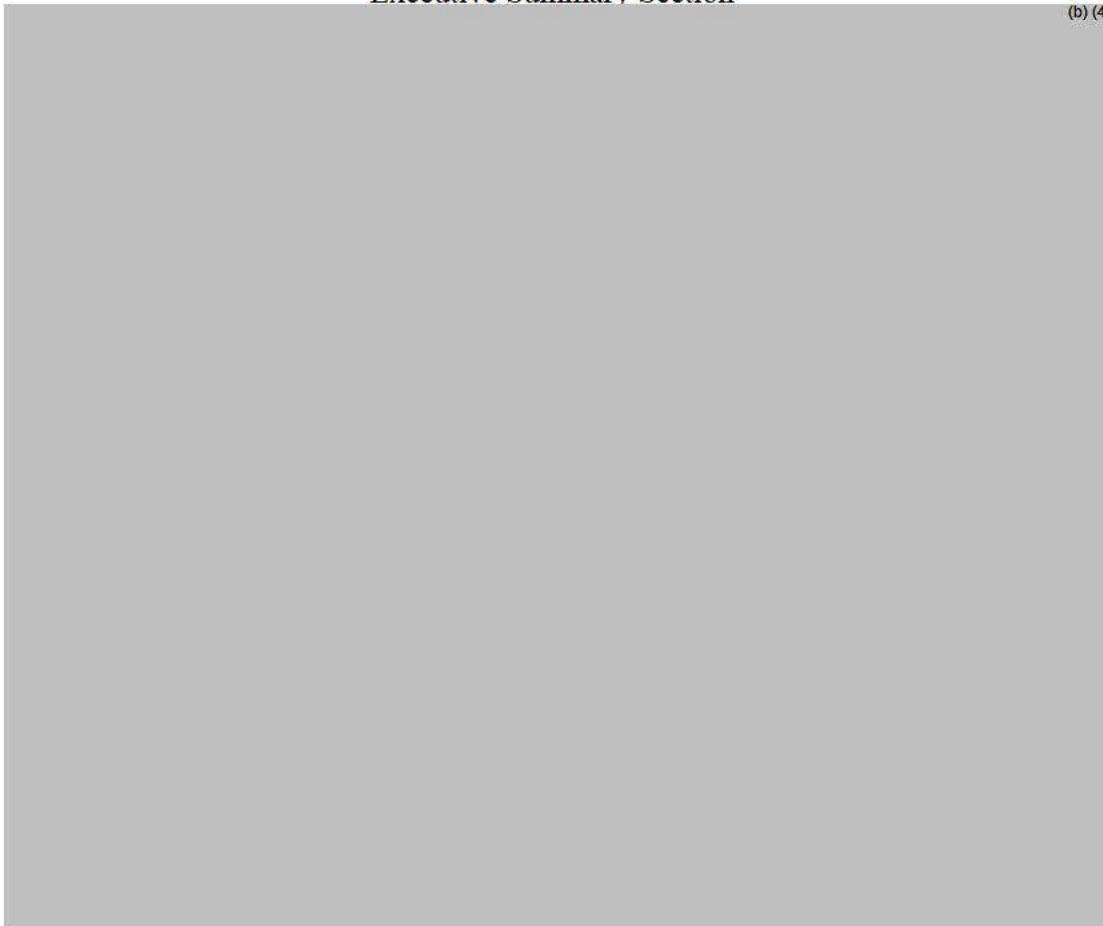
Alosetron Hydrochloride tablets are prescribed only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have chronic IBS symptoms (generally lasting 6 months or longer), anatomic or biochemical abnormalities of the gastrointestinal tract excluded and not responded adequately to conventional therapy. The starting dose is 0.5 mg twice a day and may increase to 1 mg twice a day after 4 weeks if starting dosage is well tolerated but does not adequately control IBS symptoms. The drug should be discontinued in patients who have not had adequate control of IBS symptoms after 4 weeks of treatment with 1 mg twice a day.

C. Initial and Updated Risk Assessment

(b) (4)

Executive Summary Section

(b) (4)

*D. Basis for Approvability or Not-Approval Recommendation*

CMC of this ANDA is *Adequate*. DMF, Dissolution and Bioequivalency are *Adequate* and Labeling is *pending*.

Executive Summary Section

Chemistry Assessment

I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2

3. 2.3 Introduction to the Quality Overall Summary

<i>Proprietary Name of Drug Product</i>	LOTIRONEX [®]
<i>Non-Proprietary Name of Drug Product</i>	Alosetron Tablets
<i>Non-Proprietary Name of Drug Substance</i>	Alosetron Hydrochloride
<i>Company Name</i>	Amneal Pharmaceuticals
<i>Dosage Form</i>	IR Tablets
<i>Strength(s)</i>	0.5 mg and 1 mg
<i>Route of Administration</i>	Oral
<i>Proposed Indication(s)</i>	Quick relief of severe diarrhea-predominant irritable bowel syndrome (IBS) in women

4. 2.3.S DRUG SUBSTANCE [Alosetron Hydrochloride, Amneal]

2.3.S.1 General Information

(b) (4)

ADMINISTRATIVE**A. Reviewer's Signature****B. Endorsement Block**

Chemist Name/Date: S. Dehghan/2nd IR reviewed on 31-Mar-2016

Chemistry Team Leader Name/Date: Ping Jin/4/6/2016

Project Manager Name/Date: Nuri Tawwab

TYPE OF LETTER: Approvable



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 02/09/2016 05:10:36 PM

To: alpesh@amneal.com

CC: nuri.tawwab@fda.hhs.gov

BCC:

Subject: INFORMATION REQUEST for ANDA 206647

Greetings,

Attached is the information request for ANDA 206647. Please acknowledge upon receipt.

Thanks,



CHEMISTRY REVIEW



ANDA 206647

INFORMATION REQUEST

Amneal Pharmaceuticals
Attention: Alpesh Patel
Vice President, Global Regulatory Affairs
85 Adams Avenue
Hauppauge, NY 11788

Dear Alpesh Patel:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 23, 2013, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Alosetron Hydrochloride Tablets, 0.5 mg and 1 mg.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than **February 26, 2016** in order to continue our evaluation of your ANDA.

Please note, submitting unsolicited information in your response to this Information Request may have an impact on your Target Action Date.

List of the deficiencies:

Chemistry deficiencies:

The following deficiencies represent **Minor (IR)** deficiencies:

1. Please update general information of Alosetron Hydrochloride to reflect the correct information on structure formula and specific optical rotation and be in line with (b) (4)

- 2.



3.

(b) (4)



B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide all the available CRT stability data for your drug product using updated stability specification.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

If you do not submit a complete response by **February 26, 2016**, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence.

Send your submission through the Electronic Submission Gateway
<http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm>. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST

Chemistry

REFERENCE # 208074

If you have any questions, please contact Nuri Tawwab, Regulatory Business Project Manager, at (240) 402-2766.

Sincerely,

Nuri A.
Tawwab -S

Digitally signed by Nuri A. Tawwab -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=IHS, ou=People,
cn=Nuri A. Tawwab -S,
0.9.2342.19200300.100.1.1=2001169
369
Date: 2016.02.09 17:03:11 -05'00'

Nuri Tawwab, RBPM
Regulatory Business Process Manager
Office of Program and Regulatory Operations Office
of Pharmaceutical Quality
Center for Drug Evaluation and Research



CHEMISTRY REVIEW



A. Check List (once you check a "Yes" from top down, skip the rest afterward):

- | | | |
|---|-------------------------------|---|
| ☐ First Generic? | Yes: ☐ | No: ☒ |
| ☐ MR Product? | Yes: ☐ | No: ☒ |
| ☐ Solid IR/Oral Sol. RPN > 60 or Inj. Q1/Q2 ≠ RLD? | Yes: ☐ | No: ☒ |
| ☐ Major Formulation/ Mfg. Process Change? | Yes: ☐ | No: ☒ |

B. Review Tier (3 Tier if a "Yes" and 2 Tier if all "No" are checked in A): **3 Tier:** ☐ **2 Tier:** ☒

C. Approvability: – *Not Approvable, IR -30*

ANDA 206647

**Alosetron Hydrochloride Tablets,
0.5 mg and 1 mg**

Amneal Pharmaceuticals

**Solmaz Dehghan, PharmD, PhD
OLDP/DIRP-I**

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5.	PREVIOUS DOCUMENTS:	1
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	Selective serotonin 5-HT ₃ antagonist (anti-IBS chronic symptoms)	2
11.	DOSAGE FORM:	2
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12.	STRENGTH/POTENCY:	2
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	Oral	2
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II. Review of Common Technical Document-Quality (Ctd-Q) Module 1.....	99
III. List of Deficiencies To Be Communicated.....	101
A. Deficiencies.....	101
B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response: N/A	101

Chemistry Review Data Sheet

1. ANDA #: 206647
2. REVIEW #: 1
3. REVIEW DATE: 1st IR reviewed on 2-Nov-2015
4. REVIEWER: Solmaz Dehghan, PharmD, PhD
5. PREVIOUS DOCUMENTS:

<u>Previous Document(s)</u>	<u>Document Date</u>
N/A	

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	23-Dec-2013
Patent & Exclusivity/Patent Certification/Information	02-Jul-2014
Patent & Exclusivity/Patent Certification	29-Jul-2014
Bioequivalence/Response to Information Request; Bioequivalence/Dissolution Acknowledgement; Quality/Quality Information	10-Sep-2014
Quality/Controls Information; Quality/Dissolution Data	15-Sep-2014
Quality Response to Information Request	22-May-2015
REMS Correspondence ¹	23-Jul-2015
Patent amendment	19-Nov-2015

1. This submission is not quality related.

7. NAME & ADDRESS OF APPLICANT:

Name:	Amneal Pharmaceuticals
Address:	85 Adams Avenue, Hauppauge, NY 11788, USA
Representative:	Alpesh Patel
Telephone:	(b) (6)
Fax:	631-529-3523

8. DRUG PRODUCT NAME/CODE/TYPE:

Chemistry Review Data Sheet

Proprietary Name: LOTRONEX[®]

Non-Proprietary Name (USAN): Alosetron Hydrochloride Tablets

9. LEGAL BASIS FOR SUBMISSION:

Reference Listed Drug	LOTRONEX [®]
Dosage Form	IR Tablet
Active Ingredient(s)	Alosetron Hydrochloride
Strengths	0.5 mg and 1 mg
NDA Holder	PROMETEUS LABS
NDA #	N021107

Unexpired Patents and Exclusivities

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021107	001	5360800	Jan 13, 2013	Y	Y	U - 405	
N021107	001	6284770	Oct 5, 2018			U - 405	

10. PHARMACOL. CATEGORY:Selective serotonin 5-HT₃ antagonist (anti-IBS chronic symptoms)**11. DOSAGE FORM:**

IR Tablets

12. STRENGTH/POTENCY:

0.5 mg and 1 mg

13. ROUTE OF ADMINISTRATION:

Oral

14. Rx/OTC DISPENSED: ☒ Rx ☐ OTC**15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

- ☐ SPOTS product – Form Completed
☒ Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

Chemistry Review Data Sheet

- ☐ NANO product – Form Completed (See Appendix A.4)
☒ Not a NANO product

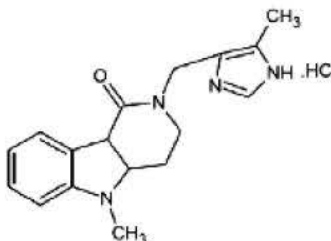
15c. PRECEDENT:

- ☐ The review of this ANDA establishes a precedent – TL concurrence
☒ Not a Precedent

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one, Mono hydrochloride

Structural Formula:



Molecular Formula: C₁₇H₁₈N₄O.HCl

Molecular Weight: 330.81 g/mol

CAS Number: 122852-69-1

17. RELATED/SUPPORTING DOCUMENTS:

A. DMF(s):

DMF #	HOLDER	ITEM REFERENCED	STATUS ¹	DATE REVIEW COMPLETED	Reviewer
	(b) (4)	Alosetron Hydrochloride	<i>Adequate</i>	01-May-2015	Bapu Gaddam
		(b) (4)	N/A	N/A	N/A
			N/A	N/A	N/A
			N/A	N/A	N/A
			N/A	N/A	N/A

Chemistry Review Data Sheet

(b) (4)	N/A	N/A	N/A
	N/A	N/A	N/A
	N/A	N/A	N/A
	N/A	N/A	N/A
	N/A	N/A	N/A
	N/A	N/A	N/A

¹ Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
RLD	NDA 021107	0.5 mg and 1 mg Oral Tablets

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A	N/A	N/A
Methods Validation	N/A	N/A	N/A
Labeling	Pending	N/A	N/A
Bioequivalence	Dissolution (Adequate) BE (Adequate)	28-Sep-2014 23-Dec-2014	Kimberly Raines Surendra Shrivastava
Toxicology/Clinical	N/A	N/A	N/A
EA	Categorical Exclusion Claim	02-Apr-2013	N/A
Radiopharmaceutical	N/A	N/A	N/A
Samples Requested	N/A	N/A	N/A

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ☒ Yes ☐ No If no, explain reason(s) below:

20. EES INFORMATION

Drug Substance			
Function	Site Information	FEI/CFN#	Status
API Manufacturer	(b) (4)	(b) (4)	Approved (11-Nov-2014)
Drug Product			
Function	Site Information	FEI/CFN#	Status
(b) (4)	@Amneal Pharmaceuticals 50 Horseblock Road Brookhaven, NY 11719	3005263655	Approved (11-Nov-2014)
(b) (4)			Pending

Chemistry Review Data Sheet

(b) (4)			
	(b) (4)		N/A
			N/A

Provided Information:

(b) (4)			
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Executive Summary Section

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable. IR-30 is recommended.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

I Drug Substance

Currently, there is no USP monograph available for Alosetron Hydrochloride.

Alosetron Hydrochloride is chemically designated as 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one, mono hydrochloride and its empirical formula is $C_{17}H_{18}N_4O \cdot HCl$. Alosetron Hydrochloride is described as a white to (b) (4) which is soluble in water and 0.1 M hydrochloric acid.

(b) (4)

II Drug Product

No USP monograph exists for this drug product.

(b) (4)

Executive Summary Section

Maximum Daily Dose (MDD): 2 mg

	Identification Threshold (IT)	Qualification Threshold (QT)
Drug Substance	0.10%	0.15%
Drug Product	0.5%	1.0%

B. Description of How the Drug Product is Intended to be Used

Alosetron Hydrochloride tablets are prescribed only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have chronic IBS symptoms (generally lasting 6 months or longer), anatomic or biochemical abnormalities of the gastrointestinal tract excluded and not responded adequately to conventional therapy. The starting dose is 0.5 mg twice a day and may increase to 1 mg twice a day after 4 weeks if starting dosage is well tolerated but does not adequately control IBS symptoms. The drug should be discontinued in patients who have not had adequate control of IBS symptoms after 4 weeks of treatment with 1 mg twice a day.

C. Initial and Updated Risk Assessment

(b) (4)

Executive Summary Section

(b) (4)

**D. Basis for Approvability or Not-Approval Recommendation**

CMC of this ANDA is not approvable, IR-30 will be sent. DMF, Dissolution and Bioequivalency are *Adequate* and Labeling is *pending*.

Executive Summary Section

Chemistry Assessment

I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2

2.3 Introduction to the Quality Overall Summary

<i>Proprietary Name of Drug Product</i>	LOTIRONEX [®]
<i>Non-Proprietary Name of Drug Product</i>	Alosetron Tablets
<i>Non-Proprietary Name of Drug Substance</i>	Alosetron Hydrochloride
<i>Company Name</i>	Amneal Pharmaceuticals
<i>Dosage Form</i>	IR Tablets
<i>Strength(s)</i>	0.5 mg and 1 mg
<i>Route of Administration</i>	Oral
<i>Proposed Indication(s)</i>	Quick relief of severe diarrhea-predominant irritable bowel syndrome (IBS) in women

2.3.S DRUG SUBSTANCE [Alosetron Hydrochloride, Amneal]

2.3.S.1 General Information

(b) (4)

A. Check List

Solid IR/Oral Sol. RPN < 60 or Injection/Ophthalmic Q1/Q2 = RLD – 2 Tier

☐ First Generic – 3 Tier☐

Other Criteria under “Exceptions List” for Table 1 of SOP – 3 Tier

☐**B. Approvability: –No, *Minor Deficiency or IR*****ANDA 206647****Alosetron Hydrochloride Tablets,
0.5 mg and 1 mg****Amneal Pharmaceuticals****Solmaz Dehghan, PharmD, PhD
OGD/DCII**

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6. SUBMISSION(S) BEING REVIEWED:	1
7. NAME & ADDRESS OF APPLICANT:	1
8. DRUG PRODUCT NAME/CODE/TYPE:	2
9. LEGAL BASIS FOR SUBMISSION:	2
10. PHARMACOL. CATEGORY:	2
Selective serotonin 5-HT ₃ antagonist (anti-IBS chronic symptoms)	2
11. DOSAGE FORM:	2
IR Tablets	2
12. STRENGTH/POTENCY:	2
0.5 mg and 1 mg	2
13. ROUTE OF ADMINISTRATION:	2
Oral	2
15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):	3
15b. NANOTECHNOLOGY PRODUCT TRACKING:	3
15c. PRECEDENT:	3
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:	3
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A.3 Novel Excipients: N/A.....	148
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B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response: N/A	153

Chemistry Review Data Sheet

1. ANDA #: 206647

2. REVIEW #: 1

3. REVIEW DATE: 05-Dec-2014

4. REVIEWER: Solmaz Dehghan, PharmD, PhD

5. PREVIOUS DOCUMENTS:

<u>Previous Document(s)</u>	<u>Document Date</u>
N/A	

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	23-Dec-2013
Patent & Exclusivity/Patent Certification/Information	02-Jul-2014
Patent & Exclusivity/Patent Certification	29-Jul-2014
Bioequivalence/Response to Information Request; Bioequivalence/Dissolution Acknowledgement; Quality/Quality Information	10-Sep-2014
Quality/Controls Information; Quality/Dissolution Data	15-Sep-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Amneal Pharmaceuticals
Address:	85 Adams Avenue, Hauppauge, NY 11788, USA
Representative:	Alpesh Patel

Chemistry Review Data Sheet

Telephone:		(b) (6)
Fax:	631-529-3523	

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: LOTRONEX[®]

Non-Proprietary Name (USAN): Alosetron Hydrochloride Tablets

9. LEGAL BASIS FOR SUBMISSION:

Reference Listed Drug	LOTRONEX [®]
Dosage Form	IR Tablet
Active Ingredient(s)	Alosetron Hydrochloride
Strengths	0.5 mg and 1 mg
NDA Holder	PROMETEUS LABS
NDA #	N021107

Unexpired Patents and Exclusivities

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021107	001	5360800	Jan 13, 2013	Y	Y	U - 405	
N021107	001	6284770	Oct 5, 2018			U - 405	

10. PHARMACOL. CATEGORY:

Selective serotonin 5-HT₃ antagonist (anti-IBS chronic symptoms)

11. DOSAGE FORM:

IR Tablets

12. STRENGTH/POTENCY:

0.5 mg and 1 mg

13. ROUTE OF ADMINISTRATION:

Oral

Chemistry Review Data Sheet

14. Rx/OTC DISPENSED: ☒ Rx ☐ OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

☐ SPOTS product – Form Completed

☒ Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

☐ NANO product – Form Completed (See Appendix A.4)

☒ Not a NANO product

15c. PRECEDENT:

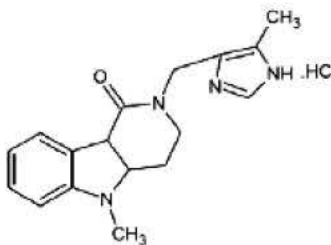
☐ The review of this ANDA establishes a precedent – TL concurrence

☒ Not a Precedent

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one, Mono hydrochloride

Structural Formula:



Molecular Formula: C₁₇H₁₈N₄O.HCl

Molecular Weight: 330.81 g/mol

CAS Number: 122852-69-1

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMF(s):

DMF #	HOLDER	ITEM REFERENCED	STATUS ¹	DATE REVIEW COMPLETED	Reviewer
	(b) (4)	Alosetron Hydrochloride	Inadequate	10-Feb-2015	Bapu Gaddam
		(b) (4)	N/A	N/A	N/A
			N/A	N/A	N/A
			N/A	N/A	N/A
			N/A	N/A	N/A

Chemistry Review Data Sheet

(b) (4)	N/A	N/A	N/A
	N/A	N/A	N/A
	N/A	N/A	N/A
	N/A	N/A	N/A
	N/A	N/A	N/A
	N/A	N/A	N/A

¹ Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
RLD	NDA 021107	0.5 mg and 1 mg Oral Tablets

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A	N/A	N/A
Methods Validation	Reviewed/Deficiencies	05-Dec-2014	Solmaz Dehghan
Labeling	Pending	N/A	Has not been conducted
Bioequivalence	Dissolution (Adequate) BE (Adequate)	28-Sep-2014 23-Dec-2014	Kimberly Raines Surendra Shrivastava
Toxicology/Clinical	N/A	N/A	N/A
EA	Categorical Exclusion Claim	02-Apr-2013	N/A
Radiopharmaceutical	N/A	N/A	N/A
Samples Requested	N/A	N/A	N/A

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ☒ Yes ☐ No If no, explain reason(s) below:

20. EES INFORMATION

Drug Substance			
Function	Site Information	FEI/CFN#	Status
API Manufacturer	(b) (4)		Approved (11-Nov-2014)
Drug Product			
Function	Site Information	FEI/CFN#	Status
(b) (4)	@Amneal Pharmaceuticals 50 Horseblock Road Brookhaven, NY 11719	3005263655	Approved (11-Nov-2014)

Chemistry Review Data Sheet

(b) (4)			
(b) (4)			(b) (4)
(b) (4)			Pending
(b) (4)	(b) (4)	N/A	
(b) (4)			(b) (4)
(b) (4)			N/A

Provided Information:

(b) (4)

Executive Summary Section

Chemistry Review for ANDA 206647

Executive Summary

I. Recommendations**A. Recommendation and Conclusion on Approvability**

Not approvable. Minor deficiency letter or IR is recommended.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)*****I Drug Substance***

Currently, there is no USP monograph available for Alosetron Hydrochloride.

Alosetron Hydrochloride is chemically designated as 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one, mono hydrochloride and its empirical formula is $C_{17}H_{18}N_4O \cdot HCl$. Alosetron Hydrochloride is described as a white to ^{(b) (4)} which is soluble in water and 0.1 M hydrochloric acid. ^{(b) (4)}

II Drug Product

No USP monograph exists for this drug product.

^{(b) (4)}

Executive Summary Section

Maximum Daily Dose (MDD): 2 mg

	Identification Threshold (IT)	Qualification Threshold (QT)
Drug Substance	0.10%	0.15%
Drug Product	0.5%	1.0%

B. Description of How the Drug Product is Intended to be Used

Alosetron Hydrochloride tablets are prescribed only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have chronic IBS symptoms (generally lasting 6 months or longer), anatomic or biochemical abnormalities of the gastrointestinal tract excluded and not responded adequately to conventional therapy. The starting dose is 0.5 mg twice a day and may increase to 1 mg twice a day after 4 weeks if starting dosage is well tolerated but does not adequately control IBS symptoms. The drug should be discontinued in patients who have not had adequate control of IBS symptoms after 4 weeks of treatment with 1 mg twice a day.

