

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

### *APPLICATION NUMBER:*

**021107Orig1s026**

*Trade Name:* **Lotronex**

*Generic Name:* **alosetron hydrochloride**

*Sponsor:* **Prometheus Laboratories, Inc.**

*Approval Date:* 01/07/2016

*Indications:* LOTRONEX is a selective serotonin 5-HT<sub>3</sub> 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.

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*APPLICATION NUMBER:*  
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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021107Orig1s026**

**APPROVAL LETTER**



NDA 21107/S-026

**SUPPLEMENT APPROVAL**

Prometheus Laboratories, Inc.  
Attention: Hector Tamburini  
Executive Director, Regulatory Affairs and CMC  
9410 Carroll Park Drive  
San Diego, California 92121

Dear Mr. Tamburini:

Please refer to your Supplemental New Drug Application (sNDA) dated and received August 18, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lotronex (alosetron hydrochloride) tablets, 0.5 and 1 mg.

We also acknowledge receipt of your amendments dated September 17, September 28, December 1, December 29, 2015, and January 6, 2016.

This supplemental new drug application provides for modifications to the approved Lotronex (alosetron) risk evaluation and mitigation strategy (REMS). This supplement is in response to our May 20, 2015 REMS Modification Notification letter.

**REQUIRED PEDIATRIC ASSESSMENTS**

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

Because none of these criteria apply to your application, you are exempt from this requirement.

**RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

The REMS for Lotronex was originally approved on September 2, 2010, and the most recent modification was approved on July 24, 2015. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. In order to minimize burden on the healthcare delivery system of complying with the REMS, we determined that you were required to make the following REMS modifications:

1. Modified REMS Goal
2. Removal of the Medication Guide as an element of the REMS
3. Modifications to the elements to assure safe use
  - The training of healthcare providers who prescribe Lotronex/alosetron hydrochloride must continue to be provided to ensure the benefits of Lotronex/alosetron hydrochloride continue to outweigh the risks of ischemic colitis and serious complications of constipation
  - The prescriber training materials are to include the Prescriber Education Slide Deck and a Safety Information Fact Sheet for Prescribers to communicate the key risk messages associated with Lotronex/alosetron hydrochloride
  - Prescribers no longer need to affix prescribing program stickers to written prescriptions for Lotronex/alosetron hydrochloride
  - Pharmacies may dispense Lotronex/alosetron hydrochloride without a prescribing program sticker affixed to a paper prescription
  - The Patient Acknowledgement Form was modified to a Patient Education Sheet and will become the primary educational tool used by prescribers for counseling patients regarding the risks of Lotronex/alosetron hydrochloride

We have determined that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208. Therefore, it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of Lotronex/alosetron hydrochloride outweigh its risks. The Medication Guide will continue to be part of the approved labeling in accordance with 21 CFR 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FD&C Act.

Your proposed modified REMS, submitted on December 29, 2015 and appended to this letter, is approved. The modified REMS consists of elements to assure safe use and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS is revised to provide for submission of REMS assessments to the FDA 18 months following the REMS modification approval and every 12 months thereafter.

The revised REMS assessment plan must include, but is not limited to, the following:

- 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 LOTRONEX and its authorized generic, and the actions patients need to take should they experience early warning signs and symptoms of these risks
- Results of an evaluation of prescriber understanding of the appropriate patient population, the risks of ischemic colitis and serious complications of constipation associated with LOTRONEX and its authorized generic, 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
- The number of prescribers and medical specialty of prescribers who reported that they completed training in the LOTRONEX REMS Program, including the number and medical specialty of prescribers contacted by Prometheus to become trained after prescribing LOTRONEX and its authorized generic and the number and medical specialty contacted who completed training, during the reporting period and cumulative
  - The number of prescribers who have not completed training and are writing prescriptions
  - Numbers of prescriptions, by year for the last five years and annually thereafter
  - 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
  - Summary and discussion of the above cases (received during the reporting period) and the clinical significance of these events
  - 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

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, 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 FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) FD&C Act. This assessment should include:

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
- c) *If the new indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* A statement about whether the

REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.

- e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
- f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including:* Provision of the reason(s) why the proposed REMS modification is necessary; the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications, provide a rationale for why the REMS does not need to be modified.*

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:

**NDA 21107 REMS CORRESPONDENCE  
(insert concise description of content in bold capital letters, e.g.,  
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT  
METHODOLOGY**

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element 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:

**NDA 21107 REMS ASSESSMENT  
  
NEW SUPPLEMENT FOR NDA 21107/S-000  
CHANGES BEING EFFECTED IN 30 DAYS  
PROPOSED MINOR REMS MODIFICATION**

*or*

**NEW SUPPLEMENT FOR NDA 21107/S-000  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED MAJOR REMS MODIFICATION**

*or*

**NEW SUPPLEMENT FOR NDA 21107/S-000  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES  
SUBMITTED IN SUPPLEMENT XXX**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)  
FOR NDA 21107/S-000  
REMS ASSESSMENT  
< other supplement identification > **PROPOSED REMS MODIFICATION (if  
included)****

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 REVISIONS FOR NDA 21107**

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.

**REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have questions, call LCDR Cheronda Cherry-France, Regulatory Project Manager, at (301) 796-7295.

Sincerely,

*{See appended electronic signature page}*

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

ENCLOSURE(S):  
REMS

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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.**  
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/s/

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JOYCE A KORVICK  
01/07/2016

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021107Orig1s026**

**RISK EVALUATION AND MITIGATION  
STRATEGY (REMS)**

**Initial REMS Approved: 09/2010**  
**Most Recent Modification: 01/2016**

**NDA 21-107**

**LOTRONEX<sup>®</sup> (alosetron hydrochloride) Tablets  
and Authorized Generic (alosetron hydrochloride) Tablets**

Selective 5-HT<sub>3</sub> antagonist

Prometheus Laboratories Inc.  
9410 Carroll Park Drive  
San Diego, CA 92121  
(888) 423-5227

**RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

**I. GOAL(S):**

The goals and objectives of the LOTRONEX REMS are to mitigate the risks of ischemic colitis (IC) and serious complications of constipation (CoC) associated with LOTRONEX and its authorized generic alosetron hydrochloride by:

- Informing prescribers of LOTRONEX/alosetron hydrochloride about:
  - the serious risks of IC and serious CoC associated with LOTRONEX/alosetron hydrochloride
  - the importance of understanding that LOTRONEX/alosetron hydrochloride 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 LOTRONEX and its authorized generic.**
  - a. Prometheus will ensure that training provided to healthcare providers who prescribe LOTRONEX and its authorized generic includes information on the serious risks of IC and CoC associated with LOTRONEX/alosetron hydrochloride, the importance of understanding that LOTRONEX/alosetron hydrochloride 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 prescribing information and the following materials in the REMS Training Kit:

- i. REMS letter for Healthcare Providers
  - ii. LOTRONEX REMS Program Prescriber Education Slide Deck
  - iii. LOTRONEX REMS Program Safety Information Fact Sheet for Prescribers
  - iv. LOTRONEX REMS Program Patient Education Sheet
  - v. Prescriber Completion of LOTRONEX REMS Program Training Form
- b. In order to facilitate training, Prometheus will:
- i. Ensure that training is provided to healthcare providers who prescribe LOTRONEX/alosetron hydrochloride by mailing or emailing the REMS Training Kit to healthcare providers who are likely to prescribe, or have prescribed LOTRONEX/alosetron hydrochloride in the 24 months preceding the REMS modification approval (01/2016). The REMS Training Kit will be distributed within 60 days after approval of the modified LOTRONEX REMS Program. Likely prescribers include, but are not limited to, general practitioners, family practitioners, internists, gastroenterologists, and nurse practitioners/physician assistants.
  - ii. Send a REMS letter for Professional Societies to the following professional societies and organizations, requesting that the letter or the content be provided to their membership within 6 and 12 months after approval of the modified LOTRONEX REMS Program.
    - American Academy of Family Physicians
    - American Academy of Nurse Practitioners
    - American Academy of Physicians Assistants
    - American College of Gastroenterology
    - American College of Physicians
    - American Gastroenterological Association
    - American Medical Association
  - iii. Ensure that prescribers can notify Prometheus when they have completed training via the LOTRONEX REMS Program website or by faxing or mailing a Prescriber Completion of LOTRONEX REMS Program 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 Prometheus has a presence.
  - vi. Maintain a LOTRONEX REMS Program Website [[www.lotronexrems.com](http://www.lotronexrems.com)] and call center (1-888-423-5227) to support prescribers.
  - vii. Monitor distribution and prescription data monthly. Contact all prescribers identified as not having completed training and provide training within 30 days of identification. 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.

- viii. Maintain a validated, secure database of healthcare providers who have notified Prometheus of completion of training, which will be defined as all training materials were reviewed independently by the healthcare provider.
- ix. Ensure that the REMS materials listed below are available on the LOTRONEX REMS Program Website or by calling the REMS call center.

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

REMS Training Kit

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

Other appended REMS materials:

- REMS Website for Prescriber Section screenshots
- REMS Website for Patients Section screenshots
- REMS letter for Professional Societies

### **III. Timetable for Submission of Assessments**

Prometheus will submit REMS Assessments to the FDA 18 months after the date of approval of the modified REMS (01/2016) 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. Prometheus will submit each assessment so that it will be received by the FDA on or before the due date.

## FDA Required REMS Safety Information for LOTRONEX<sup>®</sup> and its authorized generic alosetron hydrochloride

### Important Safety Update

The FDA has required this safety update as part of the LOTRONEX REMS Program to inform you that the **LOTRONEX REMS Program<sup>™</sup> has changed** from the previous Prescribing Program for LOTRONEX<sup>™</sup> (PPL)

#### PPL-ENROLLED Prescriber Actions:

- You are no longer required to affix prescribing program stickers to written prescriptions for LOTRONEX<sup>®</sup>/alosetron hydrochloride.
- You may prescribe LOTRONEX<sup>®</sup>/alosetron hydrochloride electronically

#### NON-ENROLLED Prescriber Actions:

- Review the LOTRONEX REMS Program<sup>™</sup> Training Kit and complete the Prescriber Completion of LOTRONEX REMS Program<sup>™</sup> Training Form which can be found at [www.lotronexrems.com](http://www.lotronexrems.com).
- You can also submit the enclosed form via e-mail to [contactclientservices@prometheuslabs.com](mailto:contactclientservices@prometheuslabs.com) or by fax to Prometheus Client Services at 1-877-816-4019.

You will find the LOTRONEX REMS Program<sup>™</sup> Training Kit enclosed. The Training Kit is also available online at [www.lotronexrems.com](http://www.lotronexrems.com) or by calling Prometheus Client Services at 1-888-423-5227, or via e-mail to [contactclientservices@prometheuslabs.com](mailto:contactclientservices@prometheuslabs.com).

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

#### Summary of Changes to the REMS Program

- ❶ Prescribers are **no** longer required to affix prescribing program stickers to written prescriptions for LOTRONEX/alosetron hydrochloride
- ❷ Pharmacies are **no** longer required to only dispense LOTRONEX/alosetron hydrochloride 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 (enclosed) is available for the prescriber to discuss with the patient.

**Indication:**

LOTRONEX/alosetron hydrochloride is a selective serotonin 5-HT<sub>3</sub> 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.lotronexrems.com](http://www.lotronexrems.com) for more information.

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

**Reporting Adverse Events:**

You are encouraged to report all suspected adverse events associated with LOTRONEX/alosetron hydrochloride to the FDA at [www.fda.gov/medwatch](http://www.fda.gov/medwatch), or 1-800-FDA-1088 or Prometheus at 1-888-423-5227.

Sincerely,

Client Services  
Prometheus Laboratories Inc.

LOT15048 08/15

# LOTRONEX<sup>®</sup> and its authorized generic alosetron hydrochloride:

## Understanding the Benefits and Risks

### **The LOTRONEX REMS Program<sup>™</sup> Prescriber Education Slide Deck**

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**Please see complete Prescribing Information for LOTRONEX<sup>®</sup>/alosetron hydrochloride.**

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# Important

## Modified LOTRONEX REMS Program™

**The modified LOTRONEX REMS Program™ has replaced the previous Prescribing Program for LOTRONEX™**

- ❶ Prescribers are no longer required to affix prescribing program stickers to written prescriptions for LOTRONEX®/alosetron hydrochloride.
- ❷ Pharmacies are no longer required to only dispense LOTRONEX®/alosetron hydrochloride 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

Please see complete Prescribing Information for LOTRONEX<sup>®</sup>/alosetron hydrochloride for full details about risks.

## Purpose

By reviewing the information provided in this presentation, Health Care Providers who prescribe LOTRONEX<sup>®</sup>/alosetron hydrochloride will better understand the:

- **Risks and benefits of LOTRONEX<sup>®</sup>/alosetron hydrochloride;**
- **Etiology of irritable bowel syndrome (IBS);**
- **LOTRONEX REMS Program<sup>™</sup>.**

## What is a 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 LOTRONEX and its authorized generic alosetron hydrochloride tablets outweigh serious gastrointestinal adverse reactions in patients.

