

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 200652Orig1s004

Trade Name: Alosetron hydrochloride tablets, 0.5 mg and 1.0 mg

Sponsor: Hikma Pharmaceuticals USA Inc.
(Formerly Roxane Laboratories, Inc.)

Approval Date: November 22, 2016

CENTER FOR DRUG EVALUATION AND RESEARCH

ANDA 200652Orig1s004

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

ANDA 200652Orig1s004

APPROVAL LETTER



ANDA 200652/S-004

SUPPLEMENT APPROVAL

Roxane Laboratories, Inc.
c/o West-Ward Pharmaceuticals Corp.
Attention: Sarah A. Smith
Director, Drug Regulatory Affairs and Labeling
1809 Wilson Road
Columbus, Ohio 43228

Dear Ms. Smith:

Please refer to your Supplemental Abbreviated New Drug Application (sANDA) dated and received September 23, 2016, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) Alosetron Hydrochloride Tablets, 0.5 mg and 1.0 mg.

We acknowledge receipt of your amendment dated November 4, 2016.

This supplemental abbreviated new drug application provides for modifications to the approved Alosetron Hydrochloride risk evaluation and mitigation strategy (REMS).

APPROVAL

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Alosetron Hydrochloride was originally approved on May 4, 2015. The most recent modification was approved on March 24, 2016. The REMS consists of elements to assure safe use (ETASU). Your proposed modification to the REMS consists of changes to reflect the inclusion of an additional ANDA into the alosetron REMS.

Your proposed modified REMS, amended on November 4, 2016, and appended to this letter, is approved.

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

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

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

**ANDA 200652 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT
METHODOLOGY**

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

We also remind you that section 505-1(f)(8) of FD&C Act 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 a proposed modification of the REMS or any REMS assessments with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

ANDA 200652 REMS ASSESSMENT

**NEW SUPPLEMENT FOR ANDA 200652/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 200652/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR ANDA 200652/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX**

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

REMS REVISIONS FOR ANDA 200652

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

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

If you have any questions, call CDR Stacy Barley, REMS Coordinator, at (301) 796-2137.

Sincerely,

{See appended electronic signature page}

Trueman W. Sharp, M.D., M.P.H.
Acting Deputy Director
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

Appendix 1
REMS

Appendix 1

Dates for submission of waiver-granted REMS assessments

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

REMS Assessment Plan

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

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

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

/s/

TRUEMAN W SHARP
11/22/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

ANDA 200652Orig1s004

REMS

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

Risk Evaluation and Mitigation Strategy (REMS)

Shared System for Alosetron

Selective 5-HT₃ antagonist

I. GOAL(S):

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

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

II. REMS ELEMENTS:

A. Elements to Assure Safe Use

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

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

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

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

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

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

- Other appended REMS materials:
 - Alosetron REMS Program website Prescriber Section screenshots
 - Alosetron REMS Program website Patients Section screenshots

FDA Required REMS Safety Information for Alosetron Tablets

Important Safety Update

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

ENROLLED Prescriber Actions:

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

NON-ENROLLED Prescriber Actions:

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

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

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

Summary of Changes to the REMS Program

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

Electronic prescriptions are now allowed

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

Indication:

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

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

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

Please visit www.AlosetronREMS.com for more information.

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

Reporting Adverse Events

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

Sincerely,

The Alosetron REMS Program

THE ALOSETRON REMS PROGRAM

Prescriber Education Slide Deck

Understanding the Benefits and Risks of Alosetron

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

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THE ALOSETRON REMS PROGRAM

Prescriber Education Slide Deck

Understanding the Benefits and Risks of Alosetron

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

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

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Important Modified Alosetron REMS Program

The modified Alosetron REMS Program has changed from the previous program

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

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

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Important

Modified Alosetron REMS Program

The modified Alosetron REMS Program has changed from the previous program

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

Section 1:

Purpose

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

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Section 1:

Purpose

Purpose of the Prescriber Education Slide Deck for Alosetron

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

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

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Purpose of the Prescriber Education Slide Deck for Alosetron

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

Risk Evaluation and Mitigation Strategy (REMS)

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

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

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Risk Evaluation and Mitigation Strategy (REMS)

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

Goals and Objectives

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

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

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

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

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

Section 2:

Indication and Usage

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

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Section 2:
Indication and Usage

Indication and Usage

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

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

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

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Indication and Usage

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

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

Indication and Usage (cont'd)

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

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

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Indication and Usage (cont'd)

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

Section 3:

Important Safety Information

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

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Section 3:
Important Safety Information