C. Initial and Updated Risk Assessment

(b) (4)

Executive Summary Section

(b) (4)

**D. Basis for Approvability or Not-Approval Recommendation**

The ANDA is inadequate. The referred DMF is reviewed and found inadequate (15-Jan-2015). The firm has mitigate (b) (4)

(b) (4)

A minor deficiency letter is recommended.

Chemistry Assessment Section

4. Chemistry Assessment

I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2

2.3 Introduction to the Quality Overall Summary

<i>Proprietary Name of Drug Product</i>	LOTRONEX [®]
<i>Non-Proprietary Name of Drug Product</i>	Alosetron Tablets
<i>Non-Proprietary Name of Drug Substance</i>	Alosetron Hydrochloride
<i>Company Name</i>	Amneal Pharmaceuticals
<i>Dosage Form</i>	IR Tablets
<i>Strength(s)</i>	0.5 mg and 1 mg
<i>Route of Administration</i>	Oral
<i>Proposed Indication(s)</i>	Quick relief of severe diarrhea-predominant irritable bowel syndrome (IBS) in women

2.3.S DRUG SUBSTANCE [Alosetron Hydrochloride, Amneal]

2.3.S.1 General Information

What are the nomenclature, molecular structure, molecular formula, and molecular weight? -Same as Item 16 above-

ADMINISTRATIVE**A. Reviewer's Signature****B. Endorsement Block**

Chemist Name/Date: S. Dehghan/05-Dec-2014

Chemistry Team Leader Name/Date: D. Roselle/18-DEC-2014

Project Manager Name/Date:

TYPE OF LETTER: Minor or IR



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 04/23/2015 04:54:31 PM

To: alpesh@amneal.com

CC:

BCC: savan.khanna@fda.hhs.gov

Subject: INFORMATION REQUEST Original ANDA 206647

Please see attached Information Request



ANDA 206647

INFORMATION REQUEST

Amneal Pharmaceuticals
Attention: Alpesh Patel
85 Adams Avenue
Hauppauge, N Y 11788
United States

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 23, 2013, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Alosetron Hydrochloride Tablets.

We are reviewing the Chemistry section of your submission and have the following comments and information requests. We request a prompt written response, no later than May 23, 2015 in order to continue our evaluation of your ANDA.

Deficiencies:

1.

2.

3.

4.

5.

(b) (4)

23.

24.

25.

26.

27.

28.

29.

30.

(b) (4)

Send your submission through the Electronic Submission Gateway
<http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm>. Prominently
identify the submission with the following wording in bold capital letters at the top of the first
page of the submission:

INFORMATION REQUEST
CHEMISTRY
REFERENCE # 104309

Please note, if information or data submitted exceeds the data requested in the IR this may result
in conversion to a Tier 2 Unsolicited Amendment (i.e., an amendment with information not
requested by FDA). If the submitted data is determined to be a tier 2 unsolicited amendment,
this may affect the goal date.

If you have any questions, please contact Savan Khanna, Product Quality Regulatory Project
Manager, at 240-402-8673.

Sincerely,

Savan N.
Khanna -S

Digitally signed by Savan N Khanna S
DN: c US o U.S. Government ou HHS
ou FDA ou People
o 92343 15000000 10011 2001350383
cn Savan N Khanna S
Date: 2015.04.23 16:52:54 -04:00

Savan Khanna
Quality Regulatory Project Manager
Office of Pharmaceutical Science
Center for Drug Evaluation and Research



CHEMISTRY REVIEW



On DMF Hold pending first DMF review.

A. Check List

Solid IR/Oral Sol. RPN < 60 or Injection/Ophthalmic Q1/Q2 = RLD – 2 Tier



First Generic – 3 Tier



Other Criteria under “Exceptions List” for Table 1 of SOP – 3 Tier



B. Approvability: –No, *Minor Deficiency*

ANDA 206647

**Alosetron Hydrochloride Tablets,
0.5 mg and 1 mg**

Amneal Pharmaceuticals

**Solmaz Dehghan, PharmD, PhD
OGD/DCII**



CHEMISTRY REVIEW



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7. NAME & ADDRESS OF APPLICANT:	1
8. DRUG PRODUCT NAME/CODE/TYPE:	2
9. LEGAL BASIS FOR SUBMISSION:	2
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Selective serotonin 5-HT ₃ antagonist (anti-IBS chronic symptoms)	2
11. DOSAGE FORM:	2
IR Tablets	2
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CHEMISTRY REVIEW



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CHEMISTRY REVIEW



Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. ANDA #: 206647

2. REVIEW #: 1

3. REVIEW DATE: 05-Dec-2014

4. REVIEWER: Solmaz Dehghan, PharmD, PhD

5. PREVIOUS DOCUMENTS:

<u>Previous Document(s)</u>	<u>Document Date</u>
N/A	

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	12/24/2013
Quality Response	9/10/2014
Quality Response	9/15/2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Amneal Pharmaceuticals
Address:	85 Adams Avenue, Hauppauge, NY 11788, USA
Representative:	Alpesh Patel
Telephone:	(b) (6)
Fax:	631-529-3523



CHEMISTRY REVIEW



Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: LOTRONEX[®]

Non-Proprietary Name (USAN): Alosetron Hydrochloride Tablets

9. LEGAL BASIS FOR SUBMISSION:

Reference Listed Drug	LOTRONEX [®]
Dosage Form	IR Tablet
Active Ingredient(s)	Alosetron Hydrochloride
Strengths	0.5 mg and 1 mg
NDA Holder	PROMETEUS LABS
NDA #	N021107

Unexpired Patents and Exclusivities

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021107	001	5360800	Jan 13, 2013	Y	Y	U - 405	
N021107	001	6284770	Oct 5, 2018			U - 405	

10. PHARMACOL. CATEGORY:

Selective serotonin 5-HT₃ antagonist (anti-IBS chronic symptoms)

11. DOSAGE FORM:

IR Tablets

12. STRENGTH/POTENCY:

0.5 mg and 1 mg

13. ROUTE OF ADMINISTRATION:

Oral

14. Rx/OTC DISPENSED: ☒ Rx ☐ OTC



CHEMISTRY REVIEW



Chemistry Review Data Sheet

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

☐ SPOTS product – Form Completed

☒ Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

☐ NANO product – Form Completed (See Appendix A.4)

☒ Not a NANO product

15c. PRECEDENT:

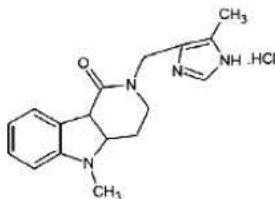
☐ The review of this ANDA establishes a precedent – TL concurrence

☒ Not a Precedent

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one, Mono hydrochloride

Structural Formula:



Molecular Formula: $C_{17}H_{18}N_4O \cdot HCl$

Molecular Weight: 330.81 g/mol

CAS Number: 122852-69-1



CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMF(s):

DMF #	HOLDER	ITEM REFERENCED	STATUS ¹	DATE REVIEW COMPLETED	Reviewer
(b) (4)	(b) (4)	Alosetron Hydrochloride	Pending	N/A	Original DMF is currently assigned to the DMF team for review
		(b) (4)	N/A	N/A	N/A
			N/A	N/A	N/A
			N/A	N/A	N/A
			N/A	N/A	N/A



CHEMISTRY REVIEW



Chemistry Review Data Sheet

(b) (4)			
	N/A	N/A	N/A
	N/A	N/A	N/A
	N/A	N/A	N/A
	N/A	N/A	N/A
	N/A	N/A	N/A

¹ Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
RLD	NDA 021107	0.5 mg and 1 mg Oral Tablets

**CHEMISTRY REVIEW**

Chemistry Review Data Sheet

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A	N/A	N/A
Methods Validation	Reviewed/Deficiencies	05-Dec-2014	Solmaz Dehghan
Labeling	Pending	N/A	Has not been conducted
Bioequivalence	Dissolution (Adequate) BE (Pending)	24-Sep-2014	Nabeel Babaa
Toxicology/Clinical	N/A	N/A	N/A
EA	Categorical Exclusion Claim	02-Apr-2013	N/A
Radiopharmaceutical	N/A	N/A	N/A
Samples Requested	N/A	N/A	N/A

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ☒ Yes ☐ No If no, explain reason(s) below:

20. EES INFORMATION

Drug Substance			
Function	Site Information	FEI/CFN#	Status
API Manufacturer	(b) (4)		Acceptable (14-Sep-2014) Re-eval 03-Jul-2015
Drug Product			
Function	Site Information	FEI/CFN#	Status
Drug Product Manufacturer	Amneal Pharmaceuticals 85 Adams Avenue, Hauppauge, NY 11788	3005263655	Pending



CHEMISTRY REVIEW



Executive Summary Section

Chemistry Review for ANDA 206647

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable. Minor deficiency letter is recommended.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

I Drug Substance

Currently, there is no USP monograph available for Alosetron Hydrochloride.

Alosetron Hydrochloride is chemically designated as 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one, mono hydrochloride and its empirical formula is $C_{17}H_{18}N_4O \cdot HCl$. Alosetron Hydrochloride is described as a white to (b) (4) which is soluble in water and 0.1 M hydrochloric acid. (b) (4)

II Drug Product

No USP monograph exists for this drug product. (b) (4)



CHEMISTRY REVIEW



Executive Summary Section

Maximum Daily Dose (MDD): 2 mg

	Identification Threshold (IT)	Qualification Threshold (QT)
Drug Substance	0.10%	0.15%
Drug Product	0.5%	1.0%

B. Description of How the Drug Product is Intended to be Used

Alosetron Hydrochloride tablets are prescribed only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have chronic IBS symptoms (generally lasting 6 months or longer), anatomic or biochemical abnormalities of the gastrointestinal tract excluded and not responded adequately to conventional therapy. The starting dose is 0.5 mg twice a day and may increase to 1 mg twice a day after 4 weeks if starting dosage is well tolerated but does not adequately control IBS symptoms. The drug should be discontinued in patients who have not had adequate control of IBS symptoms after 4 weeks of treatment with 1 mg twice a day.

C. Initial and Updated Risk Assessment

(b) (4)

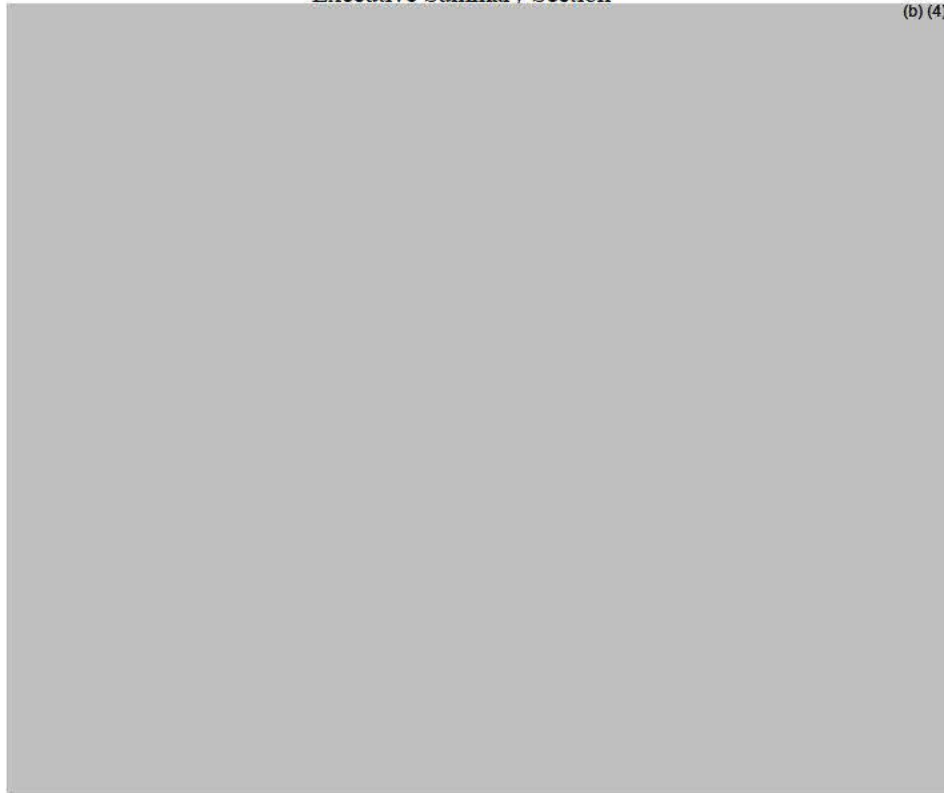


CHEMISTRY REVIEW



Executive Summary Section

(b) (4)



D. Basis for Approvability or Not-Approval Recommendation

The ANDA is inadequate. The referred DMF is not reviewed yet and is pending. (b) (4)

(b) (4)

A minor deficiency letter is recommended.



CHEMISTRY REVIEW



ADMINISTRATIVE

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: S. Dehghan/05-Dec-2014
Chemistry Team Leader Name/Date: D. Roselle
Project Manager Name/Date:
DD/DDD Name/Date: N/A

TYPE OF LETTER:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 206647

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	206647		
Drug Product Name	Alosetron Hydrochloride Tablet		
Strength(s)	EQ 0.5 mg and EQ1.0 mg base		
Applicant Name	Amneal Pharmaceuticals		
Address	85 Adams Ave., Hauppauge, NY 11788		
Applicant's Point of Contact	Alpesh Patel, Vice President, Global Regulatory Affairs; alpesh@amneal.com		
Contact's Telephone Number	(b) (6)		
Contact's Fax Number	631-527-3523		
Original Submission Date(s)	December 24, 2013		
Submission Date(s) of Amendment(s) Under Review	N/A		
Reviewer	S. P. Shrivastava, Ph.D.		
Study Number (s)	ARL/12/483	ARL/12/484	
Study Type (s)	Fasting study	Fed study	
Strength (s)	Eq. 1 mg base	Eq. 1 mg base	
Clinical Site	Accutest Research Lab (I) Pvt. Ltd. (Unit-I)		
Clinical Site Address	4 th Floor, The Grand Monarch, Near Seema Hall, Anand Nagar Road, Satellite, Ahmedabad- 380015, INDIA.		
Analytical Site	(b) (4)		
Analytical Site Address			
OSI REPORT RESULT	N/A		
OVERALL REVIEW RESULT	ADEQUATE		
REVISED/NEW DRAFT GUIDANCE INCLUDED	NO		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1, 3	Dissolution	Eq. 0.5 mg and 1 mg base	ADEQUATE
1	Fasting study	Eq. 1 mg base	ADEQUATE
1	Fed study	Eq. 1 mg base	ADEQUATE
1	Biowaiver request	Eq. 0.5 mg base	ADEQUATE

1 EXECUTIVE SUMMARY

This is a review of bioequivalence studies.

This application contains the results of fasting and fed bioequivalence (BE) studies comparing a test product, Amneal Pharmaceuticals' Alosetron Hydrochloride Tablet, 1 mg to the corresponding reference listed drug Prometheus Labs' Lotronex® (Alosetron HCl) Tablet, 1 mg. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy female subjects. The firm's fasting and fed BE studies are acceptable. The results of the BE studies calculated by the firm are summarized in the tables below.

Alosetron Hydrochloride Tablet Fasting Bioequivalence Study No. (ARL/12/483), N=48 (female) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	Test	Reference	Ratio, %	90% C.I.	
AUC _{0-t} (ng·hr/mL)	19.337	19.257	100.4121	94.1929	107.0420
AUC _∞ (ng·hr/mL)	19.694	19.671	100.1166	94.0029	106.6279
C _{max} (ng/mL)	6.330	6.478	97.7068	90.4602	105.5340

Alosetron Hydrochloride Tablet Fed Bioequivalence Study No. (ARL/12/484), N=42 (female) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	Test	Reference	Ratio, %	90% C.I.	
AUC _{0-t} (ng·hr/mL)	15.870	15.007	105.7486	99.7088	112.1543
AUC _∞ (ng·hr/mL)	16.326	15.477	105.4891	99.6360	111.6859
C _{max} (ng/mL)	4.010	3.742	107.1419	99.3821	115.5076

The dissolution-only review has been conducted.¹ There is no USP dissolution method for this product but there is an FDA-recommended method. The firm conducted acceptable dissolution testing using the FDA-recommended dissolution method (500 ml of Water (deaerated), using apparatus II (paddle) at 50 rpm (1 mg) / 75 rpm (Eq. 0.5 mg base)). However, the firm proposed specification (NLT (b) (4) (Q) in (b) (4)) was not acceptable. Based on the data submitted, the Division of Bioequivalence II (DB II) recommended the following specification; NLT (b) (4) (Q) in 20 minutes. The firm has accepted the FDA-recommended dissolution method and specification.² The dissolution data are adequate with respect to supporting waiver request of the 0.5 mg strength.

¹ DARRTS ANDA 206647, RAINES, KIMBERLY W 08/20/2014 N/A 08/20/2014 REV-BIOEQ-02(Dissolution Review)

² DARRTS ANDA 206647, BABAA, NABEEL 09/24/2014 N/A 09/24/2014 REV-BIOEQ-02(Dissolution Review)

The formulation of core tablet for the 0.5 mg strength is proportionally similar to that of 1 mg strength of the test product which underwent acceptable bioequivalence testing. The dissolution profile of 0.5 mg strength is comparable to that of 1 mg strength. The Division of Bioequivalence I (DBI) grants the waiver request for in vivo BE study requirements for the 0.5 mg strengths based on criteria set forth in 21 CFR § 320.22 (d) (2).

Note on Office of Scientific Investigation (OSI) Inspections: The evaluation of the submitted data for the fasting and fed studies does not indicate any conduct issues and no data integrity deficiency was identified by the reviewer. The OSI inspection of the study sites is NOT expected to impact the BE study outcomes of the fasting and fed studies. No OSI inspection is pending or necessary for the study sites for the fasting study in the current ANDA.

The application is acceptable with no deficiencies.

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3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Alosetron Hydrochloride Tablet, Eq. 0.5 mg base and Eq. 1 mg base
Reference Product	Lotronex [®] (Alosetron HCl) Tablet, Eq. 0.5 mg base and Eq. 1 mg base*
RLD Manufacturer	Prometheus Labs
NDA No.	021107
RLD Approval Date	Eq. 1 mg base strength was approved on February 9, 2000 Eq. 0.5 mg base strength was approved on December 23, 2003
Indications and Usage	LOTIRONEX is indicated only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have: • chronic IBS symptoms (generally lasting 6 months or longer), • had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and • not responded adequately to conventional therapy. Diarrhea-predominant IBS is severe if it includes diarrhea and one or more of the following: • frequent and severe abdominal pain/discomfort, • frequent bowel urgency or fecal incontinence, • disability or restriction of daily activities due to IBS. Because of infrequent but serious gastrointestinal adverse reactions associated with LOTIRONEX, the indication is restricted to those patients for whom the benefit-to-risk balance is most favorable. Clinical studies have not been performed to adequately confirm the benefits of LOTIRONEX in men.

*Note: Current Electronic OB lists the 1 mg strength as the RLD.

3.2 PK/PD Information³

Bioavailability	The pharmacokinetics of alosetron has been studied after single oral doses ranging from 0.05 to 16 mg in healthy men. The pharmacokinetics of alosetron have also been evaluated in healthy women and men and in patients with IBS after repeated oral dosages ranging from 1 mg twice daily to 8 mg twice daily. Alosetron was rapidly absorbed after oral administration with a mean absolute bioavailability of approximately 50% to 60% (approximate range, 30% to >90%). After administration of radiolabeled alosetron, only 1% of the dose was recovered in the feces as unchanged drug.
Food Effect	Alosetron absorption is decreased by approximately 25% by co-administration with food, with a mean delay in time to peak concentration of 15 minutes

³ Labeling of Lotronex at <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=16177#nml34090-1>

Tmax	Following oral administration of a 1 mg alosetron dose to young men, a peak plasma concentration of approximately 5 ng/mL occurred at 1 hour. In young women, the mean peak plasma concentration was approximately 9 ng/mL, with a similar time to peak. Plasma concentrations were 30% to 50% lower and less variable in men compared to women given the same oral dose. Population pharmacokinetic analysis in IBS patients confirmed that alosetron concentrations were influenced by gender (27% lower in men).
Metabolism	A study with 14C-labeled alosetron in Caucasian males (n = 3) and females (n = 3) and an Asian male (n = 1) showed similar serum metabolite profiles. Unchanged alosetron was the major component in serum, with other metabolites being present at low concentrations, none amounting to more than 15% of the unmetabolized alosetron concentration. The circulating metabolites were identified as 6-hydroxy glucuronide, 6-hydroxy sulphate, 7-hydroxy sulphate, hydroxymethyl imidazole, and mono- and bis-oxygenated imidazole derivatives of alosetron. The metabolites are unlikely to contribute to the biological activity of alosetron. Of the circulating Phase I metabolites, only the hydroxymethyl imidazole has weak pharmacological activity, around 10-fold less potent than alosetron. Total recovery of radioactivity in the excreta was $85 \pm 6\%$. The majority of the radiolabeled dose is excreted in the urine ($74 \pm 5\%$). The major urinary metabolites were the 6-hydroxy glucuronide and the mono- and bis-oxygenated imidazole derivatives of alosetron. $11 \pm 4\%$ of the radiolabeled dose was excreted in the feces with less than 1% of the dose being excreted as the unchanged alosetron. Alosetron is metabolized by human microsomal cytochrome P450 (CYP), shown in vitro to involve enzymes 2C9 (30%), 3A4 (18%), and 1A2 (10%). Non-CYP-mediated Phase I metabolic conversion also contributes to an extent of about 11%. However, in vivo data suggest that CYP1A2 plays a more prominent role in alosetron metabolism (62 to 97% of alosetron clearance) based on correlation of alosetron clearance with in vivo CYP1A2 activity measured by probe substrate, increased clearance induced by smoking, and inhibition of clearance by fluvoxamine.
Excretion	Renal elimination of unchanged alosetron accounts for only 13% of the dose. Renal clearance is approximately 112 mL/min.
Half-life	Plasma concentrations of alosetron increase proportionately with increasing single oral doses up to 8 mg and more than proportionately at a single oral dose of 16 mg. Twice-daily oral dosing of alosetron does not result in accumulation. The terminal elimination half-life of alosetron is approximately 1.5 hours (plasma clearance is approximately 600 mL/min). Population pharmacokinetic analysis in patients with IBS confirmed that alosetron clearance is minimally influenced by doses up to 8 mg.
Drug Specific Issues (if any)	WARNING: SERIOUS GASTROINTESTINAL ADVERSE REACTIONS Infrequent but serious gastrointestinal adverse reactions have been reported with the use of LOTRONEX. These events, including ischemic colitis and serious complications of constipation, have resulted in hospitalization, and rarely, blood transfusion, surgery, and death.