## Goals and Objectives

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

**The goals and objectives of the LOTRONEX REMS Program™ are to mitigate the risks of ischemic colitis (IC) and serious complications of constipation (CoC) associated with LOTRONEX®/alosetron hydrochloride by:**

- **Informing prescribers of LOTRONEX®/alosetron hydrochloride about:**
  - **the serious risks of IC and serious CoC associated with LOTRONEX®/alosetron hydrochloride**
  - **the importance of understanding that LOTRONEX®/alosetron hydrochloride 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

Please see complete Prescribing Information for LOTRONEX<sup>®</sup>/alosetron hydrochloride for full details about risks.

## Indication and Usage

- LOTRONEX<sup>®</sup>/alosetron hydrochloride 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.**
- 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 hydrochloride, 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 in men.

# Section 3:

## Important Safety Information

Please see complete Prescribing Information for LOTRONEX<sup>®</sup>/alosetron hydrochloride for full details about risks.

## Boxed Warning

**WARNING: SERIOUS GASTROINTESTINAL ADVERSE REACTIONS**

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

Please see complete Prescribing Information for LOTRONEX<sup>®</sup>/alosetron hydrochloride for full details about risks.

## Boxed Warning (cont'd)

- Alosetron hydrochloride is indicated only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have not responded adequately to conventional therapy.
- 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 resolve after alosetron hydrochloride is discontinued. Patients with resolved constipation should resume alosetron hydrochloride only on the advice of their treating prescriber.

Please see complete Prescribing Information for LOTRONEX<sup>®</sup>/alosectron hydrochloride for full details about risks.

## 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 hydrochloride during clinical trials**
  - ✓ **in addition, rare cases of intestinal perforation and death have been reported from post-marketing clinical practice**
  - ✓ **in some cases, complications of constipation required intestinal surgery, including colectomy**
- The incidence of serious complications of constipation was ~0.1%, or 1 per 1,000 patients, in women receiving either alosetron hydrochloride 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 hydrochloride should be discontinued immediately in patients who develop constipation.

Please see complete Prescribing Information for LOTRONEX<sup>®</sup>/ alosetron hydrochloride for full details about risks.

## 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 hydrochloride 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 hydrochloride 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 hydrochloride for longer than 6 months**

Please see complete Prescribing Information for LOTRONEX<sup>®</sup>/alosetron hydrochloride for full details about risks.

## Warnings and Precautions (cont'd)

### Ischemic Colitis

- Alosetron hydrochloride 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 hydrochloride should not be resumed in patients who develop ischemic colitis.

Please see complete Prescribing Information for LOTRONEX<sup>®</sup>/alosectron hydrochloride for full details about risks.

## Contraindications

- Alosetron hydrochloride should not be initiated in patients with constipation.
- Alosetron hydrochloride 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.**
- Concomitant administration of alosetron hydrochloride and fluvoxamine is contraindicated.

Please see complete Prescribing Information for LOTRONEX<sup>®</sup>/ alosetron hydrochloride for full details about risks.

## Drug Interactions

- In vivo data suggest that alosetron hydrochloride 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 hydrochloride.
- Concomitant administration of alosetron hydrochloride and fluvoxamine is contraindicated.
- Concomitant administration of alosetron hydrochloride 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.

Please see complete Prescribing Information for LOTRONEX<sup>®</sup>/ alosetron hydrochloride for full details about risks.

## Drug Interactions (cont'd)

- Caution should be used when alosetron hydrochloride and ketoconazole are administered concomitantly.
- Coadministration of alosetron hydrochloride 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 hydrochloride and its metabolites is not known.

Please see complete Prescribing Information for LOTRONEX<sup>®</sup>/ alosetron hydrochloride for full details about risks.

## Use in Specific Populations

- Pregnancy Category B.
- It is not known whether alosetron hydrochloride is excreted in human milk; caution should be exercised when alosetron hydrochloride is administered to a nursing woman.
- Safety and effectiveness in pediatric patients have not been established.
- Post-marketing 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 is prescribed for these patients.
- Increased exposure to alosetron hydrochloride and/or its metabolites is likely to occur in patients with hepatic impairment. Alosetron hydrochloride should not be used in patients with severe hepatic impairment and should be used with caution in patients with mild or moderate hepatic impairment.

Please see complete Prescribing Information for LOTRONEX<sup>®</sup>/alosetron hydrochloride for full details about risks.

## Adverse Reactions Reported in $\geq 1\%$ of IBS Patients<sup>a</sup>

<b>Gastrointestinal Adverse Reactions</b>	<b>Alosetron hydrochloride 1 mg BID (n=8,328<sup>b</sup>)</b>	<b>Placebo (n=2,363)</b>
Constipation <sup>c</sup>	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%

<sup>a</sup> Reported in  $\geq 1\%$  of alosetron hydrochloride patients and occurring more frequently on alosetron hydrochloride 1 mg twice-a-day than on placebo.

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

<sup>c</sup>  $P < 0.0001$  vs placebo.

Please see complete Prescribing Information for LOTRONEX<sup>®</sup>/ alosetron hydrochloride for full details about risks.

## Adverse Reactions

- Constipation is a frequent and dose-related side effect of treatment with alosetron hydrochloride.
- In clinical studies constipation was reported in ~29% of patients with IBS treated with alosetron hydrochloride 1 mg twice daily (n=9,316).
  - ✓ **The effect was statistically significant compared with placebo ( $P<0.0001$ );**
  - ✓ **11% of patients treated with alosetron hydrochloride 1 mg twice daily withdrew from the studies due to constipation.**
- Although the number of IBS patients treated with alosetron hydrochloride 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.

Please see complete Prescribing Information for LOTRONEX<sup>®</sup>/alosetron hydrochloride for full details about risks.

## Overdosage

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

Please see complete Prescribing Information for LOTRONEX<sup>®</sup>/ alosetron hydrochloride for full details about risks.

## Section 4:

# How to Prescribe LOTRONEX<sup>®</sup>/alosetron hydrochloride

Please see complete Prescribing Information for LOTRONEX<sup>®</sup>/alosetron hydrochloride for full details about risks.

## Dosage and Administration

- Usual Dose in Adults:
  - ✓ To lower the risk of constipation, alosetron hydrochloride 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.
  - ✓ Alosetron hydrochloride 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.

Please see complete Prescribing Information for LOTRONEX<sup>®</sup>/ alosetron hydrochloride for full details about risks.

## Dosage and Administration (cont'd)

- Usual Dose in Adults (cont't):
  - ✓ **Alosetron hydrochloride 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 hydrochloride should be discontinued immediately in patients who develop constipation or signs of ischemic colitis.**
  - ✓ **Alosetron hydrochloride should not be restarted in patients who develop ischemic colitis.**
- Clinical trial and post-marketing 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 hydrochloride is prescribed for these patients.
- Alosetron hydrochloride can be taken with or without food.

Please see complete Prescribing Information for LOTRONEX<sup>®</sup>/ alosetron hydrochloride for full details about risks.

# Section 5:

## LOTRONEX REMS Program™

Please see complete Prescribing Information for LOTRONEX®/alosetron hydrochloride for full details about risks.

## LOTRONEX REMS Program™

### Prescriber Training

- Prescribers should read the full Prescribing Information (PI) and other training materials to understand the benefits and risks of treatment with LOTRONEX®/alosetron hydrochloride for severe diarrhea-predominant IBS.
- Prescribers can communicate the completion of training by filling out the Prescriber Completion of LOTRONEX REMS Program™ Training Form:
  - online at [www.lotronexrems.com](http://www.lotronexrems.com), or
  - via e-mail at [contactclientservice@prometheuslabs.com](mailto:contactclientservice@prometheuslabs.com), or
  - by fax to Prometheus Client Services at 1-877-816-4019.

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

## LOTRONEX REMS Program™

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

# LOTRONEX REMS Program™

## Patient Education

- Once you have selected an appropriate patient for therapy:
  - ✓ provide the patient with the LOTRONEX® REMS Program 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

# LOTRONEX REMS Program™

## Patient Responsibilities

### Patients should be instructed to:

- read the LOTRONEX REMS Program Patient Education Sheet before starting LOTRONEX®/alosetron hydrochloride .
- read the Medication Guide before starting LOTRONEX®/alosetron hydrochloride and each time they refill their prescription.
- not take LOTRONEX®/alosetron hydrochloride if they are constipated.
- immediately discontinue LOTRONEX®/alosetron hydrochloride 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 LOTRONEX®/alosetron hydrochloride.
- resume LOTRONEX®/alosetron hydrochloride only if their constipation has resolved and after discussion with and the agreement of their treating prescriber.
- stop taking LOTRONEX®/alosetron hydrochloride and contact their prescriber if LOTRONEX®/alosetron hydrochloride does not adequately control IBS symptoms after 4 weeks of taking 1 mg twice-a-day.

**LOTRONEX<sup>®</sup> 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 LOTRONEX/alosetron hydrochloride. 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** LOTRONEX/alosetron hydrochloride immediately in patients who develop constipation or symptoms of ischemic colitis. Do not resume LOTRONEX/alosetron hydrochloride 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<sup>®</sup>)

**Risk of Serious Gastrointestinal Adverse Reactions**

- **Counsel** patients to discontinue LOTRONEX/alosetron hydrochloride 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** LOTRONEX/alosetron hydrochloride 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 LOTRONEX/alosetron hydrochloride in accordance with the approved indication. LOTRONEX 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<sup>®</sup>).

**\*What is the Lotronex 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 Lotronex and its authorized generic alosetron hydrochloride tablets outweigh serious gastrointestinal adverse reactions in patients. This factsheet is required by the FDA as part of the Lotronex REMS program. Please visit [www.LotronexREMS.com](http://www.LotronexREMS.com) for further information.

## Indication:

LOTROX/alosetron hydrochloride is a selective serotonin 5-HT<sub>3</sub> 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 Lotronex/alosetron hydrochloride to the FDA at [www.fda.gov/medwatch](http://www.fda.gov/medwatch), or 1-800-FDA-1088 or Prometheus at 1-888-423-5227.

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

LOT15050 08/15

# LOTRONEX REMS Program Patient Education Sheet

## FDA Required Lotronex/alosetron hydrochloride Safety Information

### What is LOTRONEX/alosetron hydrochloride?

- LOTRONEX/alosetron hydrochloride 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. LOTRONEX/alosetron hydrochloride 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 LOTRONEX/alosetron hydrochloride treatment?

- About 1 out of every 1,000 women who take LOTRONEX/alosetron hydrochloride may get serious complications of constipation. About 3 out of every 1,000 women who take LOTRONEX/alosetron hydrochloride 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 LOTRONEX/alosetron hydrochloride. 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 LOTRONEX/alosetron hydrochloride?

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

### How do I take LOTRONEX/alosetron hydrochloride?

- Take LOTRONEX/alosetron hydrochloride exactly as your doctor prescribes it.

### When should I stop taking LOTRONEX/alosetron hydrochloride and call my doctor?

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

This education sheet only discusses the most serious risk information of LOTRONEX/alosetron hydrochloride. For more safety information about LOTRONEX/alosetron hydrochloride please see the Medication Guide available at [www.LotronexREMS.com](http://www.LotronexREMS.com)

Please visit [www.LotronexREMS.com](http://www.LotronexREMS.com) for further information.

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**PRESCRIBER COMPLETION OF LOTRONEX REMS PROGRAM TRAINING FORM**

Thank you for completing the LOTRONEX 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.

*\* Required fields*

Prescriber's Information:

\*First Name: \_\_\_\_\_ Middle Name: \_\_\_\_\_

\*Last Name: \_\_\_\_\_ Suffix (Sr, Jr, III...): \_\_\_\_\_

\*Signature: \_\_\_\_\_ \*Date: \_\_\_\_\_

\*NPI #: \_\_\_\_\_

Prescriber's Office Address:

\*Address 1: \_\_\_\_\_

Address 2: \_\_\_\_\_

\*City: \_\_\_\_\_ \*State: \_\_\_\_\_ Zip code: \_\_\_\_\_

\*Phone #: \_\_\_\_\_

Fax #: \_\_\_\_\_

\*E-mail: \_\_\_\_\_

E-MAIL TO: [contactclientservices@prometheuslabs.com](mailto:contactclientservices@prometheuslabs.com)

FAX TO: Client Services, Prometheus Laboratories Inc. 1-877-816-4019

MAIL TO: Client Services  
Prometheus Laboratories Inc.  
9410 Carroll Park Drive  
San Diego, CA 92121

LOT15052 08/15

## FDA Required REMS Safety Information

### LOTRONEX<sup>®</sup> and its authorized generic alosetron hydrochloride tablets: Modified REMS

- **RISK OF SERIOUS GASTROINTESTINAL ADVERSE REACTIONS**
  - Infrequent but serious gastrointestinal adverse reactions have been reported with the use of LOTRONEX/alosetron hydrochloride. 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** immediately in patients who develop constipation or symptoms of ischemic colitis. Do not resume LOTRONEX/alosetron hydrochloride 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<sup>®</sup>)

### Important Safety Notice

The FDA has required Prometheus Laboratories to distribute this safety notice to your organization as part of the LOTRONEX REMS (Risk Evaluation and Mitigation Strategy) Program. We request that you inform your members about the following serious risks associated with Lotronex/alosetron hydrochloride and of changes to the LOTRONEX REMS Program:

### Risk of Serious Gastrointestinal Adverse Reactions

- **Counsel** patients to discontinue LOTRONEX/alosetron hydrochloride immediately and contact their prescriber 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** LOTRONEX/alosetron hydrochloride immediately if signs of ischemic colitis occur, such as rectal bleeding, bloody diarrhea, or new or worsening abdominal pain.