Boxed Warning

WARNING: SERIOUS GASTROINTESTINAL ADVERSE REACTIONS

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

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

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Boxed Warning

WARNING: SERIOUS GASTROINTESTINAL ADVERSE REACTIONS

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

Boxed Warning (cont'd)

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

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

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Boxed Warning (cont'd)

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

Warnings and Precautions

Serious Complications of Constipation

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

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

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Warnings and Precautions

Serious Complications of Constipation

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

Warnings and Precautions (cont'd)

Serious Complications of Constipation (cont'd)

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

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

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Warnings and Precautions (cont'd)

Serious Complications of Constipation (cont'd)

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

Warnings and Precautions (cont'd)

Ischemic Colitis

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

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

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Warnings and Precautions (cont'd)

Ischemic Colitis

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 - 0.3%, or 3 per 1,000 patients (95% CI 1 to 4), over 6 months
 - patient experience in controlled clinical trials is insufficient to estimate the incidence of ischemic colitis in patients taking alosetron for longer than 6 months

Warnings and Precautions (cont'd)

Ischemic Colitis (cont'd)

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

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

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Warnings and Precautions (cont'd)

Ischemic Colitis (cont'd)

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

Contraindications

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

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

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Contraindications

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

Contraindications (cont'd)

- Concomitant administration of alosetron with fluvoxamine is contraindicated.

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

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Contraindications (cont'd)

- Concomitant administration of alosetron with fluvoxamine is contraindicated.

Drug Interactions

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

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

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

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Drug Interactions (cont'd)

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

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

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Drug Interactions (cont'd)

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

Use in Specific populations

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

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

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Use in Specific populations

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- Safety and effectiveness in pediatric patients have not been established.
- Postmarketing experience suggests that elderly patients may be at greater risk for complications of constipation; therefore, appropriate caution and follow-up should be exercised if alosetron is prescribed for these patients.

Use in Specific populations (cont'd)

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

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

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Use in Specific populations (cont'd)

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

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

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

^a Reported in ≥1% of alosetron patients and occurring more frequently on alosetron 1 mg twice-a-day than on placebo.
^b Data reported from 22 repeat-dose studies in patients with IBS treated for 8 to 24 weeks.
^c $P < 0.0001$ vs placebo.

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

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Adverse Reactions

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

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

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

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Overdosage

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

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

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Overdosage

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Section 4:

How to Prescribe Alosetron Tablets

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

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Section 4:
How to Prescribe Alosetron Tablets

Dosage and Administration

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

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

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Dosage and Administration (cont'd)

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

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

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Dosage and Administration (cont'd)

- Usual Dose in Adults
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Dosage and Administration (cont'd)

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

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

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Dosage and Administration (cont'd)

- Clinical trial and postmarketing experience suggest that debilitated patients or patients taking additional medications that decrease GI motility may be at greater risk of serious complications of constipation.
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- Alosetron can be taken with or without food.

Section 5:

Alosetron

REMS Program

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

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Section 5:
Alosetron REMS Program

Training in the Alosetron REMS Program

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

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

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Training in the Alosetron REMS Program (cont'd)

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

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

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Training in the Alosetron REMS Program (cont'd)

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 - Alosetron REMS Program Safety Information Fact Sheet for Prescribers
 - Alosetron REMS Program Patient Education Sheet
 - Prescriber Completion of Alosetron REMS Program Training Form

Patient Education

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

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

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

Patient Responsibilities

Patients should be instructed to:

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

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

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Patient Responsibilities

Patients should be instructed to:

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- immediately contact their prescriber again if their constipation does not resolve after discontinuation of alosetron.

Patient Responsibilities(cont'd)

Patients should be instructed to:

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

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

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Patient Responsibilities(cont'd)

Patients should be instructed to:

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

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

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

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Alosetron REMS Program

Safety Information Fact Sheet for Prescribers

FDA Required REMS* Safety Information

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

Risk of Serious Gastrointestinal Adverse Reactions

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

Appropriate Patient Selection

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

*What is the Alosetron REMS Program?

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

Indication

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

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

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

Reporting Adverse Events:

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

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

Alosetron REMS Program Patient Education Sheet

FDA Required Alosetron Safety Information

What is alosetron?

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

What is the most serious risk information about alosetron treatment?

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

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

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

How do I take alosetron?

- Take alosetron exactly as your doctor prescribes it.

When should I stop taking alosetron and call my doctor?

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

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

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

Please visit www.AlosetronREMS.com for further information.