(b) (4)

	(b) (4) LOTROX is indicated only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have not responded adequately to conventional therapy. (b) (4) LOTROX should be discontinued immediately in patients who develop constipation or symptoms of ischemic colitis. Patients should immediately report constipation or symptoms of ischemic colitis to their (b) (4) LOTROX should not be resumed in patients who develop ischemic colitis. Patients who have constipation should immediately contact their (b) (4) if the constipation does not resolve after LOTROX is discontinued. Patients with resolved constipation should resume LOTROX only on the advice of their treating (b) (4)
--	---

3.3 OGD Recommendations for Drug Product⁴

Number of studies recommended:		2, fasting and fed
1.	Type of study:	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	Eq. 1 mg base
	Subjects:	Normal healthy females, general population
	Additional Comments:	None
2.	Type of study:	Fed
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	Eq. 1 mg base
	Subjects:	Normal healthy females, general population
	Additional Comments:	None
Analytes to measure (in plasma/serum/blood):		Alosetron in plasma
Bioequivalence based on:		90% CI of Alosetron Hydrochloride
Waiver request of in-vivo testing:		Eq. 0.5 mg base

⁴ Bioequivalence Guidance for specific products; Key word: Alosetron Hydrochloride;
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm082440.pdf>

Source of most recent recommendations:	Recently, the Agency has published a draft individual guidance outlining the bioequivalence recommendations for establishing bioequivalence to the RLD Prometheus Labs' Lotronex[®] (Alosetron Hydrochloride)⁵ Active ingredient: Alosetron Hydrochloride Form/Route: Tablets/Oral Recommended studies: 2 studies 1. Type of study: Fasting Design: Single-dose, two-way crossover <i>in-vivo</i> Strength: Eq. 1 mg base Subjects: Normal healthy females, general population Additional Comments: 2. Type of study: Fed Design: Single-dose, two-way crossover <i>in-vivo</i> Strength: 1 mg (base) Subjects: Normal healthy females, general population Additional comments: Analytes to measure (in appropriate biological fluid): Alosetron in plasma Bioequivalence based on (90% CI): Alosetron Waiver request of in vivo testing: 0.5 mg (base) based on (i) acceptable bioequivalence studies on the 1 mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Dissolution test method and sampling times: Please note that a Dissolution Methods Database is available to the public at the OGD website at http://www.fda.gov/cder/ogd/index.htm. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.										
Summary of OGD or DB History	<table> <tr> <td>Pending ANDAs (Not Yet Reviewed)</td><td>Yes</td></tr> <tr> <td>Approved ANDAs</td><td>No</td></tr> <tr> <td>Previously Reviewed ANDAs</td><td>Yes. ANDA 200652 (Roxane)⁶</td></tr> <tr> <td>Protocols</td><td>Yes; 07-030 (Roxane)⁷</td></tr> <tr> <td>Controls</td><td>Yes; Control 06-1058 (b) (4)⁸</td></tr> </table>	Pending ANDAs (Not Yet Reviewed)	Yes	Approved ANDAs	No	Previously Reviewed ANDAs	Yes. ANDA 200652 (Roxane) ⁶	Protocols	Yes; 07-030 (Roxane) ⁷	Controls	Yes; Control 06-1058 (b) (4) ⁸
Pending ANDAs (Not Yet Reviewed)	Yes										
Approved ANDAs	No										
Previously Reviewed ANDAs	Yes. ANDA 200652 (Roxane) ⁶										
Protocols	Yes; 07-030 (Roxane) ⁷										
Controls	Yes; Control 06-1058 (b) (4) ⁸										

⁵ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm082440.pdf>

⁶ DARRTS ANDA 200652; XIA, LI 04/30/2010 N/A 04/30/2010 REV-BIOEQ-01(General Review)

⁷ OGD Protocol Database; <http://fdswv04385/seltrack/ProtocolGrid.ASP>

⁸ OGD Control Database; <http://cdsogd1/controls/DOCGRID.ASP>

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	
In vitro dissolution	Yes	2
Waiver requests	Yes	1
BCS Waivers	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	Yes	1 (Dissolution Acknowledgement)

3.5 Pre-Study Bioanalytical Method Validation for Alosetron

Bioanalytical Method Validation (b) (4) effective date: 8/27/2013):
Study No. ARL/12/483 - Fasting

Information Requested	Data
Bioanalytical method validation report location	In module 5.3.1.4, refer annex 6.4 of Bio-analytical report of Clinical study report (Page No. 1 to 75)
Analyte	Alosetron
Internal standard (IS)	(b) (4)
Method description	(b) (4)

Information Requested	Data																										
	(b) (4)																										
	Analytical Method: <table> <tr> <td>Chromatographic Condition</td><td>LC-MS/MS</td></tr> <tr> <td>Mobile Phase</td><td>Buffer: acetonitrile (30: 70, v/v)</td></tr> <tr> <td>Buffer</td><td>2mM Ammonium formate in water (pH: 3.00 ± 0.05)</td></tr> <tr> <td>Column</td><td>Hypurity C18 (50 mm x 4.6 mm), 5 μ</td></tr> <tr> <td>Flow Rate</td><td>0.500 mL/minute</td></tr> <tr> <td>Injection Volume</td><td>5 μL</td></tr> <tr> <td>Auto sampler temperature</td><td>5°C</td></tr> <tr> <td>Column Oven temperature</td><td>40°C</td></tr> <tr> <td>Strong Wash</td><td>Acetonitrile</td></tr> <tr> <td>Weak wash</td><td>Water: acetonitrile (30:70, v/v)</td></tr> <tr> <td>Diluent</td><td>methanol: water (60: 40, v/v)</td></tr> <tr> <td>Polarity</td><td>Positive</td></tr> <tr> <td>Detector</td><td>MS/MS</td></tr> </table>	Chromatographic Condition	LC-MS/MS	Mobile Phase	Buffer: acetonitrile (30: 70, v/v)	Buffer	2mM Ammonium formate in water (pH: 3.00 ± 0.05)	Column	Hypurity C18 (50 mm x 4.6 mm), 5 μ	Flow Rate	0.500 mL/minute	Injection Volume	5 μL	Auto sampler temperature	5°C	Column Oven temperature	40°C	Strong Wash	Acetonitrile	Weak wash	Water: acetonitrile (30:70, v/v)	Diluent	methanol: water (60: 40, v/v)	Polarity	Positive	Detector	MS/MS
Chromatographic Condition	LC-MS/MS																										
Mobile Phase	Buffer: acetonitrile (30: 70, v/v)																										
Buffer	2mM Ammonium formate in water (pH: 3.00 ± 0.05)																										
Column	Hypurity C18 (50 mm x 4.6 mm), 5 μ																										
Flow Rate	0.500 mL/minute																										
Injection Volume	5 μL																										
Auto sampler temperature	5°C																										
Column Oven temperature	40°C																										
Strong Wash	Acetonitrile																										
Weak wash	Water: acetonitrile (30:70, v/v)																										
Diluent	methanol: water (60: 40, v/v)																										
Polarity	Positive																										
Detector	MS/MS																										
Limit of quantitation	0.100 ng/mL																										
Average recovery of drug (%)	90.85; LQC: 92.47 (%CV-6.93); MQC: 88.78 (%CV- 2.72); HQC: 91.31 (%CV- 1.68);																										
Average recovery of IS (%)	91.65																										
Standard curve concentrations (units/mL)	0.100 ng/mL to 14.000 ng/mL																										
QC concentrations (units/mL)	LLQC : 0.100 ng/mL LQC : 0.285 ng/mL MQC : 4.375 ng/mL HQC : 11.750 ng/mL																										
QC Intraday precision range (%)	LLQC : 3.13 to 5.83 LQC : 3.77 to 5.73 MQC : 1.27 to 3.38 HQC : 1.23 to 2.39																										
QC Intraday accuracy range (%)	LLQC : 96.00 to 104.00 LQC : 97.89 to 103.16																										

Information Requested	Data
	MQC : 96.59 to 98.99 HQC : 96.27 to 97.96
QC Interday precision range (%)	LLQC : 5.94 LQC : 4.86 MQC : 2.34 HQC : 1.96
QC Interday accuracy range (%)	LLQC : 101.00 LQC : 101.05 MQC : 97.74 HQC : 97.18
Bench-top stability (hrs)	8 hrs at room temperature
Stock stability (days)	18 days at 2-8°C
Processed stability (hrs)	15 hrs at room temperature ,52 hrs at 5°C
Freeze-thaw stability (cycles)	Five cycles
Long-term storage stability (days)	118 days at -70°C ± 10°C*
Dilution integrity	Concentration diluted up to 1/2 times & 1/4 times
Selectivity	No significant interference peak was observed at the retention time of Alosetron and (¹³ C, ² H ₃)-Alosetron.

Reviewer's Note: The long term stability data was provided in the addendum No. 4
(b) (4) effective date: 12/6/2013).

Bioanalytical Method Validation (b) (4) **effective date: 8/27/2013):**
Study No. ARL/12/484 - Fed

Information Requested	Data
Bioanalytical method validation report location	In module 5.3.1.4, refer annex 6.4 of Bio-analytical report of Clinical study report (Page No. 1 to 75)
Analyte	Alosetron
Internal standard (IS)	(b) (4)
Method description	(b) (4)

Information Requested	Data	
	(b) (4)	
	Analytical Method:	
Chromatographic Condition	LC-MS/MS	
Mobile Phase	Buffer: acetonitrile (30: 70, v/v)	
Buffer	2mM Ammonium formate in water (pH: 3.00 ± 0.05)	
Column	Hypurity C18 (50 mm x 4.6 mm), 5 μ	
Flow Rate	0.500 mL/minute	
Injection Volume	5 μL	
Auto sampler temperature	5°C	
Column Oven temperature	40°C	
Strong Wash	Acetonitrile	
Weak wash	Water: acetonitrile (30:70, v/v)	
Diluent	methanol: water (60: 40, v/v)	
Polarity	Positive	

Information Requested	Data	
	Detector	MS/MS
Limit of quantitation	0.100 ng/mL	
Average recovery of drug (%)	90.85	
Average recovery of IS (%)	91.65	
Standard curve concentrations (units/mL)	0.100 ng/mL to 14.000 ng/mL	
QC concentrations (units/mL)	LLQC : 0.100 ng/mL LQC : 0.285 ng/mL MQC : 4.375 ng/mL HQC : 11.750 ng/mL	
QC Intraday precision range (%)	LLQC : 3.13 to 5.83 LQC : 3.77 to 5.73 MQC : 1.27 to 3.38 HQC : 1.23 to 2.39	
QC Intraday accuracy range (%)	LLQC : 96.00 to 104.00 LQC : 97.89 to 103.16 MQC : 96.59 to 98.99 HQC : 96.27 to 97.96	
QC Interday precision range (%)	LLQC : 5.94 LQC : 4.86 MQC : 2.34 HQC : 1.96	
QC Interday accuracy range (%)	LLQC : 101.00 LQC : 101.05 MQC : 97.74 HQC : 97.18	
Bench-top stability (hrs)	8 hrs at room temperature	
Stock stability (days)	18 days at 2-8°C	
Processed stability (hrs)	15 hrs at room temperature ,52 hrs at 5°C	
Freeze-thaw stability (cycles)	Five cycles	
Long-term storage stability (days)	32 days at -20°C ± 5°C and -70°C ± 10°C*	
Dilution integrity	Concentration diluted up to 1/2 times & 1/4 times	

Information Requested	Data
Selectivity	No significant interference peak was observed at the retention time of Alosetron and (¹³ C, ² H ₃)-Alosetron.

***Reviewer's Note:** (b) (4) term stability data was provided in the addendum No. 2 effective date: 9/14/2013). The long term stability data provided in the addendum No. 4 (b) (4) effective date: 12/6/2013) should also apply to the study samples in the fed study.

Bioanalytical Addendum to Method Validation
effective date: 9/12/2013)

(b) (4)

Information Requested	Data
Bioanalytical addendum to method validation report location	In module 5.3.1.4, refer annex 6.4.1 of Bio-analytical report of Clinical study report (Page No. 1 to 36)
Analyte	Alosetron
Internal standard (IS)	(b) (4)
Method description	(b) (4)

Information Requested	Data	
	12. Transfer it in autosampler vial for injection.	
	Analytical Method:	
	Chromatographic Condition	LC-MS/MS
	Mobile Phase	Buffer: acetonitrile (30: 70, v/v)
	Buffer	2mM Ammonium formate in water (pH: 3.00 ± 0.05)
	Column	Hypurity C18 (50 mm x 4.6 mm), 5 μ
	Flow Rate	0.500 mL/minute
	Injection Volume	5 μL
	Auto sampler temperature	5°C
	Column Oven temperature	40°C
	Rinsing Solution	Water: acetonitrile (30:70, v/v)
	Diluent	methanol: water (60: 40, v/v)
	Polarity	Positive
	Detector	MS/MS
Limit of quantitation	0.100 ng/mL	
Average recovery of drug (%)	NA	
Average recovery of IS (%)	NA	
Standard curve concentrations (units/mL)	0.100 ng/mL to 14.000 ng/mL	
QC concentrations (units/mL)	LLQC : 0.100 ng/mL LQC : 0.285 ng/mL MQC : 4.375 ng/mL HQC : 11.750 ng/mL	
QC Intraday precision range (%)	LLQC : 4.00 LQC : 2.01 MQC : 2.50 HQC : 0.44	
QC Intraday accuracy range (%)	LLQC : 100.00	

Information Requested	Data
	LQC : 104.56 MQC : 100.73 HQC : 111.47
QC Interday precision range (%)	NA
QC Interday accuracy range (%)	NA
Bench-top stability (hrs)	NA
Stock stability (days)	NA
Processed stability (hrs)	NA
Freeze-thaw stability (cycles)	NA
Long-term storage stability (days)	NA
Dilution integrity	NA
Selectivity	No significant interference peak was observed at the retention time of Alosetron and (¹³ C, ² H ₃)-Alosetron.

Reviewer's Note: This addendum (b) (4) effective date: 9/12/2013) provides partial validation data as the analytical method was transferred from one instrument (Instrument ID (b) (4)) to another instrument (Instrument ID: (b) (4)). The reviewer checked that Instrument ID: (b) (4) was used in both fasting and fed studies.

SOPs submitted	Yes
Does the duration of the each of the LTSS stability parameters support the sample preparation and assay dates	Yes

Comments on the Pre-Study Method Validation:

The long term stability of 118 days at -70 °C covers the longest period for sample storage for fasting study (30 days) and fed study (32 days) at -70 °C.

Pre-study method validation is **acceptable**.

3.6 In Vivo Studies

Table 1. Summary of in vivo Bioequivalence Studies for Alosetron Hydrochloride Tablets – Fasting Study

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-t} (ng*hr/mL)	AUC _∞ (ng*hr/mL)	T _½ (hr)	K _{el} (hr ⁻¹)	
ARL/12/483	Title: A Randomized, Open Label, Balanced, Two-Treatment, Two-Period, Two-Sequence, Single Dose, Crossover, Bioequivalence Study of Alosetron Hydrochloride Tablets, 1 mg of Amneal Pharmaceuticals, USA with LOTRONEX® (alosecron hydrochloride) Tablets 1 mg of Prometheus Laboratories Inc. in Normal, Healthy, Adult, Female Human Subjects under Fasting Condition	A randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover design.	Test Product (T) Alosetron Hydrochloride Tablets, 1 mg 1 Tablet Oral [Lot No.: BE18413]	48 Normal, healthy, adult, female human subjects 33.25 ± 06.07 (21-43)	7.152 ± 3.515 (49.151)	1.125 (0.750-2.500)	21.979 ± 11.505 (52.347)	22.331 ± 11.637 (52.114)	1.539 ± 0.258 (16.752)	0.463 ± 0.082 (17.729)	Module 5.3.1.2
			Reference Product (R) LOTRONEX® (alosecron hydrochloride) Tablets 1 mg 1 Tablet Oral [Lot No.: HGHP]		7.163 ± 3.381 (47.205)	1.000 (0.500-2.250)	21.586 ± 10.757 (49.834)	21.980 ± 10.870 (49.452)	1.567 ± 0.297 (18.985)	0.458 ± 0.087 (19.013)	

Table 2. Summary of in vivo Bioequivalence Studies for Alosetron Hydrochloride Tablets – Fed Study

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-t} (ng*hr/mL)	AUC _∞ (ng*hr/mL)	T _½ (hr)	K _{el} (hr ⁻¹)	
ARL/12/484	A Randomized, Open Label, Balanced, Two-Treatment, Two-Period, Two-Sequence, Single Dose, Crossover, Bioequivalence Study of Alosetron Hydrochloride Tablets, 1 mg of Amneal Pharmaceuticals, USA with LOTRONEX® (alosecron hydrochloride) Tablets 1 mg of Prometheus Laboratories Inc. in Normal, Healthy, Adult, Female Human Subjects under Fed Condition.	A randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover study design.	Test Product (T) Alosetron Hydrochloride Tablets, 1 mg 1 Tablet Oral [Lot No.: BE18413]	42 Normal, healthy, adult, female human subjects	4.278 ± 1.627 (38.022)	2.500 (0.750-4.500)	17.042 ± 6.773 (39.740)	17.523 ± 6.989 (39.884)	1.806 ± 0.329 (18.205)	0.397 ± 0.073 (18.471)	Module 5.3.1.2
			Reference Product (R) LOTROXEX® (alosecron hydrochloride) Tablets 1 mg 1 Tablet Oral [Lot No.: HGHP]	36.69 ± 05.62 (22-45)	4.112 ± 2.006 (48.775)	2.375 (0.750-4.500)	16.441 ± 7.612 (46.299)	16.937 ± 7.800 (46.056)	1.778 ± 0.307 (17.256)	0.401 ± 0.069 (17.083)	

Reviewer's Note: as per labeling "Alosetron absorption is decreased by approximately 25% by co-administration with food, with a mean delay in time to peak concentration of 15 minutes", when the test drug is taken with a high-fat meal. In the current fed study, C_{max} was ~40% lower, AUC_t and AUC_i was ~20% lower and T_{max} delayed ~1.25 hours, compared to the fasting study.

Table 3. Statistical Summary of the Comparative BE Study Data Calculated by the Firm

Reference Scaled Average Bioequivalence Approach Used				☐ Yes ☒ No		
If No, then complete Table 3A only If Yes, then complete Tables 3A and 3B						
Alosetron Hydrochloride Tablets, 1 mg, (No of subjects completed= 48) Dose (1 x 1 mg tablet) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study (Study No.: ARL/12/483)						
Parameter	Test	N	RLD	N	Ratio	90% C.I.
AUC _{0-t}	19.337	48	19.257	48	100.4121	94.1929-107.0420
AUC _∞	19.694	48	19.671	48	100.1166	94.0029-106.6279
C _{max}	6.330	48	6.478	48	97.7068	90.4602-105.5340

Reference Scaled Average Bioequivalence Approach Used				☐ Yes ☒ No		
If No, then complete Table 3A only If Yes, then complete Tables 3A and 3B						
Alosetron Hydrochloride Tablets, 1 mg (No of subjects completed= 42) Dose (1 x 1 mg tablet) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study (Study No.: ARL/12/484)						
Parameter	Test	N	RLD	N	Ratio	90% C.I.
AUC _{0-t}	15.870	42	15.007	42	105.7486	99.7088-112.1543
AUC _∞	16.326	42	15.477	42	105.4891	99.6360-111.6859
C _{max}	4.010	42	3.742	42	107.1419	99.3821-115.5076

Table 4. Reanalysis of Study Samples - Fasting

Study No. ARL/12/483								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic ¹	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Batch repeat (Code E)	23	23	1.04	1.04	23	23	1.04	1.04
Inconsistent internal standard area response (Code B)	08	03	0.36	0.14	08	03	0.36	0.14
Sample outside assay range (code A)	08	06	0.36	0.27	08	06	0.36	0.27
Total	39	32	1.77	1.45	39	32	1.77	1.45

Note: Total two thousand two hundred eight (2208) subject samples for Test (T) and Reference (R) were analyzed.

Table 5. Reanalysis of Study Samples – Fed

Study No. ARL/12/484								
Additional information in Volume(s), Page(s)								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic ¹	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Batch repeat (Code E)	23	23	1.19	1.19	23	23	1.19	1.19
Inconsistent internal standard area response (Code B)	01	01	0.05	0.05	01	01	0.05	0.05
Total	24	24	1.24	1.24	24	24	1.24	1.24

Note: Total One thousand nine hundred thirty two (1932) subject samples for Test (T) and Reference (R) were analyzed.

Table 6. SOP's Dealing with Bioanalytical Repeats of Study Samples

Is there any other particular concern that should be investigated further?	No
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Did use of recalculated plasma concentration data change study outcome?

No PK repeats.

Comments from the Reviewer:

Fasting study:

- Code E (Batch Repeat): The firm reported that run (b) (6) was rejected because QC samples did not meet acceptance criteria. The reviewer verified from the raw data of the rejected run submitted by the firm. Code E sample repeats are justified.
- Code A (above the ULOQ): The reviewer verified that the original values and repeated values of all 14 samples reanalyzed under code A are above 14.000 ng/mL (ULOQ). The dilution factor used in the repeat analysis is 2 which has been validated for the dilution integrity. The sample repeats under code A are acceptable.
- The reviewer also verified that the samples repeated under Code B (IS variation) followed the SOP and acceptable

Fed Study:

- Code E (Batch Repeat): The firm reported that run (b) (4) was rejected because Linearity did not meet acceptance criteria. The reviewer verified from the raw data of the rejected run submitted by the firm. Code E sample repeats are justified.
- The reviewer verified that the sample repeated under Code B (IS variation) followed the SOP and is acceptable. .

3.7 Formulation

Location in appendix	Section 4.2, Page 50
If a tablet, is the RLD scored?	No
If a tablet, is the test product biobatch scored	No
Is the formulation acceptable?	ACCEPTABLE
If not acceptable, why?	

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	Dissolution data has been reviewed previously. ⁹
Source of Method (USP, FDA or Firm)	FDA
Medium	Water (deaerated)
Volume (mL)	500 mL
USP Apparatus type	Paddles (USP Apparatus II)
Rotation (rpm)	75 rpm for 0.5 mg 50 rpm for 1 mg
FDA-recommended specifications	Not less than (b) (4) (Q) is dissolved in 20 minutes
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	No
If no, reason why F2 not calculated	Rapid dissolving drug product
Is method acceptable?	Acceptable
If not then why?	

Reviewer's comments: The dissolution-only review has been conducted. There is no USP dissolution method for this product but there is an FDA-recommended method. The firm conducted acceptable dissolution testing using the FDA-recommended dissolution method (500 ml of Water (deaerated), using apparatus II (paddle) at 50 rpm (1 mg) / 75 rpm (0.5 mg)). However, the firm proposed specification (NLT (b) (4) (Q) in (b) (4) was not acceptable. Based on the data submitted, the Division of Bioequivalence II (DB II) recommended the following specification; NLT (b) (4) (Q) in 20 minutes. The firm has accepts the FDA-recommended dissolution method and specification.¹⁰

3.9 Waiver Request(s)

Strengths for which waivers are requested, if applicable ¹¹	Eq. 0.5 mg base
Waiver regulation cited?	21 CFR 320.22(d)(2)
Strengths considered for 21 CFR 320.24 (b)(6)	No
Proportional to strength tested in vivo?	Yes (Core Tablets)
Is dissolution acceptable?	Yes
Waivers granted?	WAIVER GRANTED
If not then why?	