### Changes to the REMS Program

- ❶ Prescribers are **no** longer required to affix prescribing program stickers to written prescriptions for LOTRONEX/alosetron hydrochloride
- ❷ Pharmacies are **no** longer required to only dispense LOTRONEX/alosetron hydrochloride 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.

Healthcare providers who prescribe LOTRONEX/alosetron hydrochloride will be provided training to ensure the benefits of LOTRONEX/alosetron hydrochloride continue to outweigh the risks of ischemic colitis and serious

complications of constipation. Training materials can be found at [www.lotronexrems.com](http://www.lotronexrems.com) or by calling 1-888-423-5227. By completing the LOTRONEX REMS Program Training Form a healthcare professional will be entered into a database for trained prescribers.

A non-promotional factsheet, reviewed by the FDA, with more detailed safety information on these risks, and a link to the Prescribing Information including the BOXED WARNING are available at [www.lotronexREMS.com](http://www.lotronexREMS.com).

### **Indication:**

LOTROXEX/alosetron hydrochloride is a selective serotonin 5-HT<sub>3</sub> 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

This letter does not contain the complete safety profile for LOTROXEX/alosetron hydrochloride. Please visit [www.lotronexREMS.com](http://www.lotronexREMS.com) for more information.

### **Reporting Adverse Events:**

You are encouraged to report all suspected adverse events associated with Lotronex/alosetron hydrochloride to the FDA at [www.fda.gov/medwatch](http://www.fda.gov/medwatch), or 1-800-FDA-1088 or Prometheus at 1-888-423-5227.

Sincerely,

Prometheus Laboratories Inc.

LOT15056 08/15



Prescribers



Patients

Prescribing  
InformationMedication  
Guide

## LOTROXEM REMS (Risk Evaluation and Mitigation Strategy) Program

LOTROXEM and its authorized generic alosetron hydrochloride are available by prescription as:  
LOTROXEM<sup>®</sup> (alosetron hydrochloride) Tablets.

What is the LOTROXEM REMS Program?

A REMS is a strategy to manage known or potential serious risks associated with a drug product and is required by the FDA to ensure the benefits of a drug outweigh the risks. The purpose of the LOTROXEM REMS Program is to inform prescribers about the risks of:

Serious Gastrointestinal Adverse Reactions, including ischemic colitis and serious complications of constipation, which have resulted in hospitalization and, rarely, blood transfusion, surgery, and death.

Click below for complete prescribing information, including Boxed Warning and Medication Guide:

- [LOTROXEM<sup>®</sup> \(alosetron hydrochloride\) Tablets](#)
- [Alosetron hydrochloride](#)

**INDICATION:** LOTROXEM/alosetron hydrochloride is indicated only for women with severe diarrhea-predominant irritable bowel syndrome who have: chronic irritable bowel syndrome 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 irritable bowel syndrome 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 irritable bowel syndrome. Because of infrequent but serious gastrointestinal adverse events associated with LOTROXEM/alosetron hydrochloride, 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 LOTROXEM/alosetron hydrochloride in men.



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## Prescriber Information

### What is my role in the LOTRONEX REMS Program?

Healthcare professionals are expected to complete the LOTRONEX REMS Program Prescriber Training and return the LOTRONEX REMS Program Completion of Training Form (online or paper) in order to prescribe LOTRONEX or its authorized generic.

#### Step 1: Complete the LOTRONEX REMS Program Prescriber Training

You should become familiar with the risks of IC and CoC associated with LOTRONEX/alosetron hydrochloride and the requirements of the LOTRONEX REMS Program.

As a prescriber of LOTRONEX/alosetron hydrochloride, you should comply with the LOTRONEX REMS Program by reviewing a [LOTRONEX REMS Program Prescriber Education Slide Deck](#). Then complete a Prescriber [Completion of LOTRONEX REMS Program Training Form](#) to document that you have trained on the benefits and risks of LOTRONEX/alosetron hydrochloride therapy.

#### Step 2: Educate Patients

Counsel patients on the risks associated with LOTRONEX/alosetron hydrochloride and provide the LOTRONEX REMS Program Patient Education Sheet.

### Program Resources and Education Materials

The LOTRONEX REMS Program provides the resources and educational materials you and your patients need to understand your roles and responsibilities in the program.

#### There are two ways to obtain program materials:

1. VIEW, PRINT, OR SAVE ON YOUR COMPUTER –You can view, print, or save the materials to your computer. Select items from the list below.
2. BY PHONE –you can order materials by calling the LOTRONEX REMS Program call center at 1-888-423-5227.
  - [REMS letter Healthcare Providers](#)
  - [LOTRONEX REMS Program Prescriber Education Slide Deck](#)
  - [LOTRONEX REMS Program Safety Information Fact Sheet for Prescribers](#)
  - [LOTRONEX REMS Program Patient Education Sheet](#)
  - [LOTRONEX REMS Program Professional Societies Letter](#)
  - [LOTRONEX Prescribing Information](#)
  - [alosetron hydrochloride Prescribing Information](#)

**INDICATION:** LOTRONEX/alosetron hydrochloride is indicated only for women with severe diarrhea-predominant irritable bowel syndrome who have: chronic irritable bowel syndrome 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 irritable bowel syndrome 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 irritable bowel syndrome. Because of infrequent but serious gastrointestinal adverse events associated with LOTRONEX/alosetron hydrochloride, 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 LOTRONEX/alosetron hydrochloride in men.



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## Medication Guide

### LOTROX<sup>®</sup> (LOW-trah-nex) Tablets (alosetron hydrochloride)

Before using LOTROX for the first time, you should:

- Understand that LOTROX has 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 LOTROX. 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 LOTROX?

##### A. LOTROX is 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 LOTROX. 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 LOTROX 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 LOTROX.

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

- If you are constipated, do not start taking LOTROX.
- If you get constipated while taking LOTROX, stop taking it right away and call your doctor.
- If your constipation does not get better after stopping LOTROX, call your doctor again.
- If you stopped taking LOTROX, do not start taking LOTROX 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 LOTROX 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 LOTROX 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 LOTROX 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. Is LOTROX right for you?

LOTROX 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 LOTROX works in men or children under age 18.

#### 2. What is LOTROX?

LOTROX is 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.

LOTROX does not cure IBS, and it may not help every person who takes it. For those who are helped, LOTROX 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 LOTROX, your IBS symptoms may return within 1 or 2 weeks to what they were before you started taking LOTROX.

LOTROX is not recommended for children.

#### 3. Who should not take LOTROX?

LOTROX is not right for everyone. Do not take LOTROX 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 LOTROX.
- 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<sup>®</sup>).

#### 4. What should I talk about with my doctor before taking LOTROX?

Talk with your doctor:

- about the possible benefits and risks of LOTROX
- 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 LOTROX. Other medicines may interact with how the body handles LOTROX.
- about any allergies that you have. See the end of the Medication Guide for a complete list of ingredients in LOTROX.
- if you are pregnant, planning to get pregnant, or breastfeeding.

#### 5. How should I take LOTROX?

- Take LOTROX exactly as your doctor prescribes it. You can take LOTROX with or without food.
- Begin with 0.5 mg two times a day for 4 weeks to see how LOTROX 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 LOTROX:
  - o 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 LOTROX, your doctor may increase your dose up to 1 mg two times a day.
  - o If 1 mg two times a day does not work after 4 weeks, LOTROX is not likely to help you. You should stop taking it and call your doctor.
- If you miss a dose of LOTROX, 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 LOTROX?" 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 LOTROX, tell the doctor who prescribed LOTROX.

#### 6. What are the possible side effects of LOTROX?

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

This Medication Guide does not tell you about all the possible side effects of LOTROX. 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 LOTROX?

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

Keep LOTROX and all medicines out of the reach of children.

#### 8. General information about the safe and effective use of LOTROX

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you have any questions or concerns about LOTROX, ask your doctor. Do not use LOTROX 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 LOTROX that was written for healthcare professionals. You can also contact the company that makes LOTROX (toll free) at 1-888-423-5227 or at [www.lotronex.com](http://www.lotronex.com).

#### 9. What are the ingredients of LOTROX?

**Active ingredient:** alosetron hydrochloride.

**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.

Manufactured for:

Prometheus Laboratories Inc.  
9410 Carrol Park Drive  
San Diego, CA 92121

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

Revised Month YYYY

LX002E

**INDICATION:** LOTROX (alosetron hydrochloride) is indicated only for women with severe diarrhea-predominant irritable bowel syndrome who have chronic irritable bowel syndrome 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 irritable bowel syndrome 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 irritable bowel syndrome. Because of infrequent but serious gastrointestinal adverse events associated with LOTROX (alosetron hydrochloride), 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 LOTROX (alosetron hydrochloride) in men.



## Patient Information

### INFORMATION FOR PATIENTS

I take LOTRONEX or alosetron hydrochloride tablets, what do I need to know about the LOTRONEX REMS Program?

Review the [LOTROXEM REMS Program Patient Education Sheet](#) with your Health Care Provider.

Important safety information about LOTRONEX/alo setron hydrochloride:

Serious bowel (intestine) side effects can happen suddenly including

- Serious complications of constipation
- Ischemic colitis (reduced blood flow to the bowel)

These complications may lead to hospital stay, and in rare cases blood transfusions, surgery, or death.

Stop taking LOTRONEX/alo setron hydrochloride and call your doctor right away if you get:

- Constipated while taking LOTRONEX/alo setron hydrochloride
- New or worse pain in your stomach area (abdomen)
- Blood in your bowel movements

Do not start taking LOTRONEX/alo setron hydrochloride again until your doctor tells you to do so.

### LOTROXEM/alo setron hydrochloride is:

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.

LOTROXEM/alo setron hydrochloride does not cure IBS, and it may not help every person who takes it. For those who are helped, LOTROXEM/alo setron hydrochloride 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 LOTROXEM/alo setron hydrochloride, your IBS symptoms may return within 1 or 2 weeks to what they were before you started LOTROXEM/alo setron hydrochloride.

Download the:

[LOTROXEM REMS Program Patient Education Sheet](#)



**INDICATION:** LOTROXEM/alo setron hydrochloride is indicated only for women with severe diarrhea-predominant irritable bowel syndrome who have: chronic irritable bowel syndrome 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 irritable bowel syndrome 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 irritable bowel syndrome. Because of infrequent but serious gastrointestinal adverse events associated with LOTROXEM/alo setron hydrochloride, 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 LOTROXEM/alo setron hydrochloride in men.



Reference within this site to any specific advertisement or promotion of a non-Prometheus product does not constitute an endorsement or recommendation by Prometheus.  
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 A Nestlé Health Science Company



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/s/  
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JOYCE A KORVICK  
01/07/2016

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**021107Orig1s026**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**RISK EVALUATION AND MITIGATION STRATEGY (REMS)  
MODIFICATION REVIEW**

Date: January 6, 2016

Reviewers: Bob Pratt, Pharm.D.  
Risk Management Analyst  
Division of Risk Management

Ana Tavakoli, M.A.  
Health Communications Analyst  
Division of Risk Management

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Division of Risk Management

Acting Deputy Director: Kellie Taylor, Pharm.D., M.P.H.  
Division of Risk Management

Division Director: Cynthia LaCivita, Pharm.D.  
Division of Risk Management

Subject: Evaluation of a proposed REMS modification

Drug Name(s): Lotronex<sup>®</sup> (alosetron hydrochloride)

Therapeutic Class: Selective serotonin 5-HT<sub>3</sub> antagonist

Dosage and Route: 0.5 and 1.0 mg oral tablets, one tablet twice a day

Application Type/Number: NDA 21107, Suppl-026

Applicant: Prometheus Laboratories, Inc.

OSE RCM #: 2015-1877

\*\*\* This document contains proprietary and confidential information that should not be released to the public. \*\*\*

## 1. INTRODUCTION

This review evaluates Prometheus Laboratories' (Prometheus) proposed risk evaluation and mitigation strategy (REMS) modification for Lotronex<sup>®</sup> (alosetron hydrochloride) and authorized generic, NDA 21107 (Suppl-26). The proposed modification was submitted on August 18, 2015, and amended September 17, September 28, December 1, December 29, 2015, and January 4, 2016.

### 1.1. REGULATORY HISTORY

Lotronex was approved on June 7, 2002, under 21 CFR 314 Subpart H with a risk management plan, which was subsequently approved as a REMS with elements to assure safe use (ETASU) on September 2, 2010. The REMS addresses the risk of ischemic colitis and serious complications of constipation associated with the treatment.

The regulatory history that relates to the applicant's REMS modification proposed in Supplement 26 is summarized below:

May 11, 2015: The Agency sent Prometheus a REMS Modification Notification letter, which stated that the approved REMS for Lotronex must be modified to minimize the burden on the healthcare delivery system of complying with the REMS. Prometheus 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 the dispensing system. (The Agency's version of the modified REMS document was provided to the applicant on May 20, 2015.)

