



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

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

/s/

JOYCE A KORVICK
01/07/2016