⁹ DARRTS ANDA 206647, RAINES, KIMBERLY W 08/20/2014 N/A 08/20/2014 REV-BIOEQ-02(Dissolution Review)

¹⁰ DARRTS ANDA 206647, BABAA, NABEEL 09/24/2014 N/A 09/24/2014 REV-BIOEQ-02(Dissolution Review)

¹¹ For Modified Release Dosage Forms, please note waiver is not applicable

3.10 Deficiency Comments

None

3.11 Recommendations

1. The Division of Bioequivalence **accepts** the fasting BE study (No. ARL/12/483) conducted by Amneal Pharmaceuticals on its Alosetron Hydrochloride Tablet, Eq. 1 mg base, Lot #BE18413, to Prometheus Labs ' Lotronex (Alosetron HCl) Tablet, Eq. 1 mg base, lot #HGHP.
2. The Division of Bioequivalence **accepts** the fed BE study (No. ARL/12/484) conducted by Amneal Pharmaceuticals on its Alosetron Hydrochloride Tablet, Eq. 1 mg base, Lot #BE18413, to Prometheus Labs ' Lotronex (Alosetron HCl) Tablet, Eq. 1 mg base, lot #HGHP.
3. The firm's dissolution testing data for the 0.5 mg test product using FDA-recommended method are acceptable, and DBE concurs with firm's proposed dissolution method for 1 mg strength (USP Apparatus II (paddle) at 75 rpm in 500 mL deaerated water). However, the firm's proposed specification (NLT (b) (4) (Q) in (b) (4) is not acceptable. Based on the data submitted, the Division of Bioequivalence II (DB II) recommended the following specification; NLT (b) (4) (Q) in 20 minutes. The firm has accepted the FDA-recommended dissolution method and specification.¹²

Apparatus: USP Paddle (Apparatus II)
Medium: 500 mL of the de-aerated purified water
Speed: 75 rpm
Temperature: 37° C±0.5°C
Sampling times (min): 10, 20, 30 and 45
Specifications: NLT (b) (4) (Q) in 20 minutes

4. The formulation of core tablets for the 0.5 mg strength is proportionally similar to that of 1 mg of the test product which underwent acceptable bioequivalence testing. The DBI grants the waiver request for in vivo BE study requirements for the 0.5 mg strength based on criteria set forth in 21 CFR § 320.22 (d) (2).

3.12 Comments for Other OGD Disciplines

Discipline	Comment
None	None

¹² DARRTS ANDA 206647, BABAA, NABEEL 09/24/2014 N/A 09/24/2014 REV-BIOEQ-02(Dissolution Review)

4 APPENDIX

4.1 Individual Study Review

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 7. Study Information

Study Number	ARL/12/483			
Study Title	A Randomized, Open Label, Balanced, Two-Treatment, Two-Period, Two-Sequence, Single Dose, Crossover, Bioequivalence Study of Alosetron Hydrochloride Tablets, 1 mg of Amneal Pharmaceuticals, USA with LOTRONEX® (alosectron hydrochloride) Tablets 1 mg of Prometheus Laboratories Inc. in Normal, Healthy, Adult, Female Human Subjects under Fasting Condition.			
Study Type	☒ In Vivo BE	☐ In Vitro BE	☐ Permeability	☐ Other specify)
Submission Location:				
Study Report	5.3.1.2			
Validation Report	5.3.1.4			
Bioanalytical Report	5.3.1.4			
Clinical Site (Name, Address, Phone #, Fax #)	Accutest Research Lab (I) Pvt. Ltd. (Unit-I) 4 th Floor, The Grand Monarch, Near Seema Hall, Anand Nagar Road, Satellite, Ahmedabad- 380015, INDIA. Tel: +91 79- 4023 1700			
Principal Clinical Investigator (Name, Email)	Dr. Rupesh Vala, M.B.B.S. rupesh.vala@accutestindia.com			
Dosing Dates	Period I : 01 November 2013 Period II : 07 November 2013			
Analytical Site (Name, Address, Phone #, Fax #)	(b) (4)			
Analysis Dates	Start Date : 11 November 2013 End Date : 30 November 2013			
Principal Analytical Investigator (Name, Email)	(b) (4)			
Sample Storage :				

(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)	30 Days
(b) Temperature Range (e.g., -20° C to -80° C)	-70°C ± 10°C
Long-Term Storage Stability Coverage (no. days @ temp °C)	118 days at -70°C ± 10°C

Table 8 Product information

Product	Test		Reference	
Treatment ID	T		R	
Name of Product/Brand Name	Alosetron Hydrochloride Tablets, 1 mg (Name of Product)		LOTRONEX® (alose tron hydrochloride) Tablets 1 mg (Brand Name)	
Manufacturer	Manufactured by: Amneal Pharmaceuticals, USA		Prometheus Laboratories Inc. San Diego, CA 92121	
Lot No.	BE18413		HGHP	
Manufacture Date	June 3, 2013		N/A	
Expiration Date	N/A		July 2014	
Strength	1 mg		1 mg	
Dosage Form	Tablet		Tablet	
Bio-batch Size	(b) (4)		N/A	
Production Batch Size	(b) (4)		N/A	
Potency	101.8%		98.8%	
Content Uniformity (mean, %CV)	No. of Units:	10	No. of Units:	10
	Min:	100.9%	Min:	95.2%
	Max:	102.2%	Max:	107.0%
	Mean:	101.6%	Mean:	101.5%
	AV:	1.2	AV:	9.0
Dose Administered	01 Tablet		01 Tablet	
Route of Administration	Oral		Oral	

Table 9. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Enrolled: 48 Dosed: 48 Completed: 48 Samples Analyzed: 48 Data Analyzed: 48
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	6 days
Randomization Scheme (Sequence)	Yes; SEQ: TR and RT
Blood Sampling Times (hr)	0 (pre-dose), and at 00.17, 00.33, 00.50, 00.75, 01.00, 01.25, 01.50, 1.75, 02.00, 02.25, 02.50, 02.75, 03.00, 03.50, 04.00, 04.50, 05.00, 06.00, 7.00, 08.00, 10.00 and 12.00 hours after dosing
Blood Sample Processing/Storage	(b) (4)

Comments on Study Design: Acceptable.

4.1.1.2 Clinical Results

Table 10. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No. ARL/12/483			
		Treatment Groups	
		Test Product T N=48	Reference Product R N =48
Age (years)	Mean ± SD	33.25 ± 06.07	33.25 ± 06.07
	Range	21 - 43	21 - 43
Age Groups	< 18	Nil	Nil
	18 – 40	41 (85.42 %)	41 (85.42 %)
	41 – 64	07 (14.58 %)	07 (14.58 %)
	65 – 75	Nil	Nil
	> 75	Nil	Nil
Sex	Male	Nil	Nil
	Female	48 (100.00 %)	48 (100.00 %)
Race	Asian	48 (100.00%)	48 (100.00%)
	Black	Nil	Nil
	Caucasian	Nil	Nil
	Hispanic	Nil	Nil
	Other	Nil	Nil
BMI (Kg/m ²)	Mean ± SD	22.72 ± 01.75	22.72 ± 01.75
	Range	19.15 - 24.88	19.15 - 24.88
Other Factors		-	-

Table 11. Dropout Information, Fasting Bioequivalence Study

Study No. ARL/12/483				
Subject No	Reason for dropout/replacement*	Period	Replaced?	Replaced with
None of the subjects were discontinued during entire course of the study.				

Table 12. Study Adverse Events, Fasting Bioequivalence Study

Body System/Adverse Event	Reported Incidence by Treatment Groups	
	Fasted Bioequivalence Study No. ARL/12/483	
	Test Product T N=48	Reference Product R N=48
Total	00 (00.00 %)	00 (00.00 %)

Note: Four (04) AEs were reported during post study assessment. The reported clinically significant abnormal laboratory values were considered as adverse events, as the subjects had received both treatments, there were difficult to attribute these adverse events to either of the treatments Test product (T) or Reference product (R).

Subjects Experiencing Emesis (Include in eCTD)

Subject Number*	Test/Reference	Period	Time Post-Dose	Duration Between Dosing and Emesis (hrs)
None	None			

Was the adverse event profile observed during the fasting bioequivalence study comparable for the test and reference product? Yes.

Are there any serious adverse events or death? If so, are they reported to the OGD Safety Committee? No.

Are there any other safety concerns based on the adverse event profile? No.

Table 13. Protocol Deviations, Fasting Bioequivalence Study

Study No. ARL/12/483		
Type	Subject #s (Test)	Subject #s (Ref.)
Pre-dose Housing Deviation	(b) (6)	
Blood Sample Time Point Deviation		

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Sr No	Period	Subject No	Sampling Hour	Schedule Time	Actual Time	Deviation (Min)	Deviation (Hrs)	Actual Sampling Hour	Reason	Action Taken
01	I	(b) (6)	03 50	11:40	11:47	07 00	00 12	03 62	Difficulty with vein	N A
02	I	(b) (6)	00 17	08:22	08:26	04 00	00 07	00 24	Difficulty with vein	Cannula replaced

Comments on Dropouts/Adverse Events/Protocol Deviations:

- There were no dropouts.
- The reviewer agrees with the firm that pre-dose housing deviation has no impact on the study outcome as 10 hours fasting condition prior to dosing was maintained.
- Blood sampling time deviations were minor. In addition, the firm reported that the actual blood sample time points were considered for the calculation of PK parameters. The blood sample time deviations would not affect the study outcome.
- Four (04) AEs were reported during post study assessment. Subject No. (b) (6) (Low plate late count = $89 \times 10^3/\text{mm}^3$), Subject No. (b) (6) (High WBC count = $14.8 \times 10^3/\text{mm}^3$), Subject (b) (6) (Low Haemoglobin = 8.7 g/dL) and Subject No. (b) (6) (High S. Bilirubin Total = 3.98 mg/dL, High S. Bilirubin Indirect = 3.43 mg/dL, and High S. Bilirubin Direct = 0.54 mg/dL) had clinically significant abnormal laboratory value. All reported AEs were possibly related to the study medication and mild to moderate in severity and resolved without treatment except for one subject who was treated with some vitamins.
- The clinical observations are **acceptable**.

4.1.1.3 Bioanalytical Results

Table 14. Assay Validation – Within the Fasting Bioequivalence Study

Bioequivalence Study No. ARL/12/483									
Alosetron									
Parameter	Standard Curve Samples								
Concentration (ng/mL)	0.100	0.200	0.500	1.500	2.875	5.625	8.500	11.875	14.000
Inter day Precision (%CV)	2.94	7.25	3.23	2.80	2.98	2.64	2.40	2.49	2.79
Inter day Accuracy (%Actual)	102.00	96.50	99.00	97.73	100.45	99.79	100.31	101.43	102.51
Linearity	0.9958 to 0.9998								
Linearity Range (ng/mL)	0.100 ng/mL to 14.000 ng/mL								
Sensitivity/LOQ (ng/mL)	0.100 ng/mL								
Bioequivalence Study No. ARL/12/483									
Alosetron									
Parameter	Quality Control Samples								
	LQC	M1QC	MQC	HQC					
Concentration (ng/mL)	0.285	2.000	4.376	11.752					
Inter day Precision (%CV)	6.07	4.24	3.79	4.00					
Inter day Accuracy (%Actual)	98.25	99.10	98.83	99.51					
Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?					Yes				
Are there any concerns related to sample analysis (including reanalysis, run rejection, etc.)?					No. No. During the study sample analysis 60 (54 for study and 6 for ISR) calibration curves were generated. 59 Runs were acceptable. Run (b) (6) was rejected, did not meet the M1QC, MQC and HQCs acceptance criteria of ±15% of nominal concentration.				
Were 20% of chromatograms included?					Yes. Subjects (b) (6)				

Did the firm provide 100% numerical raw data (e.g. peak height, peak area, response count of IS and analyte) in run sequence order (i.e. Run log) in the instrument printout format?	Yes
--	-----

Comments on Study Assay Validation: Acceptable.

Comments on Chromatograms: Acceptable.

Table 15. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No. (b) (4)	Effective Date of SOP (b) (4)	SOP Title
		REPEAT SAMPLE ANALYSIS

Comments: The firm's within study method validation is **acceptable**.

- The firm used same anticoagulant (K3EDTA) for methods validation, CC standards, QC samples and for analytical samples.
- The firm conducted Incurred Samples Reanalysis (ISR) in which 99.33% of ISR samples met the acceptance: 67% of the ISR results should be within 20% of the mean value [(repeat value + original value)/2].
- The analytical portion of the fasting study is **adequate**.

4.1.1.4 Pharmacokinetic Results

Table 16. Arithmetic Mean Pharmacokinetic Parameters

Fasting study – Calculated by Firm

period	C _{max}	t _{max}	AUC _{0-t}	AUC _{0-inf}	AUC _t /AUC _{inf}	K _{el}	first time_point	last time_point	T _{1/2}
	ng/mL	hrs	ngxh/mL	ngxh/mL	%	hrs ⁻¹	hrs	hrs	hrs

TEST

Mean	7.152	1.193	21.979	22.331	98.187	0.463	3.406	9.854	1.539
SD	3.515	0.376	11.505	11.637	0.844	0.082	2.244	1.750	0.258
%CV	49.151	31.549	52.347	52.114	0.859	17.729	65.883	17.762	16.752
Median	6.903	1.125	20.954	21.292	98.382	0.451	2.500	10.000	1.537
Min	2.030	0.750	5.134	5.373	95.553	0.341	0.750	6.000	0.977
Max	19.472	2.500	70.707	72.083	99.246	0.709	8.000	12.000	2.034

REFERENCE

Mean	7.163	1.167	21.586	21.980	97.905	0.458	3.865	9.583	1.567
SD	3.381	0.323	10.757	10.870	1.425	0.087	2.431	1.889	0.297
%CV	47.205	27.723	49.834	49.452	1.455	19.013	62.917	19.709	18.985
Median	6.332	1.000	18.762	19.092	98.308	0.447	3.000	10.000	1.551
Min	1.921	0.500	4.831	5.313	90.928	0.305	0.500	5.000	1.071
Max	19.086	2.250	62.234	63.221	99.308	0.647	8.000	12.000	2.274

*Tmax values are presented as median, range.

Table 17. Geometric Means and 90% Confidence Intervals - Calculated by Firm

Reference Scaled Average Bioequivalence Approach Used				☐ Yes ☒ No		
If No, then complete Table 3A only						
If Yes, then complete Tables 3A and 3B						
Alosetron Hydrochloride Tablets, 1 mg, (No of subjects completed= 48) Dose (1 x 1 mg tablet) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study (Study No.: ARL/12/483)						
Parameter	Test	N	RLD	N	Ratio	90% C.I.
AUC _{0-t}	19.337	48	19.257	48	100.4121	94.1929-107.0420
AUC _∞	19.694	48	19.671	48	100.1166	94.0029-106.6279
C _{max}	6.330	48	6.478	48	97.7068	90.4602-105.5340

Table 18. Additional Information - Calculated by Firm

Statistical Analysis Data for Ln transformed parameters			
	C_{max}	AUC_{0-t}	AUC_{0-inf}
ANOVA p-value			
Sequence	0.8200	0.8225	0.8218
Period	0.1712	0.1064	0.1048
Treatment	0.6157	0.9145	0.9754
Geometric Least Square Mean for Test Product T	6.330	19.337	19.694
Geometric Least Square Mean for Reference Product R	6.478	19.257	19.671
Ratio of Geometric Least Square Means (%) (T/R)	97.7068	100.4121	100.1166
90% Confidence Interval (T Vs. R) Lower Limit	90.4602	94.1929	94.0029
90% Confidence Interval (T Vs. R) Upper Limit	105.5340	107.0420	106.6279
Intra Subject variability (%)	22.777	18.823	18.545
Inter Subject variability (%)	45.894	50.543	49.677

Is there a Tmax difference between T and R	No.; T/R = 1.125h/1.0 h =1.125
Are any CIs marginal?	No
Were the subjects dosed in groups?	No
Is the study design replicate and/or reference-scaled?	No
Is sampling time adequate?	Yes; AUCT/AUCi >90%

Comments on Pharmacokinetic and Statistical Analysis:

1. The firm's data on Alosetron are provided in Tables 16-19 and Fig. 1.
2. The 90% CIs of $\ln C_{max}$, $\ln AUC_t$ and $\ln AUC_i$ for Alosetron in the fasting study are tight and fall well inside the BE criteria of 80.0-125.0%. As per the current DB policy, the firm's statistical analyses were checked and found acceptable. Results are provided in Tables 17-18.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The fasting *in vivo* bioequivalence study is **adequate**.

Table 19. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

MEAN PLASMA CONCENTRATIONS - SCHEDULED SAMPLING TIMES

	0.00	0.17	0.33	0.50	0.75	1.00	1.25	1.50	1.75	2.00	2.25	2.50
	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12

TEST

Mean	0.000	0.162	1.658	3.819	6.149	6.757	6.699	6.247	5.765	5.332	4.864	4.493
SD	0.000	0.360	1.657	2.864	3.379	3.553	3.283	3.025	2.792	2.595	2.291	2.150
%CV	-	222.223	99.940	74.994	54.953	52.583	49.008	48.424	48.431	48.669	47.102	47.853
Min	0.000	0.000	0.000	0.000	0.317	0.645	1.260	1.709	1.562	1.349	1.239	1.160
Max	0.000	2.074	8.006	13.104	14.617	19.472	18.686	18.645	17.639	16.407	14.440	13.809

TEST

	2.75	3	3.5	4	4.5	5	6	7	8	10	12
	T13	T14	T15	T16	T17	T18	T19	T20	T21	T22	T23
Mean	4.069	3.645	2.944	2.390	1.945	1.420	0.868	0.547	0.367	0.146	0.056
SD	2.005	1.809	1.530	1.358	1.158	0.897	0.561	0.391	0.296	0.160	0.099
%CV	49.276	49.630	51.971	56.821	59.538	63.170	64.632	71.481	80.654	109.590	176.786
Min	1.005	0.816	0.654	0.495	0.332	0.233	0.145	0.000	0.000	0.000	0.000
Max	12.882	11.489	9.896	8.693	7.316	5.530	3.165	2.280	1.714	0.812	0.502

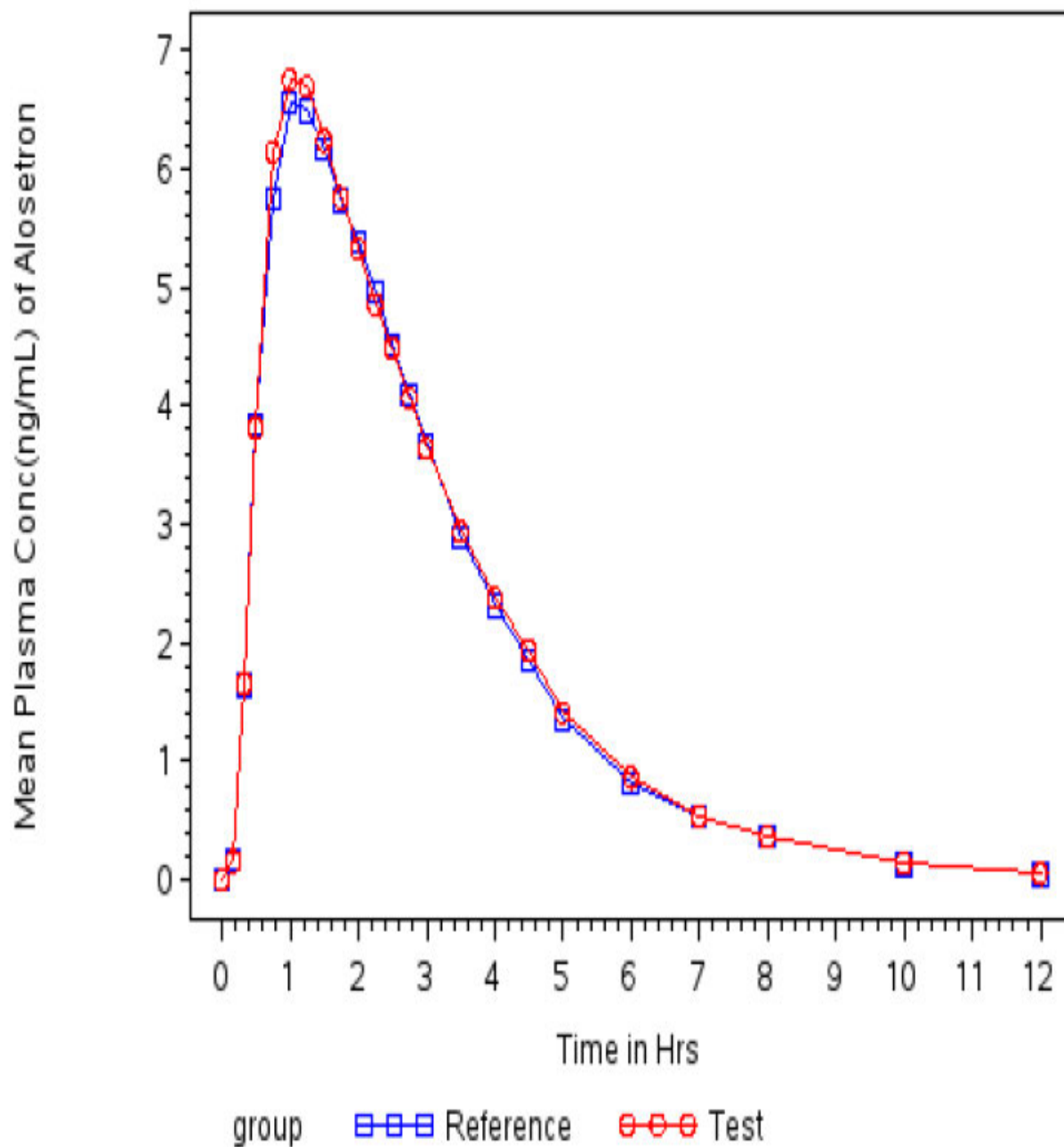
REFERENCE

	0.00	0.17	0.33	0.50	0.75	1.00	1.25	1.50	1.75	2.00	2.25	2.50
	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12
Mean	0.000	0.177	1.645	3.851	5.747	6.568	6.500	6.178	5.745	5.388	4.964	4.524
SD	0.000	0.534	2.198	3.235	3.139	3.367	2.943	2.782	2.500	2.437	2.211	2.081
%CV	-	301.695	133.618	84.005	54.620	51.264	45.277	45.031	43.517	45.231	44.541	46.000
Min	0.000	0.000	0.000	0.608	1.021	1.387	1.644	1.921	1.683	1.552	1.337	1.281
Max	0.000	3.498	12.666	16.463	13.807	19.086	18.029	17.875	16.314	15.757	13.403	12.825

REFERENCE

	2.75	3	3.5	4	4.5	5	6	7	8	10	12
	T13	T14	T15	T16	T17	T18	T19	T20	T21	T22	T23
Mean	4.092	3.669	2.895	2.325	1.858	1.364	0.823	0.539	0.367	0.133	0.053
SD	2.008	1.779	1.560	1.187	1.183	0.900	0.598	0.444	0.334	0.174	0.102
%CV	49.072	48.488	53.887	51.054	63.671	65.983	72.661	82.375	91.009	130.828	192.453
Min	1.079	1.067	0.799	0.606	0.478	0.306	0.000	0.000	0.000	0.000	0.000
Max	12.328	10.190	8.992	6.755	6.288	4.784	3.272	2.572	1.912	0.902	0.510