July 24, 2015: The Agency approves a REMS modification to include an authorized generic of Lotronex in the REMS.

August 18, 2015: Prometheus submitted a proposed REMS modification (Supplement 26) in response to the May 11, 2015 letter. The proposal includes modified REMS goals, removal of the Medication Guide from the REMS elements, and modifications to the ETASU.

September 3, 2015: A teleconference was held with Prometheus to provide general advice regarding the proposed REMS modification (Memorandum to File provided to Prometheus by email September 14, 2015).

September 17, 2015: Prometheus submitted an amendment to the proposed REMS modification, Supplement 26 (Serial No. 292).

September 17, 2015: Prometheus submitted a prior approval labeling supplement that proposed changes to the prescribing information and Medication Guide to align with the proposed REMS modification, Supplement 27.

September 24, 2015: The Agency sent an Information Request (via email) to Prometheus for the submission of pdf screenshots of the REMS webpages.

September 28, 2015: Prometheus submitted an amendment to the proposed REMS modification in Supplement 26 (Serial No. 294) that provided web page mock-ups.

November 2, 2015: A Type B Meeting teleconference was held with Prometheus (b) (4)

November 18, 2015: The Agency sent an Advice Letter to Prometheus with comments and revisions to the proposed modification of the REMS, appended materials, and supporting document.

December 1, 2015: Prometheus submitted an amendment to the proposed REMS modification, Supplement 26 (Serial No. 297).

December 9, 2015: The Agency sent an Information Request (via email) to Prometheus with comments regarding the proposed modification of the REMS and appended materials.

December 11, 2015: Prometheus responded to the December 9, 2015 Information Request by emailing revised files of the REMS document and pertinent appended materials.

December 15, 2015: The Agency sent an Information Request (via email) to Prometheus with comments regarding the REMS letter for Healthcare Providers and the REMS website.

December 15, 2015: Prometheus responded to the December 15, 2015 Information Request by emailing revised files of the REMS letter for Healthcare Providers and the REMS website.

December 22, 2015: The Agency sent an Information Request (via email) to Prometheus with comments regarding the REMS document, supporting document, Safety Information Fact Sheet for Prescribers, REMS website, and instructions for resubmission.

December 29, 2015: Prometheus submitted an amendment to the proposed REMS modification, Supplement 26 (Serial No. 300).

January 4, 2016: The Agency sent an Information Request (via email) to Prometheus with comments regarding the REMS assessment plan and supporting document and instructions for resubmission.

January 4, 2016: Prometheus responded to the January 4, 2016 Information Request by emailing a revised file of the REMS supporting document.

## **2. MATERIALS REVIEWED**

The following is a list of materials used to inform this review:

- Pratt R., DRISK REMS Modification Review for Lotronex, NDA 21107, November 16, 2015
- Prometheus, Lotronex, NDA 21107 submission, Suppl 26
  - Amended proposed REMS modification, received December 1, 2015, (Serial No. 297)
  - Amended proposed REMS modification, received December 11, 2015 by email
    - REMS document, REMS letter for Healthcare Providers, REMS letter for Professional Society, Prescriber Slide Deck, Prescriber Safety Information Fact Sheet, Prescriber Completion of Training Form, REMS website
  - Amended proposed REMS modification, received December 15, 2015 by email
    - REMS letter for Healthcare Providers, REMS website
  - Amended proposed REMS modification received December 29, 2015 (Serial No. 300)
  - Amended proposed REMS modification, received January 4, 2016 by email
    - REMS supporting document

## **3. RESULTS OF REVIEW OF PROPOSED REMS MODIFICATION**

The applicant incorporated and responded appropriately to all of the Agency's comments and revisions requested in the November 18, December 9, December 15, December 22, 2015, and

January 4, 2016, Information Requests regarding the REMS document and appended REMS materials, and the REMS supporting document.

### **3.1. REMS SUPPORTING DOCUMENT AND REMS ASSESSMENT PLAN**

The applicant's revised REMS supporting document is consistent with the REMS and appended REMS materials.

## **4. CONCLUSION AND RECOMMENDATIONS**

DRISK finds the proposed Lotronex REMS and its appended materials (attached) as submitted on December 29, 2015, and supporting document as submitted on January 4, 2016, acceptable. The REMS as currently proposed in this supplement is structured consistent with the advice we gave in the May 2015 REMS Modification Notification letter.

DRISK recommends approval of the REMS appended to this review.

The following assessment plan for this modified REMS is to be included in approval letter:

- 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 Lotronex and its authorized generic, and the actions patients need to take should they experience early warning signs and symptoms of these risks.
- Results of an evaluation of prescriber understanding of the appropriate patient population, the risks of ischemic colitis and serious complications of constipation associated with Lotronex and its authorized generic, 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.
- The number of prescribers and medical specialty of prescribers who reported that they completed training in the Lotronex REMS Program, including the number and medical specialty of prescribers contacted by Prometheus to become trained after prescribing Lotronex and its authorized generic and the number and medical specialty contacted who completed training, during the reporting period and cumulative.
- The number of prescribers who have not completed training and are writing prescriptions.
- Numbers of prescriptions, by year for the last five years and annually thereafter.
- 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.
- Summary and discussion of the above cases (received during the reporting period) and the clinical significance of these events.

- 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.

## APPENDIX

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/s/  
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ROBERT G PRATT  
01/06/2016

CYNTHIA L LACIVITA  
01/06/2016  
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**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**RISK EVALUATION AND MITIGATION STRATEGY (REMS)  
MODIFICATION REVIEW**

Date: November 16, 2015

Reviewers: Bob Pratt, Pharm.D.  
Risk Management Analyst  
Division of Risk Management

Ana Tavakoli, M.A.  
Health Communications Analyst  
Division of Risk Management

Acting Team Leader: Jamie Wilkins Parker, Pharm.D.  
Division of Risk Management

Deputy Director: Reema Mehta, Pharm.D., M.P.H.  
Division of Risk Management

Subject: Evaluation of a proposed REMS modification

Drug Name(s): Lotronex<sup>®</sup> (alosetron hydrochloride)

Therapeutic Class: Selective serotonin 5-HT<sub>3</sub> antagonist

Dosage and Route: 0.5 and 1.0 mg oral tablets, one tablet twice a day

Application Type/Number: NDA 21107, Suppl-026

applicant: Prometheus Laboratories, Inc.

OSE RCM #: 2015-1877

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## **EXECUTIVE SUMMARY**

This is a review of Prometheus Laboratories' (Prometheus) proposed Risk Evaluation and Mitigation Strategy (REMS) modification for Lotronex<sup>®</sup> (alosetron hydrochloride), NDA 21107. The proposed modification was submitted on August 18, 2015, and amended September 17 and September 28, 2015 in response to a REMS Modification Notification letter issued by the Agency on May 11, 2015.

Lotronex was approved on June 7, 2002, under 21 CFR 314 Subpart H with a risk management plan, which was subsequently approved as a REMS on September 2, 2010. The REMS addresses the risk of ischemic colitis and serious complications of constipation associated with the treatment, and consists of a Medication Guide; elements to assure safe use (ETASU) that include prescriber certification (ETASU A) and safe use conditions (ETASU D); an implementation system; and a timetable for submission of assessments.

The Agency's May 11, 2015 modification notice requested modification of the goals, removal of the Medication Guide and safe use conditions (ETASU D) from the REMS, and that prescriber certification is changed to a prescriber training program not linked to the dispensing system. These changes are required to minimize the burden on the healthcare system of complying with the REMS while ensuring the benefits of the drug outweigh the risks. The proposed modified REMS consists of a prescriber training program under ETASU A. The Division of Risk Management (DRISK) finds the proposed modification requires additional changes to the REMS document and materials, as well as to the REMS assessment plan described in the supporting document.

### **1. INTRODUCTION**

This is a review of Prometheus' proposed modification to the risk evaluation and mitigation strategy (REMS) for Lotronex (alosetron hydrochloride), NDA 21107, submitted on August 18, 2015, and amended September 17 and September 28, 2015.

#### **1.1. BACKGROUND**

Lotronex is a selective serotonin 5-HT<sub>3</sub> receptor antagonist approved for the treatment of women with severe diarrhea-predominant irritable bowel syndrome<sup>1</sup> (IBS) who have chronic IBS symptoms (generally lasting 6 months or longer), have had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and have not responded adequately to conventional therapy.

After its approval on February 9, 2000, Lotronex was voluntarily withdrawn from the U.S. market by GlaxoSmithKline on November 28, 2000, due to postmarketing cases of serious adverse events including ischemic colitis and serious complications of constipation; some of these cases were fatal or required surgery or blood transfusions. Lotronex was reintroduced to the market on June 7, 2002, with approval under 21 CFR 314 Subpart H. This approval included a more restricted indication for women in whom the benefit-to-risk balance is most favorable, the addition of a Boxed Warning, and a risk management plan (RMP) with restricted distribution to address the serious risks associated with treatment. Under the Food and Drug Administration Amendments Act of 2007, Lotronex was identified as a product with a deemed REMS based on elements to

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<sup>1</sup> Severe diarrhea is defined in the Lotronex Prescribing Information as 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.

assure safe use in the RMP. Prometheus Laboratories acquired NDA 21-107 from GlaxoSmithKline on January 4, 2008. A formal REMS proposal was submitted by the applicant and subsequently approved on September 2, 2010. A REMS Modification was approved on May 8, 2014 that made clerical revisions to the prescriber enrollment form. A second REMS modification was approved July 24, 2015, to include an authorized generic of alosetron hydrochloride in the REMS.

The REMS (as well as its predecessor RMP) is referred to as the Prescribing Program for Lotronex™ (PPL) and consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments.

The goals of the currently approved REMS are:

- To mitigate the risk of ischemic colitis (IC) and serious complications of constipation (CoC) associated with alosetron hydrochloride by ensuring that Lotronex and its authorized generic are used in only severely affected patients for whom benefits exceed the risks.
- To ensure that the risk of IC and serious CoC with the use of Lotronex and its authorized generic are communicated to patients, pharmacists, and prescribers.

A generic equivalent of Lotronex, alosetron hydrochloride (alosetron), sponsored by Roxane Laboratories (ANDA 200652) was approved on May 4, 2015. The application was approved with a REMS comparable to the Lotronex REMS after the Agency granted Roxane a waiver from the requirement to form a single, shared system (SSS) REMS with Lotronex. In issuing the waiver, the Agency concluded that the burden of creating a SSS REMS for these alosetron products outweighed the benefit of a SSS REMS. The alosetron REMS is referred to as the ‘Alosetron REMS Program.’

## **1.2. REGULATORY HISTORY**

The regulatory history that relates to the applicant’s REMS modification proposed in Supplement 26 is summarized below:

September 2, 2010: Lotronex REMS is approved, NDA 21-107/S-014

May 4, 2015: Alosetron REMS Program, alosetron hydrochloride (ANDA 200652) sponsored by Roxane is approved, which had the requirement for a single, shared system REMS waived by the Agency.

May 11, 2015: The Agency sent Prometheus a REMS Modification Notification letter to request removal of 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 the dispensing system. (The Agency’s version of the modified REMS document was provided to the applicant on May 20, 2015.) The changes are required to minimize the burden on the healthcare system of complying with the REMS.

May 26, 2015: Prometheus submitted a REMS revision to add an authorized generic to the REMS for Lotronex.

June 11, 2015: The Agency sent a CBE-30 Supplement Acknowledgement Letter to Prometheus that stated the proposed revision is considered a REMS minor modification and that the submission has been changed to a Changes Being Effected in 30 days supplement.

July 24, 2015: The Agency approves a REMS modification to include an authorized generic of Lotronex in the REMS.

August 18, 2015: Prometheus submitted a proposed REMS modification (Supplement 26) in response to the May 11, 2015 letter. The proposal includes modified REMS goals, removal of the Medication Guide from the REMS elements, and modifications to the ETASU.

September 3, 2015: A teleconference was held with Prometheus to provide general advice regarding the proposed REMS modification (*Memorandum to File provided to Prometheus by email September 14, 2015*).

September 17, 2015: Prometheus submitted an amendment to the proposed REMS modification, Supplement 26

September 17, 2015: Prometheus submitted a prior approval labeling supplement that proposed changes to the prescribing information and Medication Guide to align with the proposed REMS modification, Supplement 27

September 28, 2015: Prometheus submitted an amendment to the proposed REMS modification in Supplement 26 that provided web page mock-ups at the Agency's request (*Information Request sent by email September 24, 2015*).