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study (n=48)



4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 20. Study Information

Study Number	ARL/12/484			
Study Title	A Randomized, Open Label, Balanced, Two-Treatment, Two-Period, Two-Sequence, Single Dose, Crossover, Bioequivalence Study of Alosetron Hydrochloride Tablets, 1 mg of Amneal Pharmaceuticals, USA with LOTRONEX® (alosectron hydrochloride) Tablets 1 mg of Prometheus Laboratories Inc. in Normal, Healthy, Adult, Female Human Subjects under Fed Condition.			
Study Type	☒ In Vivo BE	☐ In Vitro BE	☐ Permeability	☐ Other specify)
Submission Location:				
Study Report	5.3.1.2			
Validation Report	5.3.1.4			
Bioanalytical Report	5.3.1.4			
Clinical Site (Name, Address, Phone #, Fax #)	Accutest Research Lab (I) Pvt. Ltd. (Unit-I) 4 th Floor, The Grand Monarch, Near Seema Hall, Anand Nagar Road, Satellite, Ahmedabad- 380015, INDIA. Tel: +91 79- 4023 1700			
Principal Clinical Investigator (Name, Email)	Dr. Rupesh Vala, M.B.B.S. rupesh.vala@accutestindia.com			
Dosing Dates	Period I : 13 August 2013 Period II : 24 August 2013			
Analytical Site (Name, Address, Phone #, Fax #)	(b) (4)			
Analysis Dates	Start Date : 26 August 2013 End Date : 07 September 2013			
Principal Analytical Investigator (Name, Email)	(b) (4)			
Sample Storage :				

(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)	26 Days
(b) Temperature Range (e.g., -20° C to -80° C)	-70°C ± 10°C
Long-Term Storage Stability Coverage (no. days @ temp °C)	32 days at -20°C ± 5°C and -70°C ± 10°C

Table 21. Product Information

Product	Test		Reference	
Treatment ID	T		R	
Name of Product/Brand Name	Alosetron Hydrochloride Tablets, 1 mg (Name of Product)		LOTRONEX® (alosectron hydrochloride) Tablets 1 mg (Brand Name)	
Manufacturer	Manufactured by: Amneal Pharmaceuticals, USA		Prometheus Laboratories Inc. San Diego, CA 92121	
Lot No.	BE18413		HGHP	
Manufacture Date	June 3, 2013		N/A	
Expiration Date	N/A		July 2014	
Strength	1 mg		1 mg	
Dosage Form	Tablet		Tablet	
Bio-batch Size	(b) (4)		N/A	
Production Batch Size			N/A	
Potency	101.8%		98.8%	
Content Uniformity (mean, %CV)	No. of Units:	10	No. of Units:	10
	Min:	100.9%	Min:	95.2%
	Max:	102.2%	Max:	107.0%
	Mean:	101.6%	Mean:	101.5%
	AV:	1.2	AV:	9.0
Dose Administered	01 Tablet		01 Tablet	
Route of Administration	Oral		Oral	

Table 22. Study Design, Single-Dose Fed Bioequivalence Study

Number of Subjects	Enrolled: 48 Dosed: 47 Completed: 42 Samples Analyzed: 42 Data Analyzed: 42
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	11 days
Randomization Scheme (Sequence)	Yes; SEQ: TR and RT
Blood Sampling Times (hr)	0 (pre-dose), and at 00.17, 00.33, 00.50, 00.75, 01.00, 01.25, 01.50, 1.75, 02.00, 02.25, 02.50, 02.75, 03.00, 03.50, 04.00, 04.50, 05.00, 06.00, 7.00, 08.00, 10.00 and 12.00 hours after dosing
Blood Sample Processing/Storage	(b) (4)
Standard FDA Meal Used?	No. See the table below. The breakfast served is high fat high calorie breakfast.

Standard FDA Meal Used?	☐ Yes ☒ No				
If No, then meal components and composition is listed in the tables below					
Composition of Non-standard FDA Meal Used in Fed Bioequivalence Study					
Ingredients	Amount	Energy (K Cal)	Protein (K Cal)	Fat (K Cal)	Carbohydrate (K Cal)
Whole Milk	240mL	156.9	31.60	80.10	45.20
French Fries	70g	220.1	10.80	101.70	107.60
Chicken fry	35g	81.3	40.80	36.90	3.60
Toasted Bread Butter	45g	123.2	15.60	3.60	104.00

ANDA 206647
Single-Dose Fed Bioequivalence Study Review

(2 slices of toast with butter)	20g	145.8	0.00	145.80	0.00
Egg Fry (2 eggs fried in butter)	~90g	209.8	53.20	156.60	0.00
TOTAL	NA	937.1	152	525	260
PERCENTAGE	NA	NA	16.22	56.00	27.79

NA = Not Applicable

Comments on Study Design:

Per FDA Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies (December, 2002), *a high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800-1000 calories) meal is recommended as a test meal for food-effect BA and fed BE studies. The test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively.* Based on the meal menu provided by the firm, the total energy from the meal is 937.1 kcal and the energy from protein, carbohydrates and fat is 152, 260 and 525 kcal, respectively. Although the firm used a modified high-fat high calorie breakfast in the fed bioequivalence study, the caloric breakdown of the test meal provided by the firm is consistent with the agency recommendation.

The study design is **acceptable**.

4.1.2.2 Clinical Results

Table 23. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No. ARL/12/484			
		Treatment Groups	
		Test Product T N=42	Reference Product R N =42
Age (years)	Mean ± SD	36.69 ± 05.62	36.69 ± 05.62
	Range	22 - 45	22 - 45
Age Groups	< 18	Nil	Nil
	18 – 40	29 (69.05 %)	29 (69.05 %)
	41 – 64	13 (30.95 %)	13 (30.95 %)
	65 – 75	Nil	Nil
	> 75	Nil	Nil
Sex	Male	00 (00.00 %)	00 (00.00 %)
	Female	42 (100.00 %)	42 (100.00 %)
Race	Asian	42 (100.00%)	42 (100.00%)
	Black	Nil	Nil
	Caucasian	Nil	Nil
	Hispanic	Nil	Nil
	Other	Nil	Nil
BMI (Kg/m2)	Mean ± SD	23.43 ± 01.51	23.43 ± 01.51
	Range	19.72 - 24.88	19.72 - 24.88
Other Factors		-	-

Table 24. Dropout Information, Fed Bioequivalence Study

Study No. ARL/12/484				
Subject No	Reason for dropout/replacement*	Period	Replaced?	Replaced with
(b) (6)	Subject was withdrawn from the study at 16:40 on (b) (6) due to adverse event. Treatment given was reference product R in Period-II.	II	NA	NA
	Subject was withdrawn from the study at 14:54 on (b) (6) due to adverse event. Treatment given was reference product R in Period-II.	II	NA	NA
	Subject was withdrawn from the study at 11:18 on (b) (6) due to adverse event. Treatment given was test product T in Period-II.	II	NA	NA
	Subject was dropped out from the study at 21:10 on (b) (6) due to personal reason. No any treatment was given.	I	NA	NA
	Subject was withdrawn from the study at 10:36 on (b) (6) due to adverse event. Treatment given was reference product R in Period-I.	I	NA	NA
	Subject was withdrawn from the study at 14:33 on (b) (6) due to adverse event. Treatment given was reference product R in Period-I.	II	NA	NA

Table 25. Study Adverse Events, Fed Bioequivalence Study

Body System/Adverse Event	Reported Incidence by Treatment Groups	
	Fed Bioequivalence Study No. ARL/12/484	
	Test Product T N=45	Reference Product R N=47
Gastrointestinal Tract		
Abdominal Pain	01 (02.22 %)	01 (02.13 %)
Vomiting	00 (00.00 %)	01 (02.13 %)
Whole Body		
Fever	00 (00.00 %)	02 (04.26 %)
Total	01 (02.22 %)	04 (08.51 %)

Subjects Experiencing Emesis (Include in eCTD)

Subject Number*	Test/Reference	Period	Time Post-Dose	Duration Between Dosing and Emesis (hrs)
(b) (6)	R	I	10:29 am	1 hr 7 min.

Was the adverse event profile observed during the fasting bioequivalence study comparable for the test and reference product? Yes

Are there any serious adverse events or death? If so, are they reported to the OGD Safety Committee? No

Are there any other safety concerns based on the adverse event profile? No

Table 26. Protocol Deviations, Fed Bioequivalence Study

Study No. ARL/12/484		
Type	Subject #s (Test)	Subject #s (Ref.)
Pre-dose Housing Deviation	(b) (6)	
Blood Sample Time Point Deviation		

Table 27. Blood Sampling Deviations, Fed Bioequivalence Study

Sr.No.	Period	Subject No.	Sampling Hour	Schedule Time	Actual Time	Deviation (Min)	Deviation (Hrs)	Actual Sampling Hour	Reason	Action Taken
01	I	(b) (6)	01.00	10:22	10:25	03.00	00.05	01.05	Difficulty with vein	Cannula Replaced
02	II	(b) (6)	03.50	12:52	12:55	03.00	00.05	03.55	Difficulty with vein	N.A

Comments on Adverse Events/ Drop Out/Protocol Deviations:

Adverse Events: A total of five (05) AEs were reported during the entire course of the study. Out of five (05), one (01) AE (02.22 %) was observed in test product (T) treated subject and four (04) AEs (08.51 %) were observed in reference product (R) treated subjects. All reported AEs were possibly or probably related to the study medication and mild to moderate in severity. All reported AEs were followed up till resolution. No serious or significant adverse events were observed during the entire course of the study.

Subject (b) (6) Per I, R was dosed at 9:22 am and had emesis at 10:29 am (1 hr 7 min post-dose). This is within 2 x T_{max} (median, 2.375 hours) for the Reference product (current study). Therefore, withdrawal of Subject (b) (6) from the study is appropriate.

Subjects (b) (6) who had adverse events, were treated with concomitant medications, e.g., Cyclopam, Paracetamol or Uthral tablets. The firm did not carry out the methods validation to demonstrate any interference in the analysis. However, all these subjects were dropped from the study. Therefore, the additional methods validation with the concomitant medications will not be requested from the firm.

Drop Out: The reviewer verified the CRFs. The adverse event and emesis were recorded on the CRFs. Dropout of subjects is appropriate.

Protocol Deviations

The reviewer agrees with the firm that pre-dose housing deviation has no impact on the study outcome as 10 hours fasting condition prior to dosing was maintained.

Blood sampling time deviations were minor. In addition, the firm reported that the actual blood sample time points were considered for the calculation of PK parameters. The blood sample time deviations would not affect the study outcome.

The clinical observations are **acceptable**

4.1.2.3 Bioanalytical Results

Table 28. Assay Validation – Within the Fed Bioequivalence Study

Bioequivalence Study No. ARL/12/484									
Alosetron									
Parameter	Standard Curve Samples								
Concentration (ng/mL)	0.100	0.200	0.500	1.500	2.875	5.625	8.500	11.875	14.000
Inter day Precision (%CV)	2.04	4.41	2.68	2.38	2.54	2.54	2.02	2.28	3.16
Inter day Accuracy (%Actual)	98.00	102.00	104.60	100.93	101.39	97.28	98.36	98.24	99.21
Linearity	0.9964 to 0.9997								
Linearity Range (ng/mL)	0.100 ng/mL to 14.000 ng/mL								
Sensitivity/LOQ (ng/mL)	0.100 ng/mL								
Bioequivalence Study No. ARL/12/484									
Alosetron									
Parameter	Quality Control Samples								
	LQC		M1QC		MQC		HQC		
Concentration (ng/mL)	0.285		2.000		4.375		11.750		
Inter day Precision (%CV)	4.91		4.02		3.88		3.70		
Inter day Accuracy (%Actual)	100.00		103.20		96.59		95.23		
Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?					Yes				
Are there any concerns related to sample reanalysis or run rejection?					No. During the study sample analysis 49 (45 for study and 4 for ISR) calibration curves were generated. 48 Runs were acceptable. Run (b) (6) was rejected, because the linearity did not meet the acceptance criteria.				
Were 20% of chromatograms included?					Yes. (b) (6)				
Did the firm provide numerical raw data (e.g. peak height, peak area, response count of IS and analyte) in run sequence order (i.e. Run log) in the instrument printout format?					Yes				

Comments on Study Assay Validation: Acceptable.

Comments on Chromatograms: Acceptable.

Table 29. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP (b) (4)	SOP Title
		REPEAT SAMPLE ANALYSIS

Comments: The firm's within study method validation for the fed study is **acceptable**.

- The firm used same anticoagulant (K3EDTA) for methods validation, CC standards, QC samples and for analytical samples.
- The firm conducted Incurred Samples Reanalysis (ISR) in which 93.41% of ISR samples met the acceptance: 67% of the ISR results should be within 20% of the mean value [(repeat value + original value)/2].
- The analytical portion of the fed study is **adequate**.

4.1.2.4 Pharmacokinetic Results

Table 30. Arithmetic Mean Pharmacokinetic Parameters

period	C_{max}	t_{max}	AUC_{0-t}	AUC_{0-inf}	AUC_t/AUC_{inf}	K_{el}	first time_point	last time_point	$T_{1/2}$
	ng/mL	hrs	ngxhr/mL	ngxhr/mL	%	hrs ⁻¹	hrs	hrs	hrs
TEST									
Mean	4.278	2.339	17.042	17.523	97.222	0.397	4.935	11.000	1.806
SD	1.627	0.769	6.773	6.989	1.065	0.073	1.920	1.343	0.329
%CV	38.022	32.861	39.740	39.884	1.096	18.471	38.908	12.213	18.205
Median	4.098	2.500	15.990	16.298	97.365	0.394	4.500	12.000	1.761
Min	1.605	0.750	7.162	7.504	93.913	0.283	1.750	8.000	1.172
Max	8.869	4.500	35.045	35.907	98.772	0.591	8.000	12.000	2.452
REFERENCE									
Mean	4.112	2.494	16.441	16.937	96.968	0.401	4.887	10.810	1.778
SD	2.006	0.973	7.612	7.800	1.032	0.069	2.015	1.401	0.307
%CV	48.775	39.010	46.299	46.056	1.064	17.083	41.224	12.961	17.256
Median	3.643	2.375	14.509	14.960	96.996	0.397	4.000	12.000	1.745
Min	1.830	0.750	7.976	8.258	93.908	0.272	1.500	8.000	1.253
Max	12.061	4.500	41.039	41.637	98.565	0.553	8.000	12.000	2.543

Table 31. Geometric Means and 90% Confidence Intervals - Firm Calculated

Reference Scaled Average Bioequivalence Approach Used				☐ Yes ☒ No		
If No, then complete Table 3A only						
If Yes, then complete Tables 3A and 3B						
Alosetron Hydrochloride Tablets, 1 mg						
(No of subjects completed= 42)						
Dose (1 x 1 mg tablet)						
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study (Study No.: ARL/12/484)						
Parameter	Test	N	RLD	N	Ratio	90% C.I.
AUC _{0-t}	15.870	42	15.007	42	105.7486	99.7088-112.1543
AUC _∞	16.326	42	15.477	42	105.4891	99.6360-111.6859
C _{max}	4.010	42	3.742	42	107.1419	99.3821-115.5076

Table 32. Additional information - Firm Calculated

Statistical Analysis Data for Ln-transformed parameters			
	C _{max}	AUC _{0-t}	AUC _{0-inf}
ANOVA p-value			
Sequence	0.5067	0.6012	0.5904
Period	0.0980	0.1836	0.1447
Treatment	0.1302	0.1174	0.1228
Geometric Least Square Mean for Test Product T	4.010	15.870	16.326
Geometric Least Square Mean for Reference Product R	3.742	15.007	15.477
Ratio of Geometric Least Square Means (%) (T/R)	107.1419	105.7486	105.4891
90% Confidence Interval (T Vs. R) Lower Limit	99.3821	99.7088	99.6360
90% Confidence Interval (T Vs. R) Upper Limit	115.5076	112.1543	111.6859
Intra Subject variability (%)	20.653	16.090	15.611
Inter Subject variability (%)	35.882	39.109	38.980

Is there a Tmax difference between T and R	No; T/R = 2.5h/2.375 h =1.0526
Are any CIs marginal?	No
Were the subjects dosed in groups?	No
Is the study design replicate and/or reference-scaled?	No
Is sampling time adequate?	Yes; AUCT/AUCi >90%

Overall Comment:

1. The firm's data on Alosetron are provided in Tables 30-33 and Fig. 2.
2. The 90% CIs of lnC_{max}, lnAUC_t and lnAUC_i for Alosetron in the fasting study are tight and fall well inside the BE criteria of 80.0-125.0%. As per the current DB policy, the firm's statistical analyses were checked and found acceptable. Results are provided in Tables 31-32.
3. As per the RLD labeling "Alosetron absorption is decreased by approximately 25% by co-administration with food, with a mean delay in time to peak concentration of 15 minutes", when the drug product is taken with a high-fat meal. In the current fed study, C_{max} was ~40% lower, AUC_t and AUC_i was ~20% lower and T_{max} delayed ~1.25 hours for both test and RLD products when compared to those in the fasting study.

Summary/Conclusions, Single-Dose Fed Bioequivalence Study:

The single dose fed bioequivalence study is **adequate**.

Table 33. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

MEAN PLASMA CONCENTRATIONS - SCHEDULED SAMPLING TIMES
TEST

	0.00	0.17	0.33	0.50	0.75	1.00	1.25	1.50	1.75	2.00	2.25	2.50
	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12
Mean	0.000	0.035	0.326	0.693	1.284	1.793	2.336	2.747	3.123	3.358	3.529	3.683
SD	0.000	0.141	0.801	1.239	1.587	1.678	1.727	1.629	1.603	1.569	1.510	1.541
%CV	-	402.858	245.706	178.788	123.599	93.587	73.930	59.302	51.329	46.725	42.789	41.841
Min	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.119	0.226	0.392	0.650	0.870
Max	0.000	0.850	4.116	6.158	7.500	7.694	7.642	6.661	6.818	7.042	7.832	8.370

TEST

	0.00	0.17	0.33	0.50	0.75	1.00	1.25	1.50	1.75	2.00	2.25	2.50
	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12
Mean	3.612	3.567	3.170	2.812	2.405	1.924	1.260	0.834	0.565	0.255	0.115	
SD	1.502	1.537	1.319	1.227	1.068	0.914	0.657	0.457	0.342	0.183	0.128	
%CV	41.584	43.090	41.609	43.635	44.408	47.506	52.143	54.797	60.531	71.765	111.305	
Min	1.082	1.420	1.337	1.108	0.826	0.661	0.370	0.216	0.131	0.000	0.000	
Max	8.650	8.869	7.065	6.313	6.013	5.093	3.577	2.406	1.917	0.967	0.604	

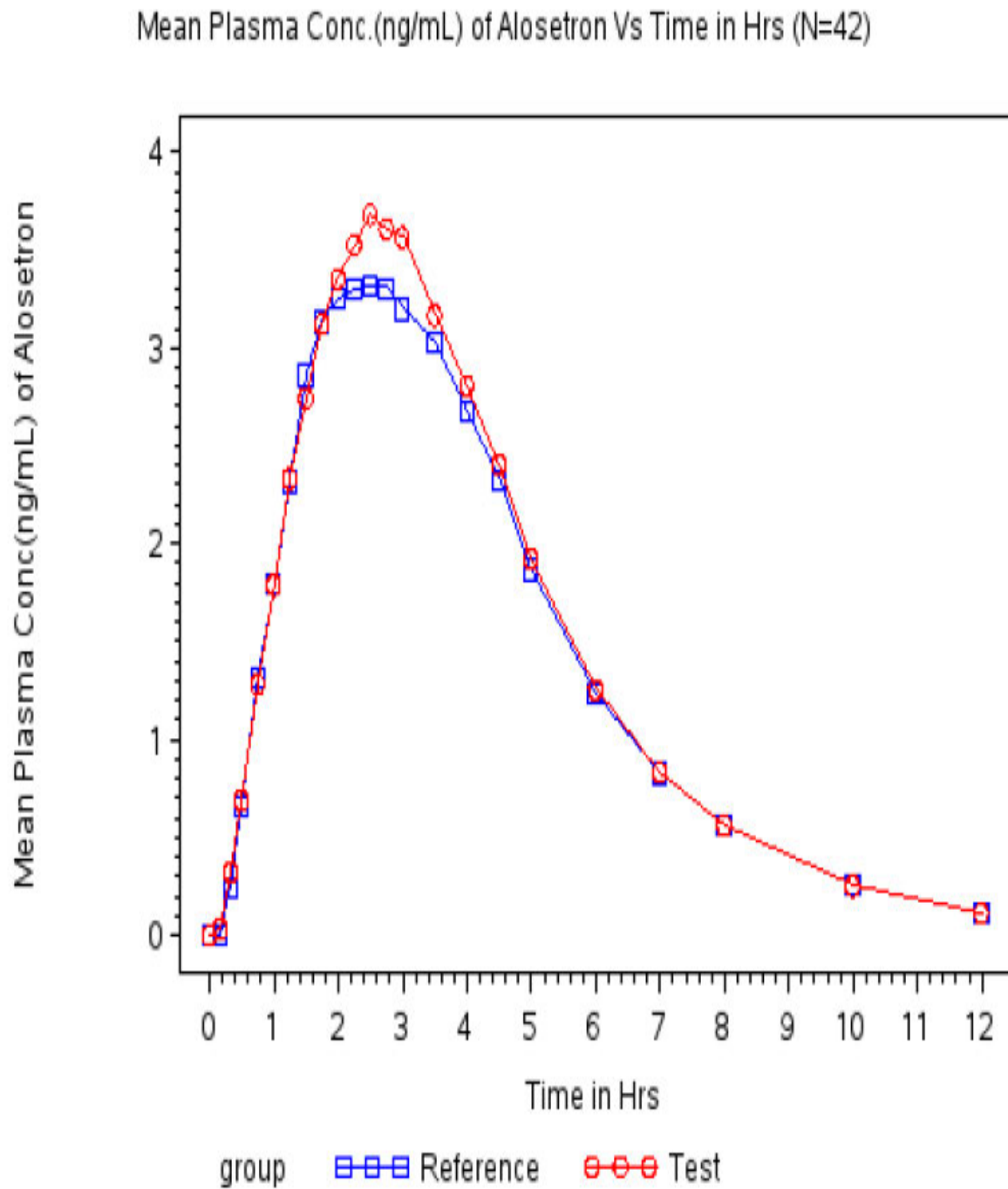
REFERENCE

	0.00	0.17	0.33	0.50	0.75	1.00	1.25	1.50	1.75	2.00	2.25	2.50
	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12
Mean	0.000	0.007	0.250	0.666	1.324	1.796	2.322	2.865	3.136	3.253	3.299	3.318
SD	0.000	0.030	0.417	1.024	1.804	1.907	2.008	2.240	2.222	1.910	1.772	1.676
%CV	-	428.572	166.800	153.754	136.254	106.181	86.478	78.185	70.855	58.716	53.714	50.513
Min	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.131	0.357	0.630	0.865	1.095
Max	0.000	0.150	1.290	4.359	8.771	8.446	8.773	11.673	12.061	9.930	9.810	9.494

REFERENCE

	2.75	3	3.5	4	4.5	5	6	7	8	10	12
	T13	T14	T15	T16	T17	T18	T19	T20	T21	T22	T23
Mean	3.310	3.199	3.033	2.684	2.332	1.872	1.237	0.830	0.569	0.261	0.113
SD	1.516	1.308	1.271	1.234	1.051	0.923	0.654	0.465	0.360	0.202	0.129
%CV	45.801	40.888	41.906	45.977	45.069	49.306	52.870	56.025	63.269	77.395	114.160
Min	1.331	1.363	1.397	1.097	0.849	0.598	0.406	0.260	0.143	0.000	0.000
Max	8.624	7.327	6.485	6.183	5.173	4.351	2.730	2.025	1.694	0.847	0.432

Figure 2. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



4.2 Formulation Data

Table 33. Components and Composition of Test Product

Ingredients	Eq. 0.5 mg base		Eq. 1 mg base	
	mg/tab	%w/w	mg/tab	%w/w
Alosetron Hydrochloride	0.562 [*]	(b) (4)	1.124 ^{\$}	(b) (4)
				(b) (4)
Microcrystalline Cellulose, (b) (4)				(b) (4)
Pregelatinized Starch, (b) (4)				
Lactose Anhydrous, (b) (4)				
Magnesium Stearate, (b) (4)				(b) (4)
				(b) (4)
				(b) (4)
Finished Product Weight	155.00	100.00	155.00	100.00

*0.562 mg of Alosetron Hydrochloride is equivalent to 0.5 mg of Alosetron.

^{\$}1.124 mg of Alosetron Hydrochloride is equivalent to 1 mg of Alosetron.

Reviewer's Note: There is [REDACTED] of Alosetron Hydrochloride Tablets 0.5 mg and 1 mg.

Table 36. Maximum Daily Intake (MDI) of Excipients and IID Limits

**Are the amounts of all inactive ingredients based on
Maximum Daily Dose (MDD) within IIG (per unit) limits?**

YES

If no, are they all above/within IIG (per day) limits?

YES

Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	Yes. The total weight of each tablet is the same. The inactive ingredients of the core (b) (4)
--	---

Comments: The formulations of test product, Alosetron HCl Tablet, 0.5 mg and 1 mg are acceptable.

Summary of In Vitro Dissolution Studies – Comparison of Alosetron HCl tablets, 1.0 mg

Overall Comment:

The dissolution-only review has been conducted.¹³ There is no USP dissolution method for this product but there is an FDA-recommended method. The firm conducted acceptable dissolution testing using the FDA-recommended dissolution method (500 ml of Water (deaerated), using apparatus II (paddle) at 50 rpm (1 mg) / 75 rpm (0.5 mg)). However, the firm proposed specification (NLT (b) (4) (Q) in (b) (4) was not acceptable. Based on the data submitted, the Division of Bioequivalence II (DB II) recommended the following specification; NLT (b) (4) (Q) in 20 minutes. The firm has accepted the FDA-recommended dissolution method and specification.¹⁴

Since greater than (b) (4) of drug release has been achieved at 20 minutes time point for both test and reference products of 1 mg and 0.5 mg strengths, the calculation of f2 values are not necessary for comparison of the dissolution profiles between the 1 mg (Lot # BE18413) and 0.5 mg (Lot # BE17813) of the test products. Both strengths of the test products are rapidly dissolving in the dissolution medium. The dissolution profiles of 1mg and 0.5 mg strengths of the test product are considered comparable.

¹³ DARRTS ANDA 206647, RAINES, KIMBERLY W 08/20/2014 N/A 08/20/2014 REV-BIOEQ-02(Dissolution Review)

¹⁴ DARRTS ANDA 206647, BABAA, NABEEL 09/24/2014 N/A 09/24/2014 REV-BIOEQ-02(Dissolution Review)

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 206647

APPLICANT: Amneal Pharmaceuticals

DRUG PRODUCT: Alosetron Hydrochloride Tablet, EQ 0.5 mg base and EQ 1.0 mg base

The Division of Bioequivalence I (DBI) has completed its review and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{ See appended electronic signature page }

Wayne DeHaven, Ph.D.
Acting Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

**DIVISION OF BIOEQUIVALENCE
DISSOLUTION ACKNOWLEDGEMENT REVIEW**

ANDA No.	206647
Drug Product Name	Alosetron Hydrochloride Tablets
Strength (s)	EQ 0.5 mg and 1 mg BASE
Applicant Name	Amneal Pharmaceuticals
Applicant Address	85 Adams Avenue Hauppauge, NY 11788
US Agent Name and the mailing address	Alpesh Patel, Vice President, Global Regulatory Affairs Same address as above
US Agent's Telephone Number	(b) (6)
US Agent's Fax Number	(631) 527-3523
Original Submission Date(s)	December 24, 2013
Submission Date(s) of Amendment(s) Under Review	September 10, 2014 – Dissolution Acknowledgement
First Generic	No
Reviewer	Nabeel Babaa, Pharm.D.
OVERALL DISSOLUTION REVIEW RESULT	ADEQUATE

EXECUTIVE SUMMARY

This is a review of the dissolution method and/or specification acknowledgement from the firm. The firm has accepted the following FDA-recommended dissolution method and specification(s).

USP Apparatus:	II (paddle)
Rotational Speed:	50 rpm (1.0 mg) 75 rpm (0.5 mg)
Temperature:	37 ± 0.5 °C
Media:	Water (deaerated)
Volume:	500 mL
Specifications:	NLT (b) (4) (Q) in 20 minutes

RECOMMENDATIONS

From a bioequivalence point of view, the firm has met the requirements for in-vitro dissolution testing. The dissolution testing section of the application is adequate and we have no further questions at this time.

DISSOLUTION COMMENT TO BE PROVIDED TO THE APPLICANT

ANDA: 206647

APPLICANT: Amneal Pharmaceuticals

DRUG PRODUCT: Alosetron Hydrochloride Tablets, EQ 0.5 mg and 1.0 mg BASE

The Division of Bioequivalence II (DBII) has completed its review of your submission acknowledged on the coversheet and has no further questions at this time. We acknowledge that you will conduct the dissolution testing of your test product using the following FDA-recommended dissolution method and specification:

USP Apparatus:	II (paddle)
Rotational Speed:	50 rpm (1.0 mg) 75 rpm (0.5 mg)
Temperature:	37 ± 0.5 °C
Media:	Water (deaerated)
Volume:	500 mL
Specifications:	NLT (b) (4) (Q) in 20 minutes

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R.Ph.
Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

Completed Assignment for 206647 ID: 24125

Reviewer: Babaa, Nabeel

Date Completed:

Verifier: Mahadevan, Chitra

Date Verified: 19SEP2014

Division: Division of Bioequivalence

Description: Diss ack

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
24125	9/18/2014	Dissolution Data (REGULAR)	Dissolution Acknowledgement	0	0
				Total:	0

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

/s/

NABEEL BABAA

09/23/2014

CHITRA MAHADEVAN

09/24/2014

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	206647
Drug Product Name	Alosetron Hydrochloride Tablets
Strength (s)	EQ 0.5 mg and 1 mg BASE
Applicant Name	Amneal Pharmaceuticals
Applicant Address	85 Adams Avenue Hauppauge, NY 11788
US Agent Name and the mailing address	Alpesh Patel, Vice President, Global Regulatory Affairs alpesh@amneal.com
US Agent's Telephone Number	(b) (6)
US Agent's Fax Number	(631) 527-3523
Original Submission Date(s)	December 24, 2013
Submission Date(s) of Amendment(s) Under Review	N/A
Reviewer	Kimberly W. Raines, Ph.D.
Dissolution Method	ADEQUATE
OVERALL REVIEW RESULT	INADEQUATE

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

The reference listed drug (RLD) for this ANDA is Prometheus Labs' LOTRONEX® (alosectron hydrochloride) Tablets, NDA 021107, approved, February 9, 2000 (EQ 1 mg BASE)¹.

There is no USP dissolution method for this product but there is an FDA-recommended method. The firm conducted acceptable dissolution testing using the FDA-recommended dissolution method (500 ml of Water (deaerated), using apparatus II (paddle) at 50 rpm (1 mg) / 75 rpm (0.5 mg)). However, the firm proposed specification (NLT (b) (4) (Q) in (b) (4) (b) (4)) is not acceptable. Based on the data submitted, the Division of Bioequivalence II (DB II) recommends the following specification; NLT (b) (4) (Q) in 20 minutes. The firm should indicate if it accepts the FDA-recommended dissolution specification.

The firm submitted an acceptable dissolution method validation report, (b) (4) "Validation of Analytical Procedure for Dissolution **Product Name: Alosetron Hydrochloride Tablets, 05 mg and 1.0 mg**".

The *in vitro* dissolution testing is **inadequate** pending firm's acceptance of the above FDA recommended method and data driven specification.

The DB II will review the bioequivalence (BE) studies and waiver request at a later date.

¹ Electronic Orange Book <http://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm>

DISSOLUTION REVIEW

I.1 Submission Content Checklist

Information	YES	NO	N/A
Is there a posted dissolution method on the FDA website?	☒	☐	☐
Did the firm use the above method?	☒	☐	☐
Is there a USP dissolution method?	☐	☒	☐
Did the firm use the USP dissolution method?	☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing?	☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)?	☒	☐	☐
Did the firm conduct dissolution testing with its own proposed method?	☐	☒	☐
Did the firm submit dissolution method validation?	☒	☐	☐

I.2 Dissolution Method As Posted on the FDA Website

External Dissolution Database:

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Alosetron HCl	Tablet	II (Paddle)	50 (for 1 mg) & 75 (for 0.5 mg)	Water (deaerated)	500	10, 20, 30 and 45	01/26/2006

Internal Dissolution Database:

Alosetron HCl

Dosage Form: Tablet

Medium: Water (deaerated)

Apparatus: II (Paddle)

Speed/RPMs: 50 (for 1 mg) & 75 (for 0.5 mg)

Modify Date: 1/26/2006

Sampling Times: 10, 20, 30 and 45

Volume: 500

Notes:

Specification:

NDA method:

Alosetron Hydrochloride Tablets

Dosage form:	Tablet
Modified Date:	10/01/2009
USP Apparatus:	II (paddle)
Rotational Speed:	75 rpm (0.5 mg) 50 rpm (1.0 mg)
Temperature:	37 ± 0.5 °C
Media:	De-aerated (b) (4) water
Volume:	500 mL
Sampling times:	20 minute for a single point determination. If required additional samples may be taken at appropriate times in order to generate a dissolution profile.
Specifications:	NLT (b) (4) drug release in 20 minutes (b) (4)
Notes:	(b) (4) DARRTS NDA 021107 New/annual report submitted 10/1/2009

OGD History:

In-House Alosetron HCl Tablets	Dissolution Method	FDA-Recommended Dissolution Specifications
ANDA 200652 ²	FDA-recommended	NLT (b) (4) (Q) in 20 minutes
ANDA 206113	FDA-recommended	pending

² DARRTS ANDA 200652 REV-BIOEQ-01(General Review) 05/20/2010

Dissolution Method SOP effective at the time of testing (Yes/No)	Yes (Analysis Date: July 12, 2013) (b) (4) “Analytical Procedure for Dissolution Product Name: Alosetron Hydrochloride Tablets, 05 mg and 1.0 mg ” <i>In place prior to 05/31/2013</i>
Were the drug product units pooled during the dissolution testing (Yes/No)?	No
Was the dissolution testing conducted on the bio-batch?	Yes Lot #: BE18413
Age of the test product at the time of dissolution testing.	One Month
Was the reference product expired at the time of dissolution testing (Yes/No)	No
Comments on the variability of the dissolution data	The variability of the dissolution data is acceptable (<10%).

II. Reviewer's Comments for Dissolution Testing

1. There is no USP method available for this product but there is an FDA-recommended method. The firm conducted acceptable dissolution testing using the following FDA-recommended dissolution method.

USP Apparatus:	II (paddle)
Rotational Speed:	50 rpm (1 mg) 75 rpm (0.5 mg)
Temperature:	37 ± 0.5 °C
Media:	Water (deaerated)
Volume:	500 mL

2. The firm's proposed specification (NLT (b) (4) (Q) in (b) (4)) is not acceptable. Based on the data submitted, the DBII recommends the following data-driven specification: NLT (b) (4) (Q) in 20 minutes. The firm should indicate if it accepts above FDA- recommended dissolution specification.

	Dissolution Data (Mean, Range)		
Firm's proposed Specification	DB II recommended Specification	1.0 mg	0.5 mg
---	NLT (b) (4) (Q) in 20 minutes	96 (b) (4)	96 (b) (4)
NLT (b) (4) (Q) in (b) (4)	---	98 (b) (4)	96 (b) (4)

It is noted that one tablet fails to meet the firm's specification at (b) (4)

3. The firm's submitted dissolution testing data on the test product, Alosetron Hydrochloride Tablets, contains drug release percentages greater than (b) (4) (maximum value = (b) (4)). Dissolution values greater than (b) (4) are justified, as all reported values are within the Assay range (NLT (b) (4) and NMT (b) (4) of the labeled amount of Alosetron) specification for the final test product formulation.

III. Deficiency Comment for Dissolution Testing

There is no USP method for this product but there is an FDA-recommended method. The firm conducted acceptable dissolution testing using the FDA-recommended method. However, the firm's proposed dissolution specification of NLT (b) (4) (Q) in (b) (4) is not acceptable. Based on the data submitted, the DB II recommends following dissolution method and specification:

USP Apparatus:	II (paddle)
Rotational Speed:	50 rpm (1.0 mg) 75 rpm (0.5 mg)
Temperature:	37 ± 0.5 °C
Media:	Water (deaerated)
Volume:	500 mL
Specifications:	NLT (b) (4) (Q) in 20 minutes

The firm should indicate if it accepts above FDA-recommended dissolution method and specifications.

IV. Dissolution Recommendations

The *in vitro* dissolution testing conducted by Amneal Pharmaceuticals on its test product, Alosetron Hydrochloride Tablets, 1.0 mg (Lot #BE18413) and 0.5 mg (Lot #BE17813), comparing to the reference product, Prometheus Labs' LOTRONEX® (alosetron hydrochloride) Tablets, 1.0 mg (Lot #HGHP) and 0.5 mg (Lot #HPND) is inadequate due to the deficiency cited above.

BIOEQUIVALENCE DEFICIENCY TO BE PROVIDED TO THE APPLICANT

ANDA: 206647

APPLICANT: Amneal Pharmaceuticals

DRUG PRODUCT: Alosetron Hydrochloride Tablets, EQ 0.5 mg and
1.0 mg BASE

The Division of Bioequivalence II (DB II) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies and waiver request will be conducted later. The following deficiency has been identified:

You have conducted acceptable dissolution testing using the FDA-recommended dissolution method. However, your proposed dissolution specification of NLT (b) (4) in (b) (4) is not acceptable. Based on the data submitted, the DB II recommends the following dissolution method and specification:

USP Apparatus:	II (paddle)
Rotational Speed:	50 rpm (1.0 mg) 75 rpm (0.5 mg)
Temperature:	37 ± 0.5 °C
Media:	Water (deaerated)
Volume:	500 mL
Specifications:	NLT (b) (4) (Q) in 20 minutes

Please indicate if you accept the above FDA-recommended dissolution method and specification.

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R.Ph.
Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

V. OUTCOME

ANDA: 206647

Completed Assignment for 206647 ID: 23652

Reviewer: Raines, Kimberly

Date Completed:

Verifier:

Date Verified:

Division: Division of Bioequivalence

Description: Alosetron HCl Tabs

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
23652	12/24/2013	Dissolution Credit (DRGC)	Dissolution Review for Dissolution-Only Credit	1	1
				Total:	1

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/s/

KIMBERLY W RAINES
08/20/2014

ANIL K NAIR
08/20/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 206647

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

From: Barley, Stacy
To: alpesh@amneal.com
Subject: ANDA 206647 alosetron: REMS information request
Date: Thursday, October 27, 2016 3:01:00 PM
Attachments: [2016 10 25 Alosetron SS rems-doc-redline-20160923.docx](#)

Hello,

Please refer to your pending Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for alosetron.

We are reviewing your September 23, 2016 REMS submission and have the following comments and information request:

The comments (b) (4) are based on the Agency's review of the proposed REMS modification for alosetron submitted under ANDA 206647. In order to facilitate further review, we ask that you respond to these comments within 7 business days.

A. General Comments

1. We have provided a revised REMS document for the alosetron REMS program. A complete REMS including the REMS document, all appended materials and REMS Supporting Document should be submitted to each application. Submit both a Word tracked changes version and a Word clean version of each of these documents, as well as a pdf version of each of the previously mentioned documents and appended materials. We ask that you respond to these comments and re-submit all documents by November 4, 2016.

2. Revise the name of the stakeholders to Alosetron Sponsors (b) (4)
(b) (4) The sponsor name should be changed throughout all the materials. This is in line with the Agency's current thinking on the naming of REMS program Sponsors. This will not affect the name of the REMS program (Alosetron REMS Program) but used only when referring to the Sponsors (Alosetron Sponsors). For example, the "Alosetron Sponsors will ensure training...." and "Alosetron REMS Program Patient Education Sheet" are correct usages.

B. REMS Document

(b) (4)

C. Website

1. Under both the Prescriber Heading and Resource Headings of the website, the new sections encompassing PDF links to each sponsors' alosetron Prescribing Information and Medication Guides should be entitled "Prescribing Information and Medication Guide." It is not necessary to use the term (b) (4) when describing the Prescribing Information.

Please continue to communicate with the Alosetron REMS contact to ensure your revisions are in alignment with the Alosetron REMS group.

Contact me if you have any questions.

Regards,

Stacy

*Stacy Barley, RN, M.S.N., M.S.H.A.
CDR (CAPT sel), USPHS Commissioned Corps
Senior Program Management Officer Consultant
REMS Coordinator
Office of Bioequivalence
OGD/CDER/FDA*

*WO 75, Room 2642
10903 New Hampshire Avenue*

Silver Spring, MD 20993

*(301) 796-2137 (office)
stacy.barley@fda.hhs.gov*

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/s/

STACY R BARLEY
11/13/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Mail: OSE Attention: Ginneh Stowe		FROM: CDR Stacy Barley, REMS Coordinator Team, 301-796-2137, CDER/OGD OGD RPM: Scott Dallas		
DATE 10/3/16	IND NO. N/A	ANDA NO. 206647	TYPE OF DOCUMENT Proposed REMS	DATE OF DOCUMENT 09/23/16
NAME OF DRUG Alosetron HCL		PRIORITY CONSIDERATION High	CLASSIFICATION OF DRUG Alosetron REMS	DESIRED COMPLETION DATE TAD: 11/25/16
NAME OF FIRM: Amneal				
REASON FOR REQUEST				
I. GENERAL				
☐ NEW PROTOCOL ☐ PROGRESS REPORT ☐ NEW CORRESPONDENCE ☐ DRUG ADVERTISING ☐ ADVERSE REACTION REPORT ☐ MANUFACTURING CHANGE/ADDITION ☐ MEETING PLANNED BY ☐ PRE--NDA MEETING ☐ END OF PHASE II MEETING ☐ RESUBMISSION ☐ SAFETY/EFFICACY ☐ CONTROL SUPPLEMENT ☐ RESPONSE TO DEFICIENCY LETTER ☐ FINAL PRINTED LABELING ☐ LABELING REVISION ☐ ORIGINAL NEW CORRESPONDENCE ☐ FORMULATIVE REVIEW ☒ OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):		☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
☐ DISSOLUTION ☐ BIOAVAILABILTY STUDIES ☐ PHASE IV STUDIES		☐ DEFICIENCY LETTER RESPONSE ☐ PROTOCOL-BIOPHARMACEUTICS ☐ IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below) ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY ☐ SUMMARY OF ADVERSE EXPERIENCE ☐ POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
☐ CLINICAL		☐ PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: The Office of Generic Drugs received a Proposed Shared System Alosetron REMS for the pending ANDA 206647 on September 23, 2017 from Amneal. The submission includes the REMS supporting documents, REMS Document and REMS materials. Alosetron currently has a waived REMS under ANDA 200652 (Roxane c/o West-Ward). This is the REMS system Amneal would like to join. We request your assistance in reviewing the REMS amendment. The TAD has passed and the REMS is the only outstanding item. Will base TAD on other pending ANDA.				
SIGNATURE OF REQUESTER CDR Stacy Barley		METHOD OF DELIVERY (Check all that apply) ☐ MAIL ☒ DARRTS ☐ HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

06/18/2013

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/s/

STACY R BARLEY
10/03/2016

From: Barley, Stacy
To: ["Candis Edwards"](#)
Cc: [Winiarski, Aleksander](#)
Subject: RE: Amneal: Alosetron REMS
Date: Tuesday, March 29, 2016 1:19:00 PM

Hello Candis,

Thank you again for the email below containing the status of your REMS as of January 12, 2016.

Do you have any additional updates regarding the REMS?

Regards,
Stacy

*Stacy Barley, RN, M.S.N., M.S.H.A.
CDR, USPHS Commissioned Corps
Senior Program Management Officer Consultant
REMS Coordinator
Office of Bioequivalence
CDER/FDA
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stacy.barley@fda.hhs.gov*

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From: Candis Edwards [<mailto:cedwards@amneal.com>]
Sent: Tuesday, January 12, 2016 4:42 PM
To: Barley, Stacy
Subject: Amneal: Alosetron REMS

Hello Stacy,

As per the conversation with Alpesh Patel, regarding a REMS update for ANDA # 206647; Alosetron Hydrochloride Tablet 0.5 mg and 1 mg, provided below is the update on the REMS status:

- Amneal is working on joining Roxane's Alosetron REMS Program
- A Confidentiality Agreement between Roxane and Amneal has been finalized
- A REMS Program Agreement between Roxane and Amneal is under review
- Discussions have been initiated between Roxane and Amneal regarding the REMS update to include Amneal's product
- Once the REMS Agreement is finalized, Amneal will join the program's weekly meeting and initiate updating the relevant documents to include Amneal's product.

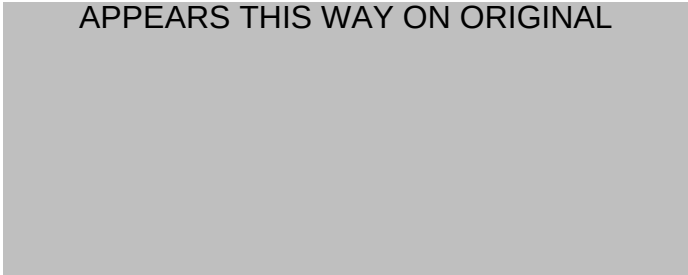
If you require any further information, please contact me as described below.

Regards,

Candis Edwards | Senior Vice President [Regulatory Affairs](#)| Amneal Pharmaceuticals |

85 Adams Avenue | Hauppauge, New York 11788 |
631.952.0214 X 338 main | 631.656.7538 direct | (b) (6) mobile | 646.351.0286 fax |
cedwards@amneal.com

APPEARS THIS WAY ON ORIGINAL



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/s/

STACY R BARLEY
03/29/2016

MEMORANDUM OF TELECONFERENCE

Teleconference Date: January 8, 2016

Application Number: ANDA 206647

Product Name: Alosetron Hydrochloride Tablets

Sponsor/Applicant Name: Amneal Pharmaceuticals LLC

Subject: Follow-up on the status of a response to the Risk Evaluation and Mitigation Strategy (REMS) Notification letter issued on January 2015.