## **2. MATERIALS REVIEWED**

The following is a list of materials used to inform this review:

- Pratt R., DRISK REMS Modification Review for Lotronex, NDA 21107, May 11, 2015
- Division of Gastroenterology and Inborn Errors Products (DGIEP), REMS Modification Notification Letter, NDA 21107, May 11, 2015
- Prometheus, Lotronex, NDA 21107 submission, Suppl 26
  - Proposed REMS modification, received August 18, 2015, (Serial No. 290)
- Prometheus, Lotronex, NDA 21107 submission, Suppl 26
  - Amended proposed REMS modification, received September 17, 2015 (Serial No. 292)
- Prometheus, Lotronex, NDA 21107 submission, Suppl 26
  - Amended proposed REMS modification received September 28, 2015 (Serial No. 294)

## **3. RATIONALE FOR THE PROPOSED REMS MODIFICATION**

Prometheus submitted the proposed REMS modification in response to the Agency's REMS Modification Notification letter issued May 11, 2015. In that letter, the Agency requested modification of the REMS goals; removal of the Medication Guide and safe use conditions (ETASU D) from the REMS; and that prescriber certification be changed to a prescriber training program (ETASU A) not linked to the dispensing system. The modified program reduces unnecessary burden on the healthcare system of complying with the REMS primarily by eliminating the outdated prescribing sticker program.

For the elements to assure safe use, the Agency determined that the training of healthcare providers who prescribe alosetron must continue to be provided to ensure the benefits of the drug continue to outweigh the risks of ischemic colitis and serious complications of constipation. The prescriber training materials are to include the prescribing information, a Prescriber Education Program Slide Deck, and a newly developed one-page Safety Information Fact Sheet for

Prescribers to communicate the key risk messages associated with alosetron. In addition, prescribers no longer need to affix prescribing program stickers to written prescriptions for alosetron and pharmacies no longer need to only dispense alosetron for a paper prescription affixed with a prescribing program sticker. Also, the Patient Acknowledgement Form is to be modified to a Patient Education Form and becomes the primary educational tool used by prescribers for counseling patients regarding the risks of alosetron.

#### **4. RESULTS OF REVIEW OF PROPOSED REMS MODIFICATIONS**

The applicant's proposed modifications to the REMS goals and elements received August 18, 2015, and amended on September 17 and September 28, 2015, are described below. The proposed modification addresses the Agency's notification dated May 11, 2015 to modify the approved REMS, and harmonizes naming conventions with the REMS modification approved July 24, 2015 that added an authorized generic to the REMS.

##### **4.1. GOALS**

The proposed modified REMS goals align with the changes requested by the Agency and address the modification approved in July 2015 that included an authorized generic in the REMS. The modified goals are stated as:

The goals and objectives of the Lotronex REMS are to mitigate the risks of ischemic colitis (IC) and serious complications of constipation (CoC) associated with Lotronex and its authorized generic alosetron hydrochloride by:

- Informing prescribers of Lotronex/alosetron hydrochloride about:
  - the serious risks of IC and serious CoC associated with Lotronex/alosetron hydrochloride
  - the importance of understanding that Lotronex/alosetron hydrochloride should only be used in severely affected diarrhea-predominant irritable bowel syndrome patients for whom 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.

*Reviewer comment: We agree with the applicant's proposed goals, as these are the goals reflected in the REMS document attached to the May 20, 2015 REMS Modification Notification Letter.*

##### **4.2. REMS ELEMENTS**

The REMS document is generally acceptable with the exception of the proposed name of the safety information fact sheet for prescribers and the patient education sheet, which require revision as described in the sections below. Minor edits to the REMS document are shown in the redlined version attached to this review.

###### **4.2.1. Medication Guide**

Prometheus removed the Medication Guide (MG) from the REMS, as requested.

*Reviewer comment: The Medication Guide will continue to be part of the approved labeling and distributed as required under 21 CFR 208.*

## 4.2.2. Elements to Assure Safe Use

### 4.2.2.1. Removal of ETASU D

The safe-use conditions (prior ETASU D) that required patients to sign an acknowledgement form, and that required pharmacists to dispense the product only with documentation of safe use using the prescribing program sticker, have been removed.

### 4.2.2.2. Modifications to ETASU A

The modified REMS document changes ETASU A from a requirement for special certification of prescribers, to a requirement that the applicant provide training to healthcare providers on the serious risks; the importance of understanding the indicated population; and the importance of counseling patients about the risks.

The applicant's proposed appended materials under ETASU A include the following:

#### 1. REMS letter to Healthcare Providers

The REMS letter to Healthcare Providers is a one-time letter sent to inform providers who are likely to prescribe, or have prescribed Lotronex/alosetron hydrochloride in the 24 months preceding the REMS modification, about the changes to the program and to provide the training materials.

Prometheus proposed that prescribers who previously enrolled in the Prescribing Program for Lotronex (PPL) are adequately trained in the safety risk message, which is unchanged in the modified program, and that their trained status will be transferred to the new Lotronex REMS program. For this reason, (b) (4)

#### *Reviewer Comments:*

*We agree with Prometheus that prescribers who are already enrolled in the Prescribing Program for Lotronex are adequately trained in understanding the benefits and risks of Lotronex/alosetron hydrochloride, and do not need to complete re-training in the modified program.* (b) (4)

*Additionally, an electronic version of this letter should be appended to the REMS Supporting Document. See the Agency's recommended version appended to this review.*

## 2. REMS letter for Professional Societies

The REMS letter to Professional Societies requests the Society to provide the letter to their membership within 6 months and again within 12 months after approval of the REMS modification.

Prometheus proposed a letter that describes the indication, the changes to the REMS program, [REDACTED] the indication and usage of alosetron, instructions for how prescribers access the training materials, the important safety information, and the process for reporting adverse events. [REDACTED] (b) (4)

### *Reviewer Comments:*

*The REMS letter to Professional Societies is for the society to distribute to their membership within 6 months and again within 12 months after approval of the modified Lotronex REMS Program.* [REDACTED] (b) (4)

*See a clean version of the Agency's recommended letter appended to this review. Additionally, an electronic version of this letter should be appended to the REMS Supporting Document. See the Agency's recommended version appended to this review.*

## 3. Prescriber Completion of Training Form

The applicant is to ensure that prescribers can notify them when they have completed training via the REMS program website or by mailing or faxing a Completion of Training Form. Completion of training will be defined as all training materials were reviewed independently by the healthcare provider.

### *Reviewer Comments:*

*We agree with the applicant's proposal, but request that a signature and date line be added to the form.*

## 4. Lotronex REMS Prescriber Education Program

The prescriber education program slide deck is a required material in the REMS Training Kit.

Prometheus proposed that the Lotronex REMS Prescriber Education Program is re-named the Lotronex REMS Prescriber Education Program Slide Deck, because the word 'Program' is utilized to encompass all the components of the REMS program.

### *Reviewer Comments:*

*We agree with the applicant's proposal to re-name the slide deck as stated.*

*There are several instances in the slides where Prometheus has replaced 'Lotronex' in the currently approved REMS with 'alosetron hydrochloride' when referencing the prescribing information (of which there is a Lotronex version and an authorized generic version). We believe this change is not substantive and will not be a source of confusion for prescribers with regard to which product (i.e., Prometheus' Lotronex and its authorized generic, compared with Roxane's alosetron) is covered by which REMS training program. In addition, the proposed Lotronex REMS program name is that requested by the Agency and remains distinct from the Alosetron REMS program name.*

*The prescriber education program slide deck is otherwise acceptable with the editorial changes outlined in the redlined version appended to this review.*

#### 5. Safety Information Fact Sheet for Prescribers

The Safety Information Fact Sheet is a newly developed tool for prescribers that communicates the key risk messages associated with Lotronex. The development of the fact sheet was requested in the Agency's REMS Modification Notification letter issued May 11, 2015.

*Reviewer Comments:*

*We agree with the applicant's general approach for the development of a fact sheet, but find it to be too dense with information and less reader-friendly than is ideal. We have revised the fact sheet based on safety information fact sheets from other approved REMS programs.*

*For the sake of consistency across the appended REMS materials, the fact sheet should be re-named the Lotronex REMS Program Safety Information Fact Sheet for Prescribers.*

#### 6. Lotronex Patient Education Form

The Lotronex Patient Acknowledgement Form in the currently approved REMS (as part of the safe-use conditions) is to be modified to a Patient Education Form, and become the primary educational tool used by prescribers for counseling patients regarding the risks of Lotronex in lieu of the MG. The form no longer requires a signature or placement of a copy in the patient's medical record.

Prometheus proposed that the patient education form is better identified as a patient education sheet because the document will not require the patient or prescriber to fill out any information or collect a signature.

*Reviewer Comments:*

*We agree with the applicant's proposal to re-name the education form as an education sheet.* (b) (4)

*For the sake of consistency across the appended REMS materials, the education sheet should be re-named the Lotronex REMS Program Patient Education Sheet. The sub-heading should read: FDA Required Lotronex Safety Information.*

*The patient education sheet is otherwise acceptable with the editorial changes outlined in the redlined version appended to this review.*

#### 7. REMS Website

The REMS website screenshot sections for prescribers and patients are materials appended to the REMS. The currently approved REMS includes a section for pharmacists. There are no requirements for pharmacists in the modified program, and so the website section for pharmacists will be removed.

All of the appended materials in the modified REMS are to be available on the website.

*Reviewer Comments:*

*The applicant should ensure the REMS website is independent of links to the promotional and/or commercial website and non-REMS materials about the product. Do not include a link from the REMS website back to the commercial website. The REMS website should also be accessible directly through a search engine. The REMS website, including all REMS materials will be available for the duration of the REMS.*

*The following is a link to helpful guidelines developed by HHS that Prometheus may consider in developing the website:*

*[http://www.usability.gov/sites/default/files/documents/guidelines\\_book.pdf?post=yes](http://www.usability.gov/sites/default/files/documents/guidelines_book.pdf?post=yes)*

#### **4.2.3. Implementation System**

There is no implementation system in the modified REMS.

#### **4.2.4. Timetable for Submission of Assessments**

Prometheus proposed a timetable in agreement with that sent in the modification notification letter.

*Reviewer Comments:*

*After further internal discussion, we believe the timetable should be changed to allow for increased time to obtain survey participants for the first assessment of the modified REMS. Prometheus is to submit REMS assessments to the Agency 18 months from the date of approval of the modified REMS and every 12 months thereafter. This is reflected in the attached redlined REMS document.*

#### **4.3. REMS SUPPORTING DOCUMENT**

Prometheus submitted a revised supporting document that describes changes to the REMS goals, elements, implementation system, and assessment plan.

- The REMS goals listed in the supporting document align with the modified REMS document and the changes requested by the Agency in the REMS modification notification.
- The introduction to the supporting information for the proposed ETASU describes how the elements, [REDACTED] (b) (4) and that patients are educated on the risks.

*Reviewer comment: The language requires editing because the ETASU only ensure that training will be provided to prescribers. See the Agency's redlined version of the supporting document appended to this review.*

#### **Healthcare Provider Training Reminder Letter**

In the modified REMS, the applicant is to monitor distribution and prescription data monthly, contact prescribers identified as not having completed training, and provide the training; [REDACTED] (b) (4)

Prometheus submitted a Program Training Reminder Letter appended to the REMS supporting document, which describes how the letter will serve as one contact option in addition to email or telephone.

*Reviewer Comments:*

*We agree with the applicant's proposal to use a reminder letter as one option to follow-up with prescribers who have not completed training. The method and details of prescriber follow-up contact are not prescribed by the Lotronex REMS. See the Agency's appended redlined version of the letter for recommended editorial changes to the letter.*

## 5. REMS ASSESSMENT PLAN

The REMS assessment plan is summarized in the supporting document and will be addressed in the REMS modification approval letter. The applicant's proposed assessment plan (b) (4) and has also eliminated a number of metrics assessed in the currently approved REMS, and makes other appropriate changes to the plan, which reflects the modified program. The following revisions are proposed:

- (b) (4)

*Reviewer comment:*

*Success of the modified program may be defined, in part, by prescribers and patients demonstrating a level of knowledge and understanding about the risks that is similar to what has been observed in the assessments of the currently approved REMS. The surveys of prescribers should include those who completed training in the modified REMS and those who have not reported completion of training; similar survey findings in knowledge and understanding between these two prescriber groups would lend a measure of support for eliminating the REMS in the future. Pharmacists have no requirements in the modified REMS. Therefore, surveys of pharmacists are no longer required.*

*In the currently approved REMS, patients can volunteer to participate in surveys by submitting an enrollment form that is included with the dispensed prescription or provided to the patient by the prescribing physician. The Agency has removed the enrollment form and the requirement for prescribers to inform patients about the survey and provide them with the form; however, this form may continue to be used outside of the REMS as an option for inviting patients to participate in the survey.*

- Report on the number of prescribers who have completed training instead of the number of prescribers who enrolled in the REMS.
- Remove the report of whether pharmacists are filling prescriptions written by prescribers not enrolled in the program. Remove the report on failures by pharmacists to adhere to the dispensing or "sticker" program requirements and corrective actions taken to address non-compliance. (Prometheus also proposes to continue assessments to evaluate whether prescribers not enrolled in the program are writing prescriptions.)