FDA Participants :

CDR Stacy Barley, REMS Coordinator, Office of Bioequivalence, Office of Generic Drugs

Sponsor/Applicant Participants :

Alpesh Patel, Vice President, Global Regulatory Affairs, Amneal Pharmaceuticals

1.0 BACKGROUND:

On January 22, 2015, Amneal Pharmaceuticals LLC (Amneal) was issued a REMS Notification letter. The letter informed Amneal that Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. In accordance with section 505-1 of the FDCA, the FDA determined that a REMS was necessary for products containing alosetron hydrochloride to ensure the benefits of the drug outweigh the risk of ischemic colitis and serious complications of constipation.

The FDA letter also stated that pursuant to section 505-1(i) of the FDCA, an ANDA and the listed drug it references must use a single, shared system for the elements to assure safe use (ETASU) unless FDA waives that requirement. Amneal was provided the contact information for Prometheus (the sponsor of the reference listed drug Lotronex) to begin discussions related to the development and submission of a single shared system REMS.

Amneal prefers to work with Roxane when joining the REMS however no CDA has been signed.

2.0 DISCUSSION: A call was placed to Amneal to inquire about to status of the REMS and to ensure they were aware that a REMS modification was approved on yesterday for Lotronex and aolsetron products. Amneal was reminded that the lack of a REMS could impact their action and action date. Amneal verbalized understanding and will have a discussion with their team next week.

3.0 ACTION ITEMS: Amneal will follow up with the FDA next week regarding their plan to submit the REMS.

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/s/

STACY R BARLEY
01/08/2016

MEMORANDUM OF TELECONFERENCE

Teleconference Date: October 1, 2015

Application Number: ANDA 206647

Product Name: Alosetron Hydrochloride Tablets

Sponsor/Applicant Name: Amneal Pharmaceuticals LLC

Subject: Follow-up on the status of a response to the Risk Evaluation and Mitigation Strategy (REMS) Notification letter issued on January 2015.

FDA Participants :

CDR Stacy Barley, REMS Coordinator, Office of Bioequivalence, Office of Generic Drugs

Sponsor/Applicant Participants :

Candis Edwards, Senior Vice President, Clinical Affairs/Regulatory Affairs, Amneal Pharmaceuticals

1.0 BACKGROUND:

On January 22, 2015, Amneal Pharmaceuticals LLC (Amneal) was issued a REMS Notification letter. The letter informed Amneal that Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. In accordance with section 505-1 of the FDCA, the FDA determined that a REMS was necessary for products containing alosetron hydrochloride to ensure the benefits of the drug outweigh the risk of ischemic colitis and serious complications of constipation.

The FDA letter also stated that pursuant to section 505-1(i) of the FDCA, an ANDA and the listed drug it references must use a single, shared system for the elements to assure safe use (ETASU) unless FDA waives that requirement. Amneal was provided the contact information for Prometheus (the sponsor of the reference listed drug Lotronex) to begin discussions related to the development and submission of a single shared system REMS.

As of today, the sponsor has not submitted the REMS.

2.0 DISCUSSION: A call was placed to Amneal. Amneal was aware that they can either work with Prometheus or now work with Roxane (sponsor of a new approved ANDA that was granted a waived REMS). Amneal stated they would reach out to Roxane to discuss joining the Shared REMS.

3.0 ACTION ITEMS: Amneal will follow up with the FDA by October 9, 2015 to provide updates on the status of the REMS discussion between them and Roxane.

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/s/

STACY R BARLEY
10/01/2015



ANDA 206647

PRE-APPROVAL REMS NOTIFICATION

Amneal Pharmaceuticals LLC
85 Adams Avenue
Hauppauge, NY 11788

ATTENTION: Pamela Fitzpatrick
Director, Clinical Regulatory Affairs

Dear Ms. Vanam,

Please refer to your Abbreviated New Drug Application (ANDA) received March 31, 2010, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Alosetron Hydrochloride Tablets, 0.5 mg and 1 mg.

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for products containing alosetron hydrochloride to ensure the benefits of the drug outweigh the risk of ischemic colitis and serious complications of constipation.

We acknowledge receipt of your proposed REMS, included in your submission dated December 23, 2013, which contains a Medication Guide, elements to assure safe use and an implementation system.

Pursuant to section 505-1(i) of the FDCA, an ANDA and the listed drug it references must use a single, shared system for the elements to assure safe use (ETASU) unless FDA waives that requirement. As you note in your December 23, 2013 submission, development of a single shared system for Alosetron Hydrochloride Tablets, 0.5 mg and 1 mg tablets requires you to contact Prometheus Therapeutics & Diagnostics, the sponsor of the reference listed drug (RLD), (Lotronex[®] (alosetron hydrochloride) Tablets, NDA 021107) to begin discussions relating to the development and submission of a single shared system REMS. Our understanding is that this contact has already taken place. We note that Prometheus has identified (b) (6) as their contact for single shared system development. (b) (6) can be reached at (b) (6)

Discussions relating to the development and submission of a single shared system REMS should include any other parties that have submitted ANDAs for alosetron. We have included the

enclosed disclosure authorization letter to help facilitate these discussions. Please complete and return it to us as soon as possible.

If you have any questions, call Edward Taylor, Regulatory Project Manager, at (240) 402-6094.

Sincerely,

{See appended electronic signature page}

John R. Peters, M.D.
Acting Director
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Instructions to ANDA applicant: Prepare the following disclosure authorization letter on applicant's letterhead. Prominently identify the submission containing the disclosure letter with the following wording in bold capital letters at the top of the first page of the submission:

ANDA ##### REMS CORRESPONDENCE

ANDA 206647
John R. Peters, M.D.
Acting Director, Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

RE: FDA Sharing of Non-Public Information concerning ANDA 206647 with Prometheus Therapeutics and Diagnostics and ANDA applicants

Dear Dr. Peters:

On behalf of Amneal Pharmaceuticals LLC., the applicant of the above-referenced regulated product(s), I authorize the United States Food and Drug Administration (FDA) and its staff to share the information described below with Prometheus Therapeutics and Diagnostics and any abbreviated new drug application (ANDA) applicants for alosetron hydrochloride for the purpose of facilitating the development of a single shared system REMS for alosetron hydrochloride. I understand that the information may contain confidential commercial information within the meaning of 18 U.S.C. § 1905 and 5 U.S.C. § 552(b)(4) that is exempt from public disclosure. I agree to hold FDA harmless for any injury caused by FDA's sharing the information with the parties referenced above.

Information to be shared: The existence of ANDA 206647. I understand that, after disclosure, FDA may not be able to withhold information and documents containing such information under 5 U.S.C. 552(b)(4) or FDA's regulations.

Authorization is given to FDA and its staff to disclose the above-mentioned information without deleting confidential commercial information. As indicated by my signature, I am authorized to provide this consent on behalf of Amneal Pharmaceuticals LLC. and my full name, title, address, telephone number, and facsimile number is set out below for verification.

Sincerely,
(Signature)
(Printed name)
(Title)
(Telephone & Facsimile Numbers)

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/s/

JOHN R PETERS
01/22/2015

BIOEQUIVALENCE AMENDMENT

ANDA 206647

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810



APPLICANT: Amneal Pharmaceuticals

TEL: (b) (4)

ATTN: Alpesh Patel

FAX: (631) 527-3523

FROM: Heidi Lee

FDA CONTACT PHONE: 240-402-8989

Dear Sir or Madam:

This facsimile is in reference to the bioequivalence data submitted on December 24, 2013, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Alosetron Hydrochloride Tablets, eq. 0.5 mg base and eq. 1 mg base.

The Division of Bioequivalence II has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ page(s). This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

A partial response to this fax will not be processed as an amendment and will not start a review. Please submit official archival copies of your response to the ANDA. Please notify the above Project Manager when your amendment has been submitted.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Dissolution Acknowledgement Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response**. **Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket.** Please direct any questions concerning this communication to the project manager identified above.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

BIOEQUIVALENCE DEFICIENCY

ANDA: 206647

APPLICANT: Amneal Pharmaceuticals

DRUG PRODUCT: Alosetron Hydrochloride Tablets, eq. 0.5 mg base and eq. 1.0 mg base

The Division of Bioequivalence II (DB II) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies and waiver request will be conducted later. The following deficiency has been identified:

You have conducted acceptable dissolution testing using the FDA-recommended dissolution method. However, your proposed dissolution specification of NLT (b) (4) in (b) (4) is not acceptable. Based on the data submitted, the DB II recommends the following dissolution method and specification:

USP Apparatus:	II (paddle)
Rotational Speed:	50 rpm (1.0 mg) 75 rpm (0.5 mg)
Temperature:	37 ± 0.5 °C
Media:	Water (deaerated)
Volume:	500 mL
Specifications:	NLT (b) (4) (Q) in 20 minutes

Please indicate if you accept the above FDA-recommended dissolution method and specification.

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R.Ph.
Director
Division of Bioequivalence II
Office of Generic Drugs
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/

XIAOJIAN JIANG on behalf of ETHAN M STIER
08/22/2014

From: Margand, Iain
Sent: Tuesday, June 03, 2014 8:35 AM
To: 'Pavan Kumar'
Subject: RE: ANDA # 206647; Alosetron Hydrochloride Tablets 0.5 mg and 1 mg

Hello Pavan,

It is permissible for Amneal to utilize (b) (4) in lieu of the USPS when sending PIV filing notification to the NDA patent holder(s) and/or assignee(s) with regards to ANDA 206647.

Regards,

Iain

From: Pavan Kumar [<mailto:pkumar@amneal.com>]
Sent: Monday, June 02, 2014 3:07 PM
To: Margand, Iain
Subject: ANDA # 206647; Alosetron Hydrochloride Tablets 0.5 mg and 1 mg

Dear Sir,

As annotated in the acceptance to file letter for ANDA # 206647; Alosetron Hydrochloride Tablets 0.5 mg and 1 mg, Amneal is to notify the respective NDA/Patent holders of this Paragraph IV ANDA submission via certified mail with return receipt request. Amneal respectfully requests the Agency to allow us to submit this notification via (b) (4) so that the notifications are delivered in a timely manner, and so that they can be tracked accurately and verified that they were received by the intended parties.

Your prompt attention to this matter is greatly appreciated.

Have a nice day.



Pavan Kumar | Associate Director - Regulatory Affairs | Amneal Pharmaceuticals |
85 Adams Avenue, Hauppauge NY 11788 |
631.952.0214 |ext. 331 | 631.299.3995 fax | (b) (6) mobile |
pkumar@amneal.com

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

/s/

IAIN MARGAND
06/03/2014



ANDA 206647

Amneal Pharmaceuticals
Attention: Alpesh Patel
85 Adams Avenue
Hauppauge, NY 11788

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Alosetron Hydrochloride Tablets, 0.5 mg and 1 mg

DATE OF APPLICATION: December 24, 2013

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 24, 2013

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:
 - 1) Each owner of the patent or the representative designated by the owner to receive the notice;
 - 2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.
 - 3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).
- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.
- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(5)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.
- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.
- You must submit a copy of a court order or judgment or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Erin Lee
Regulatory Project Manager
240-276-8573

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
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/

SHANNON L HILL

05/28/2014

Signing for Wm Peter Rickman

ANDA FILING CHECKLIST
(CTD or eCTD FORMAT)
FOR COMPLETENESS AND ACCEPTABILITY of an APPLICATION

ANDA: 206647

APPLICANT: Amneal Pharmaceuticals

RELATED APPLICATION(S):

DRUG NAME: **Alosetron**

DOSAGE FORM: Tablets, 0.5 mg and 1 mg

LETTER DATE: 12/23/2013

RECEIVED DATE: 12/24/2013

- ☒ P-IV
☐ FIRST GENERIC
☐ EXPEDITED REVIEW REQUEST: MaPP 5240.1 or MaPP 5240.3 or **GDUFA** (Approved/Denied)
☐ PEPFAR
☐ PET

Electronic or Paper Submission: Gateway

Type II DMF#

(b) (4)

BASIS OF SUBMISSION:

NDA/ANDA: NDA 21107

FIRM: PROMETHEUS LABORATORIES INC

RLD: LOTRONEX

****Document Room Note:** for New Strength amendments and supplements, if specific reviewer(s) have already been assigned for the original, please assign to those reviewer(s) instead of the default random team(s).

Review Team:

CHEM Team: DC2 Team 21 ☒ Activity	DBE Team: DBE Team 7, Minglei Cui ☒ Activity
RPM: Erin Lee ☒ FYI	DBE PM: Chitra Mahadevan ☒ FYI
CHEM PQRPM: Frank J. Nice ☒ FYI	Division of Clinical Review: ☐ Activity
CHEM Team Leader: Radhika Rajagopalan ☐ No Assignment Needed in DARRTS	DMF Review Team Leader: Dave Skanchy ☒ FYI
Dissolution Review: ~DissoTeam~ ☐ FYI	
Labeling Reviewer: Chan Park ☒ Activity	Micro Review: ☐ Activity
SPECIAL INSTRUCTIONS FOR DOCUMENT ROOM (applicable only for a response to a refuse to receive):	

Regulatory Reviewer: Ogochukwu Umejei

Recommendation:

Date: **05/12/14**

☒ **FILE**

☐ **REFUSE to RECEIVE**

Comments: EC-1
Therapeutic Code: 8015639 (Irritable Bowel Syndrome)
On Cards: Yes
Archival copy: Gateway
Sections: I

- **For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to:** <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>
- **For a Comprehensive Table of Contents Headings and Hierarchy please go to:** <http://www.fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf>
- **For more CTD and eCTD informational links see the final page of the ANDA Checklist**

1. Edit Application Property Type in DARRTS where applicable for

- a. First Generic Received
☐ Yes ☒ No
- b. Market Availability
☒ Rx ☐ OTC
- c. Pepfar
☐ Yes ☒ No
- d. Product Type
☐ Small Molecule Drug
- e. USP Drug Product (at time of filing review)
☐ Yes ☒ No

2. Edit Submission Patent Records in DAARTS

☐ Yes

3. Edit Contacts Database with Bioequivalence Recordation where applicable

☐ Yes

4. EER (internal notation: RSB to submit at time of filing)

☒ Yes

5. GDUFA Obligation Met (Filing Fee, Type II DMF Fee, and Facility Fee)

☒ Yes - (internal notation-if not met contact: cder-om-collection@fda.hhs.gov)

6. DMF Complete Assessment

☒ Yes

ADDITIONAL COMMENTS REGARDING THE ANDA:

No Comments

Application Establishments Status Milestones Comments Contacts Product/Process

Application: A 206647/000 Subtype: N/A Sponsor: AMNEAL PHARMS

Drug Name: ALOSETRON HYDROCHLORIDE

FEI / CFN	Establishment Name	Profile Code	Last Milestone Name	Last Compliance			OAI Alert	EER Re-eval Date
				Date	Status	Date		
3005263655	AMNEAL PHARMACEUTICALS	TCM	SUBMITTED TO OC	12-MAY-2014	PN	12-MAY-2014		
								(b) (4)

Current Overall OC Recmnd: Date: 12-MAY-2014

Recommendation: PENDING

Overall Re-eval Date:

Overall OC Recommendation History:

Date Recommendation Overall Re-eval Date

OAI Alert Comments

GDUFA DMF COMPLETENESS ASSESSMENT CHECKLIST

For evaluation of initial COMPLETENESS for review of a Type II Drug Master File which has paid the required GDUFA DMF fee.

DMF Number: (b) (4)	
HOLDER: (b) (4)	
DRUG NAME (Subject): ALOSETRON HYDROCHLORIDE	
LETTER DATE: 02/21/2014	
RECEIVED DATE: 02/21/2014	
Electronic or Paper Submission: Electronic	
☒ 1. Expedited Assessment per DLPS ☒ 2. Referenced by ANDA ☐ 3. Referenced by PAS	
ANDA or PAS Number(s): 206647	

Primary Reviewer: Weixiang Dai	Review Recommendation for Initial Completeness Assessment
Date: 02/26/2014	☒ COMPLETE ☐ INCOMPLETE

1. Has the GDUFA fee been paid? Enter date paid: 09/25/2013 Payment ID: 8001872
☒ Yes ☐ No
2. Is the DMF active?
☒ Yes ☐ No
- If no, DMF is INCOMPLETE per policy. Issue Incomplete Letter to DMF holder.
3. Has the DMF been reviewed, after November 30, 2007, for chemistry, manufacturing and controls (CMC) by FDA in the context of a review of a prior application?
☐ Yes ☒ No
- If "yes," the DMF is COMPLETE per policy. If "no," review DMF with checklist.

ADDITIONAL COMMENTS REGARDING THE DMF:	
Agent:	(b) (4)
Contact Person:	(b) (4)
Phone Number:	(b) (4)
Fax Number:	(b) (4)
Email:	(b) (4)

ANDA #: 206647 Contact Person: Alpesh Patel Phone Number: (b) (4) Email: alpesh@amneal.com	ANDA #: Contact Person: Phone Number: Email:
---	---

MODULE 1: ADMINISTRATIVE

		COMMENT (S)
1.1	1.1.2 Signed and Completed Application Form (356h) (Rx/OTC Status) Rx (original signature) Refer to the links provided for the newly revised form 356h and updated instructions. http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM321897.pdf http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/ucm082348.pdf ** PLACE ESTABLISHMENT CONTACT INFORMATION IN SECTION 29: MANUFACTURING STEPS AND/OR TYPE OF TESTING**	
1.2	Cover Letter Yes Is the drug product subject to REMS requirements? ☒ Yes ☐ No Refer to the link below to determine if the product is a REMS product. http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm111350.htm If the product is subject to REMS, send an email to Mary Dempsey informing her the ANDA has been submitted (done)	
1.2.1	Form FDA 3674 (PDF) B	
*	Table of Contents (paper submission only) N/A	

1.3.2	Field Copy Certification 21CFR 314.94(d)(5) (original signature) Yes	
1.3.3	Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other: (no qualifying statement) 1. Debarment Certification (original signature) Yes 2. List of Convictions statement (original signature) Yes	
1.3.4	Financial Certifications Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) Yes Disclosure Statement (Form FDA 3455) N/A	
1.3.5	Patent Information Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations Patent Certification [21 CFR 314.94 (a)(12)/505(j)(2)(A)(vii)] 1. Patent number(s) '770 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☐ PIII ☐ PIV ☒ Statement of Notification (21 CFR 314.95/505(j)(2)(B)) ☐ 3. Expiration of Patent(s): a. Pediatric exclusivity submitted? No b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: State marketing intentions? PIV	

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

[FDA Home](#) [Drug Databases](#) [Orange Book](#)

[Start Over](#) | [Back to Search Page](#)

Active Ingredient Search Results from "OB_Rx" table for query on "alosetron."

Displaying records 1 to 2 of 2

Download data

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N021107		No	ALOSETRON HYDROCHLORIDE	TABLET; ORAL	EQ 0.5MG BASE	LOTRONEX	PROMETHEUS LABS
N021107		Yes	ALOSETRON HYDROCHLORIDE	TABLET; ORAL	EQ 1MG BASE	LOTRONEX	PROMETHEUS LABS

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Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

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Patent and Exclusivity Search Results from query on Appl No 021107 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021107	001	6284770	Oct 5, 2018			U - 405	

Exclusivity Data

There is no unexpired exclusivity for this product.

Patent Use Codes

This page defines the patent use codes.

Code	Definition
U - 405	FOR WOMEN WITH SEVERE DIARRHEA-PREDOMINANT IRRITABLE BOWEL SYNDROME (IBS)

1.4.1	References Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient Yes b. Type II DMF# (b) (4) c. Type III DMF authorization letter(s) for container closure Yes d. Type III or V DMF authorization letter(s) for sterile product sterilization process N/A 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) N/A	
1.12.4	Request for Comments and Advice - Proprietary name requested N/A If Yes, did the firm provide the request as a separate electronic amendment labeled "Proprietary Name Request" at initial time of filing 1. Yes Select 2. No - contact the firm to submit the request as a separate electronic amendment.	
1.12.11	Basis for Submission NDA#: NDA 21107 Ref Listed Drug: LOTRONEX Firm: PROMETHEUS LABORATORIES INC ANDA suitability petition required? N/A If Yes, provide petition number and copy of approved petition ANDA Citizen's Petition Required? N/A If Yes, provide petition number and copy of petition	
1.12.12	Comparison between Generic Drug and RLD-505(j)(2)(A) 1. Conditions of use Same as RLD 2. Active ingredients Same as RLD 3. Inactive ingredients Justified 4. Route of administration Same as RLD 5. Dosage Form Same as RLD 6. Strength Same as RLD	
1.12.14	Environmental Impact Analysis Statement (cite 21CFR 25.31 and 25.15(d), if applicable) Yes	
1.12.15	Request for Waiver (cite 21 CFR 320.22 or 320.24(b)(6)) Request for Waiver of In-Vivo BA/BE Study(ies) Yes	(for 0.5mg strength)

Guidance on Alosetron Hydrochloride

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Alosetron Hydrochloride

Form/Route: Tablets/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover *in-vivo*
Strength: 1 mg (base)
Subjects: Normal healthy females, general population
Additional Comments:

2. Type of study: Fed
Design: Single-dose, two-way crossover *in-vivo*
Strength: 1 mg (base)
Subjects: Normal healthy females, general population
Additional comments:

Analytes to measure (in appropriate biological fluid): Alosetron in plasma

Bioequivalence based on (90% CI): Alosetron

Waiver request of in vivo testing: 0.5 mg (base) based on (i) acceptable bioequivalence studies on the 1 mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at <http://www.fda.gov/cder/ogd/index.htm>. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

1.14.1	Draft Labeling (Multi Copies N/A for E-Submissions) 1.14.1.1 4 copies of draft for paper submission only (each strength and container) Yes 1.14.1.2 Side by side labeling comparison of container(s) and carton(s) for each strength with all differences visually highlighted and annotated 1.14.1.3 1 package insert (content of labeling) in PDF and WORD format, and SPL submitted electronically 1.14.1.4 Labeling Comprehension Studies Refer to Pharmacy Bulk Package Sterility Assurance Table (for PBP's only) See link below for table: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM352612.pdf	
	Listed Drug Labeling 1.14.3.1 1 side by side labeling (package and patient insert) comparison with all differences visually highlighted and annotated Yes 1.14.3.3 RLD package insert, 1 RLD container label, and if applicable, 1 RLD outer container label Yes	

MODULE 2: Quality Overall Summary

		COMMENT (S)
2.3	Quality Overall Summary (QOS) E-Submission: PDF Yes Word Processed e.g., MS Word Yes Additional information regarding QbR may be found at the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120971.htm Question based Review (QbR) Yes 2.3.S Drug Substance (Active Pharmaceutical Ingredient) Yes 2.3.S.1 General Information 2.3.S.2 Manufacture 2.3.S.3 Characterization 2.3.S.4 Control of Drug Substance 2.3.S.5 Reference Standards or Materials 2.3.S.6 Container Closure System 2.3.S.7 Stability 2.3.P Drug Product Yes 2.3.P.1 Description and Composition of the Drug Product 2.3.P.2 Pharmaceutical Development 2.3.P.2.1 Components of the Drug Product 2.3.P.2.1.1 Drug Substance 2.3.P.2.1.2 Excipients 2.3.P.2.2 Drug Product Oral Solids: Immediate Release or Modified Release (Matrix Technology or Compressed Film Coated Components) tablet scoring data per Draft <i>Guidance for Industry, Tablet Scoring: Nomenclature, Labeling and Data for Evaluation</i> (if applicable) 2.3.P.2.3 Manufacturing Process Development 2.3.P.2.4 Container Closure System 2.3.P.3 Manufacture 2.3.P.4 Control of Excipients 2.3.P.5 Control of Drug Product 2.3.P.6 Reference Standards or Materials 2.3.P.7 Container Closure System 2.3.P.8 Stability	