*Reviewer comment: The prescriber training program is unlinked from dispensing in the modified REMS. As pharmacists no longer have requirements under the modified program, the proposal to remove the specified reports is acceptable.*

*Prescribers do not enroll in the modified program. However, we agree that Prometheus may assess whether untrained prescribers are writing prescriptions.*

- Remove the report on the distribution and dispensing of the Medication Guide.  
*Reviewer comment: The Medication Guide has been removed from the REMS. Assessments of its distribution and dispensing are no longer required.*

### **5.1. REVISED REMS ASSESSMENT PLAN**

Based on recommendations in DRISK's REMS modification review of May 11, 2015 and the applicant's proposal, the applicant's REMS assessment plan should be revised to include, but is not limited to, the following:

- 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 Lotronex and its authorized generic, and the actions patients need to take should they experience early warning signs and symptoms of these risks.
- Results of an evaluation of prescriber understanding of the appropriate patient population, the risks of ischemic colitis and serious complications of constipation associated with Lotronex and its authorized generic, 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.
- The number of prescribers and medical specialty of prescribers who reported that they completed training in the Lotronex REMS Program, including the number of prescribers contacted by Prometheus to become trained after prescribing Lotronex and its authorized generic and the number contacted who completed training, during the reporting period and cumulative.
- The number of prescribers who have not completed training and are writing prescriptions.
- Numbers of prescriptions, by year for the last five years and annually thereafter.
- Number of cases of the following events reported (from any source) during the reporting period and cumulative:
  - i. All reports of ischemic colitis;
  - ii. All reports involving ischemic changes, ischemia, or necrosis of the colon
  - iii. All reports involving constipation requiring hospitalization or emergency room visit;
  - iv. 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;
  - v. All reports of death, regardless of causality.
- Summary and discussion of the above cases (received during the reporting period) and the clinical significance of these events.
- 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.

## **6. DISCUSSION**

Prometheus submitted a proposed modification to the REMS in response to the Modification Notification letter sent by the Agency on May 11, 2015. The proposed modified REMS consists of

a prescriber training program under ETASU A. The proposal removes the Medication Guide and ETASU D safe-use conditions from the REMS and modifies the requirement for special certification of prescribers. The modified program reduces unnecessary burden on the healthcare system primarily by eliminating the outdated prescribing sticker program.

We agree with Prometheus that prescribers who are already enrolled in the Prescribing Program for Lotronex are adequately trained in understanding the benefits and risks of Lotronex/alosetron hydrochloride, and do not need to complete re-training in the modified program. We believe the use of one REMS letter targeted to PPL-enrolled and non-enrolled prescribers will avoid potential distribution errors while addressing the need to inform healthcare providers about the REMS program modifications, availability of training materials, and the actions that all prescribers need to take in order to prescribe Lotronex/alosetron hydrochloride. We also believe that this messaging may be sent in electronic format in addition to hard copy and have provided email versions for the REMS letter for Healthcare Providers as well as the REMS letter for Professional Societies.

The prescriber education slide deck is suitable with minor editing and relies on much of the same benefit-risk content as is found in the currently approved program. We have made numerous changes to the Safety Information Fact Sheet for Prescribers as well as the Patient Education Sheet in order to make them more user-friendly and improve the messaging of these documents. We also have general comments and several edits to the REMS websites that aim to improve the layout.

Assessments of knowledge and understanding of prescribers and patients should continue for the purpose of assessing the modified REMS. Although the Agency removed the patient pre-enrollment form as a requirement under the REMS, this form and the survey program may continue to be used outside of the REMS at the applicant's discretion.

DRISK finds the proposed modification requires additional changes to the REMS document and materials, as well as to the REMS assessment plan and supporting document.

## **7. RECOMMENDATIONS FOR THE REVIEW DIVISION**

We recommend that the following comments on the Lotronex/alosetron hydrochloride REMS modification proposal be sent to the applicant. Please request that the applicant respond to these comments by the close of business on December 2, 2015, to facilitate further review.

The comments below are based on DRISK's interim review of the REMS modification proposal for Lotronex/alosetron hydrochloride. Appended to this review is the REMS Document and appended REMS materials, including our redlined versions. The applicant should be reminded that the REMS supporting document must be consistent with all changes made to the REMS document.

## **8. COMMENTS TO BE SENT TO THE APPLICANT**

### **8.1. REMS DOCUMENT**

Remove the header from all pages, and add the dates for approval of the initial REMS and most recently modified REMS, as shown on the appended redlined version (Appendix A). See additional comments below related to the appended materials and timetable for submission of assessments.

## 8.2. REMS LETTER FOR HEALTHCARE PROVIDERS

- We agree that prescribers who are already enrolled in the Prescribing Program for Lotronex are adequately trained in understanding the benefits and risks of Lotronex/alosetron hydrochloride, and do not need to complete re-training in the modified program. It will be sufficient for these prescribers to be notified of the changes to the program. (b) (4)

- The outside of the mailed envelope should state: "FDA Required REMS Safety Information": it should be printed in red, bolded, and a minimum size 14 font. It may be on two lines and should be boxed, for example:

**FDA Required REMS  
Safety Information**

- The REMS letter to Healthcare Providers should also be formatted in an electronic version, which should be appended to the REMS supporting document. The electronic version of the letter should be email- and handheld device-friendly. The subject of the email should be, "FDA Required REMS Safety Information: LOTRONEX". The objective of these changes is to improve the communication of the risk message among the growing healthcare provider population of hand-held device users. See the appended recommended version of an electronic REMS letter to Healthcare Providers (Appendix C).

## 8.3. PRESCRIBER EDUCATION SLIDE DECK

We agree with your proposal to re-name the Prescriber Education Program to the Prescriber Education Slide Deck.

The slide deck is acceptable with the editorial changes outlined in the appended redlined version (Appendix D).

## 8.4. SAFETY INFORMATION FACT SHEET FOR PRESCRIBERS

For the sake of consistency in naming conventions across the appended REMS materials, the fact sheet should be re-named the Lotronex REMS Program Safety Information Fact Sheet for Prescribers. We have revised the fact sheet for prescribers to make it more reader-friendly and to improve the messaging. See the appended clean version of the Agency's recommended fact sheet for prescribers (Appendix E).

## 8.5. PATIENT EDUCATION SHEET

- We agree with your proposal to re-name the patient education form as a patient education sheet. (b) (4)

- For the sake of consistency in naming conventions across the appended REMS materials, the education sheet should be re-named the Lotronex REMS Program Patient Education Sheet. The sub-heading should read: FDA Required Lotronex/alosetron hydrochloride Safety Information. We have revised the patient education sheet to make it more reader-friendly and to improve the messaging. See the appended redlined version of the Agency's patient education sheet for edits and comments (Appendix F).

#### **8.6. PRESCRIBER COMPLETION OF LOTRONEX REMS PROGRAM TRAINING FORM**

We agree with your proposed completion of training form, but request that a signature and date line be added to the form. See the appended redlined version (Appendix G).

#### **8.7. REMS WEBSITE SECTIONS**

Ensure that the REMS website is independent of links to the promotional and/or commercial website and non-REMS materials about the product. Do not include a link from the REMS website back to the commercial website. The REMS website should also be accessible directly through a search engine. The REMS website, including all REMS materials will be available for the duration of the REMS.

The following is a link to helpful guidelines developed by DHHS that you may consider in developing the website:

[http://www.usability.gov/sites/default/files/documents/guidelines\\_book.pdf?post=yes](http://www.usability.gov/sites/default/files/documents/guidelines_book.pdf?post=yes)

See the appended versions of the REMS website sections for prescribers and patients for further edits and comments (Appendix H and Appendix J).

#### **8.8. REMS LETTER FOR PROFESSIONAL SOCIETIES**

- We have revised the letter to Professional Societies. See the appended clean version of the Agency's recommended letter (Appendix K).
- We request that you ask the professional societies to distribute the REMS letter to Professional Societies to their membership within 6 months and again within 12 months after approval of the modified Lotronex REMS Program. (b) (4)
- See Comments under Section 8.2 with regard to envelope formatting and electronic letter distribution. See Appendix C for the recommended version of an electronic REMS letter for Professional Societies.

#### **8.9. REMS ASSESSMENT PLAN**

- We believe that surveys of prescribers and patients should continue for the purpose of assessing the modified REMS. The surveys of prescribers should include those who completed training in the modified REMS and those who have not reported completion of training.
- In the currently approved REMS, patients can volunteer to participate by submitting a survey pre-enrollment form that is included with the dispensed prescription or provided to the patient

by the prescribing physician. We have removed this enrollment form as a requirement under the REMS; however, this form and the survey program may continue to be used outside of the REMS.

- The timetable for submission of assessments should be changed to allow for increased time to obtain survey participants for the first assessment of the modified REMS. Submit REMS assessments to the Agency 18 months from the date of approval of the modified REMS and every 12 months thereafter.
- The assessment plan should be revised to include, but is not limited to, the following:
  - 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 Lotronex and its authorized generic, and the actions patients need to take should they experience early warning signs and symptoms of these risks.
  - Results of an evaluation of prescriber understanding of the appropriate patient population, the risks of ischemic colitis and serious complications of constipation associated with Lotronex and its authorized generic, 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.
  - The number of prescribers and medical specialty of prescribers who reported that they completed training in the Lotronex REMS Program, including the number of prescribers contacted by Prometheus to become trained after prescribing Lotronex and its authorized generic and the number contacted who completed training, during the reporting period and cumulative.
  - The number of prescribers who have not completed training and are writing prescriptions.
  - Numbers of prescriptions, by year for the last five years and annually thereafter.
  - 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.
  - Summary and discussion of the above cases (received during the reporting period) and the clinical significance of these events.
  - 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.

#### **8.10. REMS PROGRAM TRAINING REMINDER LETTER**

We agree with your proposal to use a reminder letter as one option to follow-up with prescribers who have not completed training. See the appended redlined version of the Agency's training reminder letter (Appendix L); this letter should be appended to the REMS supporting document.

**8.11. REMS SUPPORTING DOCUMENT**

We have made revisions to your proposed supporting document. See the appended redlined version of the Agency's recommended changes (Appendix M). We remind you that the REMS supporting document must be consistent with all changes made to the REMS document and materials.

## APPENDIX

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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.**  
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/s/  
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ROBERT G PRATT  
11/16/2015

JAMIE C WILKINS PARKER  
11/16/2015

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**021107Orig1s026**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

**From:** [Sharon Hamm](#)  
**To:** [Cherry-France, Cheronda](#)  
**Subject:** RE: NDA 021107 REMS Delay Proposal Request for April 15, 2016 (Information/Guidance Request)  
**Date:** Tuesday, March 15, 2016 9:57:08 AM

---

Thanks so much!  
Sharon

---

**From:** Cherry-France, Cheronda [mailto:Cheronda.Cherry-France@fda.hhs.gov]  
**Sent:** Tuesday, March 15, 2016 9:35 AM  
**To:** 'Sharon Hamm' [REDACTED] (b) (6)  
**Subject:** RE: NDA 021107 REMS Delay Proposal Request for April 15, 2016 (Information/Guidance Request)

Sharon:

I had to relook at your email. ☹ Yes, let me clarify we accept your postponement of April 15, 2016 . I wanted you to acknowledge receipt of the email by March 15<sup>th</sup>  
I do apologize for not being clear.

Thanks,

*Roni*

Cheronda Cherry-France, RN BSN MHA  
LCDR, U.S. Public Health Service Commissioned Corps  
Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III  
CDER/FDA

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(301) 796-7295 (office)  
(301) 796-9906 (fax)  
[Cheronda.Cherry-France@fda.hhs.gov](mailto:Cheronda.Cherry-France@fda.hhs.gov)

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---

**From:** Sharon Hamm [REDACTED] (b) (6)

**Sent:** Friday, March 11, 2016 6:01 PM  
**To:** Cherry-France, Cheronda  
**Subject:** RE: NDA 021107 REMS Delay Proposal Request for April 15, 2016 (Information/Guidance Request)

Roni

Thanks so much for following up and for your reply. We understand from your note below that you are looking for the change in ownership revisions to the REMS (company name elements) to be submitted both as part of the AR (scheduled for April 15<sup>th</sup>), **and** as a separate submission. As a reminder, our email request was for the submission to be postponed until *April 15<sup>th</sup>*, to coincide with our Annual Report timing, but also to allow sufficient time to make the requisite changes to reflect the change in owner for the REMS and labeling, so as to minimize confusion for patients and caregivers. Your note however indicated *March 15<sup>th</sup>* (next week), which would not allow sufficient time to make the changes in both labeling and REMS. We are wondering if your intent was *April* as originally requested, and not March date which is next week? Please clarify. Thank you,  
Sharon

---

**From:** Cherry-France, Cheronda [<mailto:Cheronda.Cherry-France@fda.hhs.gov>]  
**Sent:** Friday, March 11, 2016 11:54 AM  
**To:** 'Sharon Hamm' [REDACTED] (b) (6)  
**Subject:** NDA 021107 REMS Delay Proposal Request for April 15, 2016 (Information/Guidance Request)

Sharon,

Happy to provide you some guidance.

- **Change in Ownership:** Yes, we agree that the change in ownership limited to the new company name and address is a REMS Revision. In addition to including the change in ownership in your Annual Report, you must as a separate submission, submit the change in ownership to your NDA. 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 REVISIONS FOR NDA/BLA #####**

If you plan to propose other changes beyond the change in ownership in this submission, we remind you to refer to the Guidance for Industry titled “Risk Evaluation and Mitigation Strategies: Modifications and Revisions” to determine the appropriate type of submission.

- **REMS:** We agree with your proposal to delay implementation of the REMS modified on January 7, 2016 to accommodate for change in ownership. Please confirm by responding to this email that the implementation will be **no later than Tuesday, March 15, 2016.**

Please let me know if you have additional questions.

Thanks,

*Roni*

Cheronda Cherry-France, RN BSN MHA  
LCDR, U.S. Public Health Service Commissioned Corps  
Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III  
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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.**  
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/s/  
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CHERONDA L CHERRY-FRANCE  
03/16/2016

**From:** [Moyer, Vicki](#)  
**To:** [Tamburini, Hector \(hector.tamburini@prometheuslabs.com\)](mailto:hector.tamburini@prometheuslabs.com)  
**Cc:** [Cherry-France, Cheronda](#); [Davis, Anissa](#); [Moyer, Vicki](#)  
**Subject:** Lotronex NDA 21107 S-026 information request REMS assessment  
**Date:** Monday, January 04, 2016 9:32:07 AM

---

Dear Mr. Tamburini,

We have reviewed the amendment to Lotronex NDA 21107 S-026, dated and received on 12/29/2015.

Please clarify the requirement for the reporting of prescriber specialties in the REMS assessments. The assessment metric in question is the following:

“The number of prescribers and medical specialty of prescribers who reported that they completed training in the Lotronex REMS Program, including the number of prescribers contacted by Prometheus to become trained after prescribing Lotronex and its authorized generic and the number contacted who completed training, during the reporting period and cumulative.”

We wish to clarify that reporting the number of prescribers contacted by Prometheus to become trained after prescribing Lotronex and its authorized generic and the number contacted who completed training is to include the medical specialty of these prescribers. It will benefit us to know the specialties of all prescribers, including untrained prescribers as well as trained prescribers. Therefore, please revise this assessment plan metric in your supporting document to state the following:

“The number of prescribers and medical specialty of prescribers who reported that they completed training in the Lotronex REMS Program, including the number and medical specialty of prescribers contacted by Prometheus to become trained after prescribing Lotronex and its authorized generic and the number and medical specialty contacted who completed training, during the reporting period and cumulative.”

Please email the following documents to us by the close of business today 1/4/2016:

- Word document version of redlined REMS supporting document with the requested changes
- PDF version of clean REMS supporting document compiled with its appended files

In addition, please submit identical documents of these files as eCTD files to the NDA supplement as soon as possible. In the cover letter for the eCTD submission, indicate that the files being submitted are identical to the files sent by email today.

Kind regards and happy new year,

*Vicki Moyer, M.S.*  
Safety Regulatory Project Manager  
CDER/OND/DGIEP  
301 796 6148

[vicki.moyer@fda.hhs.gov](mailto:vicki.moyer@fda.hhs.gov)

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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.**  
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/s/  
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VICKI A MOYER  
01/04/2016

**From:** [Moyer, Vicki](#)  
**To:** [Tamburini, Hector \(hector.tamburini@prometheuslabs.com\)](mailto:hector.tamburini@prometheuslabs.com)  
**Cc:** [Cherry-France, Cheronda](#); [Moyer, Vicki](#)  
**Subject:** Lotronex NDA 21107 S-026 information request  
**Date:** Tuesday, December 22, 2015 3:32:49 PM  
**Attachments:** [FDA Lotronex safety-info-fact-sheet\\_track-changes\\_22 Dec15.docx](#)  
[FDA lotronex-rems-support-doc\\_12.22.2015.docx](#)  
[FDA lotronex-rems-track-changes\\_22 Dec15.docx](#)

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Dear Mr. Tamburini,

With reference to your proposed REMS modification under NDA 21107 S-026, we have reviewed your amendment submitted December 1, 2015, and your email communications of December 11 and 15, 2015, and have additional comments in order for the REMS to be acceptable. After making the necessary changes described below, please submit the following eCTD files to the NDA supplement as instructed. We request your submission by December 28, 2015.

If you believe there are changes necessary in addition to those described below, please communicate those to us prior to submission.

Happy holidays!

Kind regards,

*Vicki Moyer, M.S.*  
Safety Regulatory Project Manager  
CDER/OND/DGIEP  
301 796 6148  
[vicki.moyer@fda.hhs.gov](mailto:vicki.moyer@fda.hhs.gov)

#### REMS document

1. As shown on the attached FDA redlined version:
  - Insert “the” under the second sub-bullet of GOAL(S) on page 1
  - Change the capitalization of “For” to “for” under ‘Other appended REMS materials’ on page 3.
2. Submit a redlined Word document version and a clean Word document version of the REMS document.

#### REMS supporting document

3. As shown on the attached FDA redlined version:
  - Delete “its” from the title on page 1
  - Insert “the” under the second sub-bullet of GOALS on page 4
4. Append the Healthcare provider training reminder letter to the supporting document.
5. Append the email communication version of the REMS letter for Healthcare Providers to the supporting document.
6. Append the email communication version of the REMS letter for Professional Societies to the supporting document.

7. Submit a redlined Word document version and a clean Word document version of the supporting document.
8. Submit a single, clean pdf version of the supporting document compiled with its appended files (bullets 4,5,6 above)

Safety Information Fact Sheet for Prescribers

9. As shown on the attached FDA redlined version:
  - Delete stray bullet and period at the bottom of the box.
10. Submit a redlined Word document version and a clean Word document version of the Safety Information Fact Sheet.

REMS Website

11. Submit a clean pdf version of the Website for Patients Section screenshot showing the Medication Guide link on the webpage header.

REMS and appended materials

12. Submit a single, clean pdf version of the REMS document compiled with its appended materials in the following order:
  - REMS document
  - REMS letter for Healthcare Providers (hard copy version only)
  - Prescriber Education Slide Deck
  - Safety Information Fact Sheet for Prescribers
  - Patient Education Sheet
  - Prescriber Completion of Program Training Form
  - REMS letter for Professional Societies (hard copy version only)
  - REMS Website screenshots

14 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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VICKI A MOYER  
12/22/2015

**From:** Cherry-France, Cheronda  
**To:** "Tamburini, Hector"  
**Cc:** Moyer, Vicki; Davis, Anissa  
**Subject:** Lotronex REMS: regarding NDA 21107 S-026 (Healthcare Providers, Website Homepage, & Website for Prescribers)  
**Date:** Tuesday, December 15, 2015 2:22:00 PM  
**Importance:** High

---

Hi Hector:

We have reviewed your email communication of December 11, 2015, regarding NDA 21107 S-026 and have additional comments. After making the necessary changes described below, send redlined and clean versions of only the documents named below by email to Vicki Moyer for further interim review. **Please respond by Thursday, December 17, 2015.**

REMS Letter for Healthcare Providers

1. Your proposed REMS letter for Healthcare Providers (b) (4)  
[Redacted]  
[Redacted]  
[Redacted]  
[Redacted]  
[Redacted]  
[Redacted] In addition, we believe all training kit materials should be available and at hand in the mailing.

REMS Website Homepage

2. Under "What is the LOTRONEX REMS Program?"
  - a. Clarify whether the two bulleted items after "Click below for the complete prescribing information, including Boxed Warning and Medication Guide:" will be hyperlinks.
  - b. In the second bullet, delete (b) (4) after Alosetron hydrochloride

REMS Website for Prescribers

- 
3. In the left column delete the bullets for (b) (4)  
[Redacted]
- 
4. In the right column delete the following text shown below as strikethrough:
  - LOTRONEX REMS Program Patient Education Sheet (b) (4)  
[Redacted]
  - LOTRONEX REMS Program Professional Societies (b) (4) Letter
- 

Thanks,

*Roni*

Cheronda Cherry-France, RN BSN MHA  
LCDR, U.S. Public Health Service Commissioned Corps

Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III  
CDER/FDA

*White Oak Building 22 Room: 5237  
10903 New Hampshire Avenue  
Silver Spring, Maryland  
Use zip code **20903** if shipping via United States Postal Service (USPS)*

(301) 796-7295 (office)

(301) 796-9906 (fax)

[Cheronda.Cherry-France@fda.hhs.gov](mailto:Cheronda.Cherry-France@fda.hhs.gov)

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

**If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-6295. Thank you.**

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/s/

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CHERONDA L CHERRY-FRANCE  
12/15/2015

**From:** [Moyer, Vicki](#)  
**To:** [Tamburini, Hector \(hector.tamburini@prometheuslabs.com\)](mailto:hector.tamburini@prometheuslabs.com)  
**Cc:** [Cherry-France, Cheronda](#); [Davis, Anissa](#); [Moyer, Vicki](#)  
**Subject:** Lotronex NDA 21107 S-026 information request  
**Date:** Wednesday, December 09, 2015 1:27:01 PM  
**Attachments:** [S-027 proposed-pi-lotronex-trackchange\\_12.8.2015.docx](#)

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Dear Mr. Tamburini,

Upon further review, we have found additional revisions to your REMS modification proposal (S-026) that are required for the REMS to be acceptable. Certain revisions are based on labeling changes that also affect S-027. These changes to your labeling reflect the changes to your REMS program. As it will no longer be a restricted distribution program, references to the REMS and REMS appended materials have been deleted (see attached label). After making the necessary changes described below, send redlined and clean versions of only the documents named below by [email](#) to Vicki Moyer for further interim review. Please respond by Friday, December 11, 2015.

We will review the revised documents. Once we have determined that the revisions address our concerns, we will then notify you to officially re-submit a complete REMS and supporting document to S-026. Please submit changes to the label via the Gateway to S-027.

Kind regards,

*Vicki Moyer, M.S.*  
Safety Regulatory Project Manager  
CDER/OND/DGIEP  
301 796 6148  
[vicki.moyer@fda.hhs.gov](mailto:vicki.moyer@fda.hhs.gov)

REMS Document

- Title: Delete “its” from the phrase “its Authorized Generic”
- Page 2, sub-bullet b.vi.: Delete “add URL” from [add URL [www.lotronexrems.com](http://www.lotronexrems.com)]

(b) (4)

Prescriber Completion of Training Form

- Add an asterisk before the “Signature\_\_\_\_\_” and “Date\_\_\_\_\_” fields as Required fields

REMS Website

- Create a tab on the top of the REMS home page header called “Medication Guide” that opens the Medication Guide (which is part of the approved labeling). This link should direct users to a separate webpage that contains only the Medication Guide.
- Website for Prescribers:

(b) (4)

26 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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VICKI A MOYER  
12/09/2015



NDA 021107/S-026

**GENERAL ADVICE**

Prometheus Laboratories, Inc.  
Attention: Hector Tamburini  
Executive Director, Regulatory Affairs & CMC  
9410 Carroll Park Drive  
San Diego, CA 92121

Dear Mr. Tamburini:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lotronex (alosetron hydrochloride) tablets, 0.5 mg and 1 mg.

We also refer to your August 18, 2015 submission containing your proposed modification to the risk evaluation and mitigation strategy (REMS) for Lotronex and your September 17 and September 28, 2015 amendments submitted regarding the August submission.

We have reviewed the referenced material and have the following comments:

**REMS Document**

1. Remove the header from all pages, and add the dates for approval of the initial REMS and most recently modified REMS, as shown on the appended redlined version (Appendix A). See additional comments below related to the appended materials and timetable for submission of assessments.

**REMS Letter for Healthcare Providers**

2. We agree that prescribers who are already enrolled in the Prescribing Program for Lotronex are adequately trained in understanding the benefits and risks of Lotronex/alosetron hydrochloride, and do not need to complete re-training in the modified program. It will be sufficient for these prescribers to be notified of the changes to the program. (b) (4)

[Redacted content]

3. The outside of the mailed envelope should state: "FDA Required REMS Safety Information": it should be printed in red, bolded, and a minimum size 14 font. It may be on two lines and should be boxed, for example:

**FDA Required REMS  
Safety Information**

4. The REMS letter to Healthcare Providers should also be formatted in an electronic version, which should be appended to the REMS supporting document. The electronic version of the letter should be email- and handheld device-friendly. The subject of the email should be, "FDA Required REMS Safety Information: LOTRONEX". The objective of these changes is to improve the communication of the risk message among the growing healthcare provider population of hand-held device users. See the appended recommended version of an electronic REMS letter to Healthcare Providers (Appendix C).

#### **Prescriber Education Slide Deck**

5. We agree with your proposal to re-name the Prescriber Education Program to the Prescriber Education Slide Deck.  
  
The slide deck is acceptable with the editorial changes outlined in the appended redlined version (Appendix D).

#### **Safety Information Fact Sheet for Prescribers**

6. For the sake of consistency in naming conventions across the appended REMS materials, the fact sheet should be re-named the Lotronex REMS Program Safety Information Fact Sheet for Prescribers. We have revised the fact sheet for prescribers to make it more reader-friendly and to improve the messaging. See the appended clean version of the Agency's recommended fact sheet for prescribers (Appendix E).

#### **Patient Education Sheet**

7. We agree with your proposal to re-name the patient education form as a patient education sheet. (b) (4)



8. For the sake of consistency in naming conventions across the appended REMS materials, the education sheet should be re-named the Lotronex REMS Program Patient Education Sheet. The sub-heading should read: FDA Required Lotronex/alosetron hydrochloride

Safety Information. We have revised the patient education sheet to make it more reader-friendly and to improve the messaging. See the appended redlined version of the Agency's patient education sheet for edits and comments (Appendix F).