MODULE 2.7: Clinical Summary

		COMMENT (S)
2.7	Clinical Summary (Bioequivalence)Model BE Data Summary Tables http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf ** In addition to the standard tables, see the link above for tables specifically designed for in-vitro binding studies ** http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM364105.pdf E-Submission: PDF Select Word Processed: e.g., MS Word Select 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods 2.7.1.1 Background and Overview Table 1. Submission Summary Yes Table 4. Bioanalytical Method Validation Yes Table 6. Formulation Data Yes Table 10. Study Information Yes Table 11. Product Information Yes Table 17. Comparative Physiochemical Data of Ophthalmic Solution Products N/A 2.7.1.2 Summary of Results of Individual Studies Table 5. Summary of In Vitro Dissolution Yes (include complete comparative In Vitro Dissolution Data (individual) with Certificate of Analysis [CoA] for Test and Reference products including: potency, assay, content uniformity, date of manufacture and lot number) Table 9. Reanalysis of Study Samples Yes Table 12. Dropout Information Yes Table 13. Protocol Deviation Yes Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analysis Yes 2.7.1.3 Comparison and Analyses of Results Across Studies Table 2. Summary of Bioavailability (BA) Studies Yes Table 3. Statistical Summary of the Comparative BA Data: 1. Unscaled Average – Table A 2. Reference-scaled Average BE Studies – Tables A and B BE Studies Select Table 16. Composition of Meal Used in Fed Bioequivalence Study Yes 2.7.1.4 Appendix Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples Yes 2.7.4.1.3 Demographic and Other Characteristics of Study Population Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study Yes 2.7.4.2.1.1 Common Adverse Events Table 8. Incidence of Adverse Events in Individual Studies Yes	

MODULE 3: 3.2.S DRUG SUBSTANCE

		COMMENT (S)
3.2.S.1	General Information) Yes (Do not refer to DMF) 3.2.S.1.1 Nomenclature 3.2.S.1.2 Structure 3.2.S.1.3 General Properties	
3.2.S.2	Manufacturer Drug Substance (Active Pharmaceutical Ingredient) Must correlate to the establishment information submitted in annex to Form FDA 356h. 1. Name and Full Address(es) of the Facility(ies) Yes 2. Contact name, phone and fax numbers, email address Yes 3. U.S Agent's name (if applicable) N/A 4. Specify Function or Responsibility Yes 5. Type II DMF number for API Yes 6. CFN, FEI or DUNS numbers (if available) Yes	

3.2.S.2.1 MANUFACTURER (ALOSETRON HYDROCHLORIDE)**Table 1. Drug Substance Manufacturer Establishment Information**

(b) (4)

3.2.S.3**Characterization Yes**

Provide the following in tabular format as follows:

IUPAC Chemical Name	Code #	Chemical Structure	Process/ Degradation Impurity	Source/ Mechanism

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf>

3.2.S.4**Control of Drug Substance (Active Pharmaceutical Ingredient)****3.2.S.4.1 Specification**

Testing specifications and data from drug substance manufacturer(s) Yes

3.2.S.4.2 Analytical Procedures Yes**3.2.S.4.3 Validation of Analytical Procedures**

(API that is USP or reference made to DMF, must provide verification of USP or DMF procedures) Yes

1. Spectra and chromatograms for reference standards and test samples Yes

2. Samples-Statement of Availability and Identification of:

a. Drug Substance Select

b. API lot numbers

API Manufacturing Lot #	Drug Product Manufacturing Batch #	API Batch Analysis with Spectra and Chromatographs
Amneal NY Lot # B130135 (Vendor Lot # 2014/3/002/13)	0.5 mg Batch # BE17813 1 mg Batch # BE18413	Module 3.2.S.4.4

3.2.S.4.4 Batch Analysis

1. COAs specifications and test results from drug substance mfgr(s) Yes

2. Drug Product manufacturer's Certificates of analysis Yes

3.2.S.4.5 Justification of Specification Yes

Provide data in tabular format:

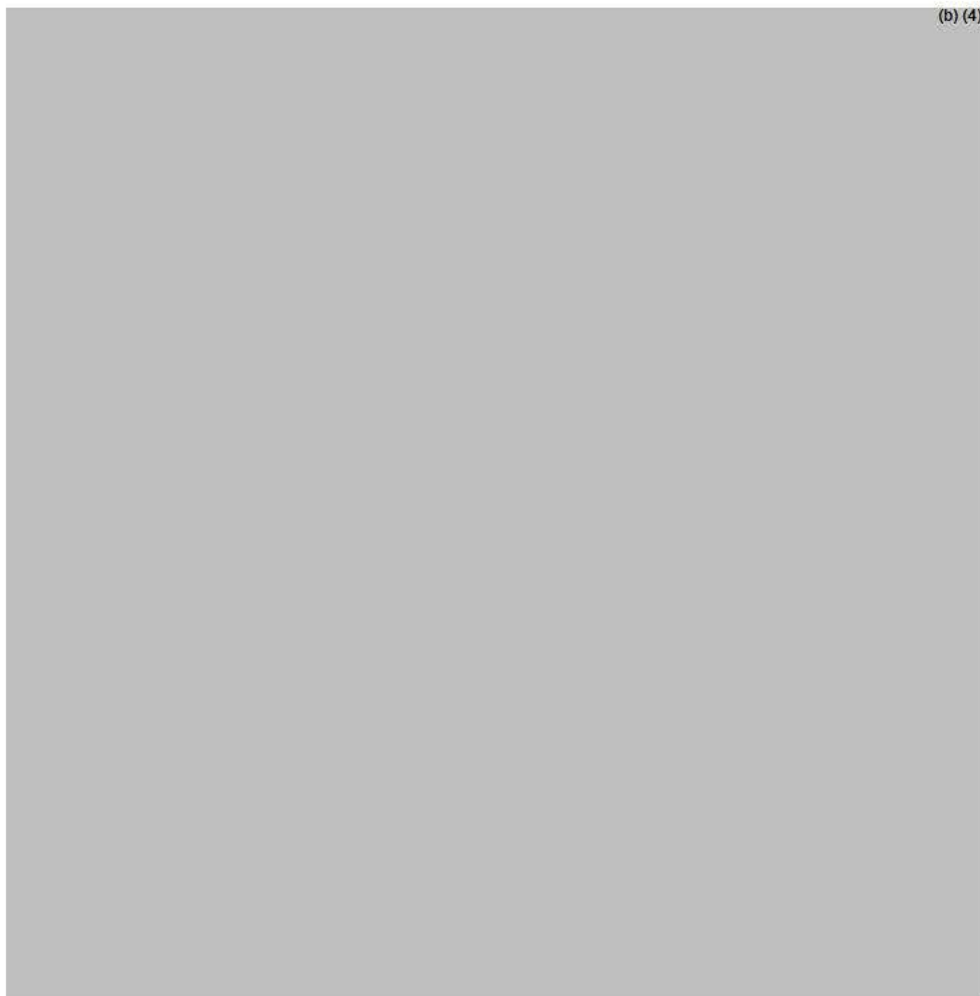
Chemical Name	Code#	MDD	IT	QT	TDI of Impurity	Proposed AC for Unspecified Impurities	Proposed AC for Specified Impurities	Justification if AC>QT for Specified Impurities

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf>

3.2.S.5	Reference Standards or Materials (Do not refer to DMF) Yes	
3.2.S.6	Container Closure Systems Yes	
3.2.S.7	Stability 1. Retest date or expiration date of API Yes	(b) (4); is this ok?

MODULE 3: 3.2.P DRUG PRODUCT

		COMMENT (S)
3.2.P.1	Description and Composition of the Drug Product 1. Unit composition with indication of the function of the inactive ingredient(s) Select 2. Inactive ingredients and amounts are appropriate per IIG (per/dose justification) (provide justification in a tabular format) Select 3. Conversion from % to mg/dose values for inactive ingredients (if applicable) Select 4. (b) (4) 5. Injections: If the reference listed drug is packaged with a drug specific in the	



(b) (4)

3.2.P.2	Pharmaceutical Development 1. Pharmaceutical Development Report Yes 2. Microbial Attributes a. Container/Closure Integrity Testing Report for Sterile Products b. Antimicrobial Effectiveness Testing for Multi-dose sterile products							
3.2.P.3	Manufacture 3.2.P.3.1 Drug Product Must correlate to the establishment information submitted in annex to Form FDA 356h for the finished dosage manufacturer and all outside contract testing laboratories. 1. Name and Full Address(es) of the Facility(ies) Yes 2. Contact name, phone and fax numbers, email address Yes 3. U.S Agent's name (if applicable) N/A 4. Specify Function or Responsibility Yes 5. CGMP Certification (from both applicant and drug product manufacturer if different entities) Yes 6. CFN, FEI or DUNS numbers (if available) 3005263655 <table border="1" data-bbox="240 695 1266 1289"> <thead> <tr> <th data-bbox="240 695 537 785">Company Name / Address</th> <th data-bbox="537 695 1015 785">Functions</th> <th data-bbox="1015 695 1266 785">Facility Establishment Identifier # and DUNS #:</th> </tr> </thead> <tbody> <tr> <td data-bbox="240 785 537 1289"> * Amneal Pharmaceuticals 50 Horseblock Road Brookhaven, NY 11719 </td> <td data-bbox="537 785 1015 1289" style="background-color: #cccccc;"> (b) (4) </td> <td data-bbox="1015 785 1266 1289"> Refer Table 2 </td> </tr> </tbody> </table> 3.2.P.3.2 Batch Formula 3.2.P.3.3 Description of Manufacturing Process and Process Controls 1. Description of the Manufacturing Process and (for aseptic fill products) Facility Yes 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified Yes 3. Master packaging records for intended marketing container(s) Yes 4. If sterile product N/A 5. Reprocessing Statement (cite 21CFR 211.115, submitted by the drug product manufacturer and the applicant, if different entities) Yes 3.2.P.3.4 Controls of Critical Steps and Intermediates Yes 3.2.P.3.5 Process Validation and/or Evaluation 1. Terminally Sterilized Product N/A a. Validation of production terminal sterilization process b. Validation of depyrogenation of all product containers and closures c. Validation of container-closure package integrity 2. Aseptically Filled Product N/A • Validation (bacterial retention studies) of sterilizing grade filter(s) • Validation of the sterilization of sterile bulk drug or product contact equipment, components, containers, and closures • Validation of depyrogenation of product containers and closures	Company Name / Address	Functions	Facility Establishment Identifier # and DUNS #:	* Amneal Pharmaceuticals 50 Horseblock Road Brookhaven, NY 11719	(b) (4)	Refer Table 2	
Company Name / Address	Functions	Facility Establishment Identifier # and DUNS #:						
* Amneal Pharmaceuticals 50 Horseblock Road Brookhaven, NY 11719	(b) (4)	Refer Table 2						

	- Validation of aseptic filling process/line/room (media fills/process simulations) - Validation of container-closure package integrity																											
3.2.P.4	Controls of Excipients (Inactive Ingredients) Source of inactive ingredients identified Yes 3.2.P.4.1 Specifications - Testing specifications (including identification and characterization) Yes - Suppliers' COA (specifications and test results) Yes 3.2.P.4.2 Analytical Procedures USP/NF 3.2.P.4.3 Validation of Analytical Procedures N/A 3.2.P.4.4 Justification of Specifications: - Applicant COA Yes																											
3.2.P.5	Controls of Drug Product 3.2.P.5.1 Specification(s) Yes 3.2.P.5.2 Analytical Procedures Yes 3.2.P.5.3 Validation of Analytical Procedures (if using USP procedure, must provide verification of USP procedure) Yes Samples - Statement of Availability and Identification of: - Finished Dosage Form Yes - Lot numbers and strength of Drug Products 1.4 Sample Statement The sample of ANDA Submission Batches of Alosetron hydrochloride Tablets, 0.5 mg and 1 mg (listed in following table), is the basis of this ANDA, is available and will be provided upon agency's request. <table border="1"> <thead> <tr> <th>Dosage Strength</th> <th>Bio/ANDA Submission Batches</th> </tr> </thead> <tbody> <tr> <td>Alosetron hydrochloride Tablets 0.5 mg</td> <td>Batch # BE17813</td> </tr> <tr> <td>Alosetron hydrochloride Tablets 1 mg</td> <td>Batch # BE18413</td> </tr> </tbody> </table> 3.2.P.5.4 Batch Analysis Certificates of Analysis for Finished Dosage Form Yes 3.2.P.5.5 Characterization of Impurities Yes Provide in tabular format as below: <table border="1"> <thead> <tr> <th>IUPAC Chemical Name</th> <th>Code #</th> <th>Chemical Structure</th> <th>Degradation Impurity</th> <th>Source/ Mechanism</th> </tr> </thead> <tbody> <tr><td></td><td></td><td></td><td></td><td></td></tr> <tr><td></td><td></td><td></td><td></td><td></td></tr> <tr><td></td><td></td><td></td><td></td><td></td></tr> </tbody> </table> http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf	Dosage Strength	Bio/ANDA Submission Batches	Alosetron hydrochloride Tablets 0.5 mg	Batch # BE17813	Alosetron hydrochloride Tablets 1 mg	Batch # BE18413	IUPAC Chemical Name	Code #	Chemical Structure	Degradation Impurity	Source/ Mechanism																
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Alosetron hydrochloride Tablets 1 mg	Batch # BE18413																											
IUPAC Chemical Name	Code #	Chemical Structure	Degradation Impurity	Source/ Mechanism																								

	3.2.P.5.6 Justification of Specifications Yes	
3.2.P.7	Container Closure System 1. Summary of Container/Closure System (if new resin, provide data) Yes 2. Components Specification and Test Data Yes 3. Packaging Configuration and Sizes Yes 4. Container/Closure Testing (recommended additional testing for all plastic)Yes a. Solid Orals: water permeation, light transmissionYes b. Liquids: leachables, extractables, light transmissionSelect 5. Source of supply and suppliers address Yes	
3.2.P.8	3.2.P.8.1 Stability and Conclusions (Finished Dosage Form) 1. Stability Protocol submitted Yes 2. Expiration Dating Period for Marketed Packaging 24 months 3. Expiration Dating Period for Bulk Packaging (if applicable) 3 months 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment (From Applicant and Drug Product Manufacturer, if different entities) Post Approval Stability Protocol and Commitments Yes 3.2.P.8.3 Stability Data 1. Accelerated stability data a. Four (4) time points 0,1,2,3 Yes -OR- b. . Refer to the Final Guidance for Industry <i>ANDAs: Stability Testing Drug Substances and Products</i> , dated June 2013 Select c. For liquid and semi-solid products, upright and inverted/horizontal storage orientation Select 180 Day Calculation Please Enter Start Date: 07/01/2013 Your Result: 9/23/2013 180 Days 6 months 30 months 40 Months 84 Days Clear 2. Batch numbers on stability records the same as the test batch Yes 3. Date accelerated stability study initiated Yes	

	4. Date accelerated stability sample(s) removed from stability chamber for each testing time point Yes	
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MODULE 3: 3.2.R REGIONAL INFORMATION (Drug Substance)

		COMMENT (S)
3.2.R Drug Substance	3.2.R.1.S Executed Batch Records for drug substance (if available) N/A 3.2.R.2.S Comparability Protocols N/A 3.2.R.3.S Methods Validation Package Yes Methods Validation Package (3 copies for paper and N/A for E-Submissions) (Required for Non-USP drugs)	

MODULE 3: 3.2.R REGIONAL INFORMATION (Drug Product)

		COMMENT (S)
3.2.R Drug Product	3.2.R.1.P.1 Executed Batch Records Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation Yes a. Theoretical Yield b. Actual Yield c. Packaged Yield	

	Bulk Package Reconciliation for all bulk packaging considered a commercial container is required if bulk packaging is used to achieve the minimum package requirement. Provide the following information in their respective sections: a. Bulk Package Label (1.14.1) Select b. Bulk Package Stability (3.2.P.8) 1. If bulk is to be shipped, provide accelerated stability data at 0,3,6 months Select 2. If bulk is only warehoused for repackaging, provide RT stability data at 0,3,6 months Select c. Bulk Package Container and Closure information (3.2.P.7) Select 3.2.R.1.P.2 Information on Components Select 3.2.R.2.P Comparability Protocols Select 3.2.R.3.P Methods Validation Package Select Methods Validation Package (3 copies for paper and N/A for E-Submissions) (Required for Non-USP drugs)	
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MODULE 5: CLINICAL STUDY REPORTS

		COMMENT (S)
5.2	Tabular Listing of Clinical Studies Yes	
5.3.1 (complete study data)	Bioavailability/Bioequivalence 1. Formulation data same? a. Comparison of all Strengths (proportionality of multiple strengths) Yes b. Parenterals, Ophthalmics, Otics and Topicals (21 CFR 314.94 (a)(9)(iii)-(v) N/A)	

2.7.1.1.1 Overview of Formulations

Table 6 provides the composition of Amneal's Alosetron Hydrochloride Tablets, 0.5 mg and 1mg.

Table 6. Formulation Data: Alosetron Hydrochloride Tablets, 0.5 mg and 1 mg

Ingredients	0.5 mg		1 mg	
	mg/tab	%w/w	mg/tab	%w/w
Alosetron Hydrochloride	0.562 [*]	(b) (4)	1.124 [†]	(b) (4)
Microcrystalline Cellulose, (b) (4)				(b) (4)
Pregelatinized Starch, (b) (4)				(b) (4)
Lactose Anhydrous, (b) (4)				(b) (4)
Magnesium Stearate, (b) (4)				(b) (4)
Finished Product Weight	155.00	100.00	155.00	100.00

^{*}0.562 mg of Alosetron Hydrochloride is equivalent to 0.5 mg of Alosetron.

[†]1.124 mg of Alosetron Hydrochloride is equivalent to 1 mg of Alosetron.

2. Lot Numbers and strength of Products used in BE Study(ies)

Table 11. Product Information

Product	Test	Reference
Treatment ID	T	R
Name of Product/Brand Name	Alosetron Hydrochloride Tablets, 1 mg (Name of Product)	LOTIRONEX [®] (alosectron hydrochloride) Tablets 1 mg (Brand Name)
Manufacturer	Manufactured by: Amneal Pharmaceuticals, USA	Prometheus Laboratories Inc. San Diego, CA 92121
Lot No.	BE18413	HGHP
Manufacture Date	June 3, 2013	N/A
Expiration Date	N/A	July 2014
Strength	1 mg	1 mg
Dosage Form	Tablet	Tablet
Bio-batch Size	(b) (4)	N/A
Production Batch Size	(b) (4)	N/A
Potency	101.8%	98.8%
Content Uniformity (mean, %CV)	No. of Units: 10	No. of Units: 10
	Min: 100.9%	Min: 95.2%
	Max: 102.2%	Max: 107.0%
	Mean: 101.6%	Mean: 101.5%
	AV: 1.2	AV: 9.0
Dose Administered	01 Tablet	01 Tablet
Route of Administration	Oral	Oral

3. Study Type: IN-VIVO PK STUDY(IES)

(Continue with the appropriate study type box below)

See Module 2.7 Clinical Summary for placement of BA/BE Summary for tables 9 – 16.

The study data that support the BA/BE summary tables should be provided in the corresponding sections below:

5.3.1.2 Comparative BA/BE Study Reports

5.3.1.3 In Vitro-In-Vivo Correlation Study Reports (exception: all dissolution data should be placed in 2.7)

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

Case Report Forms should be placed under the study to which they pertain, and appropriately tagged. Refer to The eCTD Backbone File Specification for Study Tagging
[//www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf](http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

5.4 Literature References

Possible Study Types:

Study Type

IN-VIVO BE STUDY(IES) with PK ENDPOINTS (i.e., fasting/fed/sprinkle)

1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) Select

Table 3AA. Statistical Summary of the Comparative Bioavailability Data for Unscaled Average BE Studies: Study No. ARL/12/483 - Fasting

Reference Scaled Average Bioequivalence Approach Used				☐ Yes ☒ No		
If No, then complete Table 3A only If Yes, then complete Tables 3A and 3B						
Alosetron Hydrochloride Tablets, 1 mg, (No of subjects completed= 48) Dose (1 x 1 mg tablet) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study (Study No.: ARL/12/483)						
Parameter	Test	N	RLD	N	Ratio	90% C.I.
AUC _{0-t}	19.337	48	19.257	48	100.4121	94.1929-107.0420
AUC _∞	19.694	48	19.671	48	100.1166	94.0029-106.6279
C _{max}	6.330	48	6.478	48	97.7068	90.4602-105.5340

Table 3AB. Statistical Summary of the Comparative Bioavailability Data for Unscaled Average BE studies: Study No. ARL/12/484 - Fed

Reference Scaled Average Bioequivalence Approach Used				☐ Yes ☒ No		
If No, then complete Table 3A only If Yes, then complete Tables 3A and 3B Alosetron Hydrochloride Tablets, 1 mg (No of subjects completed= 42) Dose (1 x 1 mg tablet) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study (Study No.: ARL/12/484)						
Parameter	Test	N	RLD	N	Ratio	90% C.I.
AUC _{0-t}	15.870	42	15.007	42	105.7486	99.7088-112.1543
AUC _∞	16.326	42	15.477	42	105.4891	99.6360-111.6859
C _{max}	4.010	42	3.742	42	107.1419	99.3821-115.5076

	2. EDR Email: Data Files Submitted ☐ Select 3. In-Vitro Dissolution ☐ Select	
Study Type	IN-VIVO BE STUDY with CLINICAL ENDPOINTS Division of Clinical Review Consult Complete ☐ Yes ☐ No	
Study Type	IN-VITRO BE STUDY(IES) (i.e., in vitro binding assays) ☐ Select 1. Study(ies) meets BE criteria (90% CI of 80-125) ☐ Select 2. EDR Email: Data Files Submitted ☐ Select 3. In-Vitro Dissolution ☐ Select	
Study Type	NASALLY ADMINISTERED DRUG PRODUCTS Refer to the attached links for Nasal Product BE Tables: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM209446.pdf AND http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM271017.pdf Division of Bioequivalence Consult Complete ☐ Yes ☐ No	
Study Type	IN-VIVO BE STUDY(IES) with PD ENDPOINTS (e.g., topical corticosteroid vasoconstrictor studies) Division of Bioequivalence Consult Complete ☐ Yes ☐ No	
Study Type	TRANSDERMAL DELIVERY SYSTEMS Division of Clinical Review Consult Complete ☐ Yes ☐ No	

Updated 1/24/2014

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

/s/

OGOCHUKWU UMEJEI
05/20/2014

SHANNON L HILL
05/28/2014
Signing for Iain Margand