### **Prescriber Completion of Lotronex REMS Program Training Form**

9. We agree with your proposed completion of training form, but request that a signature and date line be added to the form. See the appended redlined version (Appendix G).

### **REMS Website Sections**

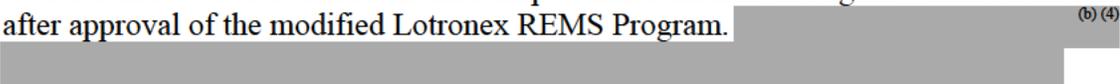
10. Ensure that the REMS website is independent of links to the promotional and/or commercial website and non-REMS materials about the product. Do not include a link from the REMS website back to the commercial website. The REMS website should also be accessible directly through a search engine. The REMS website, including all REMS materials will be available for the duration of the REMS.

The following is a link to helpful guidelines developed by DHHS that you may consider in developing the website:

[http://www.usability.gov/sites/default/files/documents/guidelines\\_book.pdf?post=yes](http://www.usability.gov/sites/default/files/documents/guidelines_book.pdf?post=yes)

See the appended versions of the REMS website sections for prescribers and patients for further edits and comments (Appendix H and Appendix J).

### **REMS Letter for Professional Societies**

11. We have revised the letter to Professional Societies. See the appended clean version of the Agency's recommended letter (Appendix K).
12. We request that you ask the professional societies to distribute the REMS letter to Professional Societies to their membership within 6 months and again within 12 months after approval of the modified Lotronex REMS Program. (b) (4)  

13. See Comments under Section 8.2 with regard to envelope formatting and electronic letter distribution. See Appendix C for the recommended version of an electronic REMS letter for Professional Societies.

### **REMS Assessment Plan**

14. We believe that surveys of prescribers and patients should continue for the purpose of assessing the modified REMS. The surveys of prescribers should include those who completed training in the modified REMS and those who have not reported completion of training.
15. In the currently approved REMS, patients can volunteer to participate by submitting a survey pre-enrollment form that is included with the dispensed prescription or provided to the patient by the prescribing physician. We have removed this enrollment form as a

requirement under the REMS; however, this form and the survey program may continue to be used outside of the REMS.

16. The timetable for submission of assessments should be changed to allow for increased time to obtain survey participants for the first assessment of the modified REMS. Submit REMS assessments to the Agency 18 months from the date of approval of the modified REMS and every 12 months thereafter.
17. The assessment plan should be revised to include, but is not limited to, the following:
  - a. 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 Lotronex and its authorized generic, and the actions patients need to take should they experience early warning signs and symptoms of these risks.
  - b. Results of an evaluation of prescriber understanding of the appropriate patient population, the risks of ischemic colitis and serious complications of constipation associated with Lotronex and its authorized generic, 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.
  - c. The number of prescribers and medical specialty of prescribers who reported that they completed training in the Lotronex REMS Program, including the number of prescribers contacted by Prometheus to become trained after prescribing Lotronex and its authorized generic and the number contacted who completed training, during the reporting period and cumulative.
  - d. The number of prescribers who have not completed training and are writing prescriptions.
  - e. Numbers of prescriptions, by year for the last five years and annually thereafter.
  - f. Number of cases of the following events reported (from any source) during the reporting period and cumulative:
    - i. All reports of ischemic colitis;
    - ii. All reports involving ischemic changes, ischemia, or necrosis of the colon
    - iii. All reports involving constipation requiring hospitalization or emergency room visit;
    - iv. 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;
    - v. All reports of death, regardless of causality.
  - g. Summary and discussion of the above cases (received during the reporting period) and the clinical significance of these events.
  - h. 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.

### **REMS Program Training Reminder Letter**

18. We agree with your proposal to use a reminder letter as one option to follow-up with prescribers who have not completed training. See the appended redlined version of the Agency's training reminder letter (Appendix L); this letter should be appended to the REMS supporting document.

## REMS Supporting Document

19. We have made revisions to your proposed supporting document. See the appended redlined version of the Agency's recommended changes (Appendix M). We remind you that the REMS supporting document must be consistent with all changes made to the REMS document and materials.

Appended to this letter is the REMS Document and appended REMS materials, including our redlined versions. We remind you that the REMS supporting document must be consistent with all changes made to the REMS document.

We request your response to these comments by the close of business on December 2, 2015, to facilitate further review.

If you have any questions, call LCDR Cheronda Cherry-France, Regulatory Project Manager, at (301) 796-7295.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure:  
Appendix A thru M

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/s/

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JOYCE A KORVICK  
11/18/2015

**From:** [Moyer, Vicki](#)  
**To:** [Tamburini, Hector \(hector.tamburini@prometheuslabs.com\)](mailto:hector.tamburini@prometheuslabs.com)  
**Cc:** [Davis, Anissa](#); [Cherry-France, Cheronda](#); [Moyer, Vicki](#)  
**Subject:** Lotronex NDA 21107 S026 information request  
**Date:** Thursday, September 24, 2015 8:25:20 AM

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Dear Hector,

FDA is reviewing the REMS modification amendment to Supplement 2026, dated and received on September 17, 2015.

Prometheus provided Word documents with language describing the proposed REMS webpages for both prescribers and patients. The review team has requested actual screenshots of the webpage in pdf form to facilitate the review.

Please submit this requested information to the NDA by 9/28/15.

Kind regards,

*Vicki Moyer, M.S.*  
Safety Regulatory Project Manager  
CDER/OND/DGIEP  
301 796 6148  
[vicki.moyer@fda.hhs.gov](mailto:vicki.moyer@fda.hhs.gov)

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/s/  
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VICKI A MOYER  
09/24/2015

**From:** [Moyer, Vicki](#)  
**To:** [Tamburini, Hector \(hector.tamburini@prometheuslabs.com\)](mailto:hector.tamburini@prometheuslabs.com)  
**Cc:** [Davis, Anissa](#); [Moyer, Vicki](#)  
**Subject:** Lotronex NDA 21107 S-026 teleconference summary  
**Date:** Friday, September 11, 2015 7:28:38 PM  
**Attachments:** [FDA feedback REMS mod N21107 S026\(final\).pdf](#)

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Dear Hector,

Attached is a summary of our preliminary feedback on Lotronex NDA 21107 S-026 as discussed in the teleconference between FDA and Prometheus on September 3, 2015.

Kind regards,

*Vicki Moyer, M.S.*  
Safety Regulatory Project Manager  
CDER/OND/DGIEP  
301 796 6148  
[vicki.moyer@fda.hhs.gov](mailto:vicki.moyer@fda.hhs.gov)

**FDA feedback on Lotronex NDA 21107 S026 REMS modification and meeting summary  
September 3, 2015 FDA and Prometheus Teleconference**

FDA attendees:

Bob Pratt, Risk Management Analyst, Division of Risk Management (DRISK)  
Jamie Wilkins-Parker, Acting Team Leader, DRISK  
Reema Mehta, Acting Deputy Director, DRISK  
Anahita Tavakoli, Health Communications Analyst, DRISK  
Peter Diak, Team Leader, CDER/Office of Compliance (OC)  
Haley Seymour, Consumer Safety Officer, CDER/OC  
Vicki Moyer, Safety Regulatory Project Manager, Division of Gastroenterology and Inborn Errors Products (DGIEP)  
Joyce Korvick, Deputy Director for Safety, DGIEP  
Laurie Muldowney, Acting Clinical Team Leader, DGIEP  
Anissa Davis-Williams, Regulatory Project Manager, DGIEP

These are high level comments with regard to your recently submitted proposed REMS modification.

- Any changes that you propose to the modified REMS document that was sent to you by the FDA on May 20, 2015 should include adequate rationale to support your proposed changes.
- The formatting and structure of the REMS document that was sent to you by the FDA on May 20, 2015 must be maintained.
- A REMS letter to Professional Societies is an appended REMS material and needs to be provided in your resubmission. This should be listed in the same section of the REMS document where all of the appended materials under ETASU A appear, under 'Other appended REMS materials'.
- The Prescribing Information (which includes the MedGuide) is not an appended REMS material. Therefore, these must be removed from your resubmission. Changes to the Prescribing Information need to be submitted separately as a prior approval labeling supplement.
- The Prescriber Completion of Training Form should include a statement that all training materials were reviewed independently by the healthcare provider.
- The purpose of the REMS letter for Healthcare Providers is to describe the changes to the REMS program and provide a copy of the training materials.
-  (b) (4)
- Prometheus agreed to provide an amended REMS submission by 9/18/2015. The submission will include each document and tool (e.g. the REMS document, each letter, slide deck, etc.) as a separate file for ease of review.

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/s/  
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VICKI A MOYER  
09/14/2015



NDA 21107/S-026

**ACKNOWLEDGMENT --  
PRIOR APPROVAL SUPPLEMENT**

Prometheus Laboratories, Inc.  
Attention: Hector Tamburini  
Executive Director, Regulatory Affairs and CMC  
9410 Carroll Park Drive  
San Diego, California 92121

Dear Mr. Tamburini:

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

**NDA NUMBER:** 21107  
**SUPPLEMENT NUMBER:** 026  
**PRODUCT NAME:** Lotronex (alosetron hydrochloride) Tablets, 1 mg  
**DATE OF SUBMISSION:** August 18, 2015  
**DATE OF RECEIPT:** August 18, 2015

This supplemental application proposes the following modifications to the approved risk evaluation and mitigation strategy (REMS) for Lotronex (alosetron hydrochloride): modifications to the REMS goals, REMS document and appended materials, elements to assure safe use (ETASU), and removal of the Medication Guide as an element of the REMS.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 17, 2015, in accordance with 21 CFR 314.101(a). If the application is filed, the goal date will be February 14, 2016.

**SUBMISSION REQUIREMENTS**

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have questions, call me at (301) 796-6148.

Sincerely,

*{See appended electronic signature page}*

Vicki A. Moyer, M.S  
Safety Regulatory Project Manger  
Division of Gastroenterology and Inborn Errors  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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VICKI A MOYER  
08/28/2015

## REQUEST FOR CONSULTATION

TO (Division/Office):

**Mail: OSE/ DEPI**

**Attention- Aleksander (Alek) Winiarski**

FROM: Vicki Moyer, Safety Regulatory Project Manager, 301-796-6148

OND/ODEIII/DGIEP

Date: <b>8/19/15</b>	IND NO. <b>N/A</b>	NDA NO. <b>21107</b>	TYPE OF DOCUMENT REMS modification Prior Approval Supplement	DATE OF DOCUMENT 8/18/15
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NAME OF DRUG Lotronex	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG IBS	DESIRED COMPLETION DATE 2/14/16
--------------------------	------------------------------------	-------------------------------	------------------------------------

NAME OF FIRM: Prometheus

### REASON FOR REQUEST

#### I. GENERAL

- |  |   |  |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL<br><input type="checkbox"/> PROGRESS REPORT<br><input type="checkbox"/> NEW CORRESPONDENCE<br><input type="checkbox"/> DRUG ADVERTISING<br><input type="checkbox"/> ADVERSE REACTION REPORT<br><input type="checkbox"/> MANUFACTURING CHANGE/ADDITION<br><input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE--NDA MEETING<br><input type="checkbox"/> END OF PHASE II MEETING<br><input type="checkbox"/> RESUBMISSION<br><input type="checkbox"/> SAFETY/EFFICACY<br><input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br><input type="checkbox"/> FINAL PRINTED LABELING<br><input type="checkbox"/> LABELING REVISION<br><input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br><input type="checkbox"/> FORMULATIVE REVIEW<br><input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
|--|---|--|

#### II. BIOMETRICS

- |  |  |
|--|--|
| STATISTICAL EVALUATION BRANCH<br><br><input type="checkbox"/> TYPE A OR B NDA REVIEW<br><input type="checkbox"/> END OF PHASE II MEETING<br><input type="checkbox"/> CONTROLLED STUDIES<br><input type="checkbox"/> PROTOCOL REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW): | STATISTICAL APPLICATION BRANCH<br><br><input type="checkbox"/> CHEMISTRY REVIEW<br><input type="checkbox"/> PHARMACOLOGY<br><input type="checkbox"/> BIOPHARMACEUTICS<br><input type="checkbox"/> OTHER (SPECIFY BELOW): |
|--|--|

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION<br><input type="checkbox"/> BIOAVAILABILTY STUDIES<br><input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|--|--|

#### IV. DRUG EXPERIENCE

- |  |   |
|--|---|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br><input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br><input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br><input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br><input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br><input type="checkbox"/> POISON RISK ANALYSIS |
|--|---|

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS/SPECIAL INSTRUCTIONS:**

Please review the major REMS modification prior approval supplement

Cover Letter: <\\CDSESUB1\evsprod\NDA021107\0290\m1\us\12-cov-let\cover.pdf>

EDR Location (SDN 1297): <\\CDSESUB1\evsprod\NDA021107\021107.enx>

SIGNATURE OF REQUESTER Vicki Moyer, Safety Regulatory Project Manager (on behalf of Joyce Korvick)	METHOD OF DELIVERY (Check all that apply) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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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.**  
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/s/  
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VICKI A MOYER  
08/19/2015