Prescriber Completion of Alosetron REMS Program Training Form

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

***Indicates Required Field**

Name of Prescriber (print)*

(First) (Last)

Signature* Date*

NPI Number* _____

Specialty*

- Gastroenterology
- Colon & Rectal Surgery
- Family Medicine
- Obstetrics/Gynecology
- General Surgery
- Nurse Practitioner
- Cardiovascular Diseases
- Other (Please specify) _____
- Internal Medicine
- Nuclear Medicine
- Physician Assistant

Office Name _____

Office Address* _____

Office City* _____ State* _____ Zip Code* _____

Office Phone Number* _____ Office Fax Number* _____

Email* _____

Confirmation Correspondence Preference (please select one): Fax Email

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

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

Alosetron REMS

PO Box 29292, Phoenix, AZ 85038

Fax Number: 1-800-535-6805

Alosetron REMS Program

Risk Evaluation and Mitigation Strategy

Web Mockups

V19

FOOTER

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

Please consult the [Prescribing Information](#).

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



For Patients

For Prescribers

Alosetron REMS (Risk Evaluation and Mitigation Strategy)

What is the Alosetron REMS Program?

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

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

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

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

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

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



For Patients

For Prescribers

Patient Role in the Alosetron REMS Program

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

 [Alosetron REMS Program Patient Education Sheet](#)

Medication Guide

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

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

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





For Patients

For Prescribers

Prescriber Role in the Alosetron REMS Program

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

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

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

Prescriber Training

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

To train in the Alosetron REMS Program via web:

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

To train in the Alosetron REMS Program via fax:

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

Resources



Prescriber Completion of Alosetron REMS Program Training Form



Alosetron REMS Program Patient Education Sheet



Alosetron REMS Program Prescriber Education Slide Deck



Alosetron REMS Program Safety Information Fact Sheet for Prescribers



REMS Letter to Healthcare Providers

Prescribing Information and Medication Guide



Alosetron Prescribing Information (Amneal Pharmaceuticals LLC)



Alosetron Medication Guide (Amneal Pharmaceuticals LLC)



Alosetron Prescribing Information (Par Pharmaceutical, Inc.)



Alosetron Medication Guide (Par Pharmaceutical, Inc.)



Alosetron Prescribing Information (Roxane Laboratories, Inc.)



Alosetron Medication Guide (Roxane Laboratories, Inc.)



Next

PRESCRIBER AGREEMENT



For Patients

For Prescribers

The Alosetron REMS Program – Prescriber Completion of Training

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

[Complete Training](#)

PRESCRIBER ONLINE TRAINING FORM



For Patients

For Prescribers

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

Prescriber Information

First Name	<input type="text"/>
Last Name	<input type="text"/>
Specialty	<input type="text" value="-- Please Select --"/>
National Provider Identifier (NPI)	<input type="text"/>
Office Name	<input type="text"/>
Address 1	<input type="text"/>
Address 2	<input type="text"/> (Optional)
City	<input type="text"/>
State	<input type="text" value="-- Please Select --"/>
Zip Code	<input type="text"/>
Phone	<input type="text"/>
Fax	<input type="text"/>
Email	<input type="text"/>
Correspondence Confirmation Preference	<input type="radio"/> Email <input type="radio"/> Fax

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

<input type="text" value="Signature (First and Last Name as typed above)"/>	<input type="text" value="Date MM/DD/YYYY"/>	<input type="checkbox"/> I'm not a robot	 reCAPTCHA Privacy - Terms
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Submit

PRESCRIBER ONLINE TRAINING FORM – OTHER SPECIALTY SELECTED



For Patients

For Prescribers

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

Prescriber Information

First Name	<input type="text"/>
Last Name	<input type="text"/>
Specialty	Other <input type="text"/>
	<input type="text" value="-- Please Specify --"/>
National Provider Identifier (NPI)	<input type="text"/>
Office Name	<input type="text"/>
Address 1	<input type="text"/>
Address 2	<input type="text"/> (Optional)
City	<input type="text"/>
State	<input type="text" value="-- Please Select --"/>
Zip Code	<input type="text"/>
Phone	<input type="text"/>
Fax	<input type="text"/>
Email	<input type="text"/>
Correspondence Confirmation Preference	<input type="radio"/> Email <input type="radio"/> Fax

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

<input type="text" value="Signature (First and Last Name as typed above)"/>	<input type="text" value="Date MM/DD/YYYY"/>	<input type="checkbox"/> I'm not a robot	
			<input type="button" value="Submit"/>

PRESCRIBER TRAINING CONFIRMATION



For Patients

For Prescribers

Congratulations!

You have successfully trained in the Alosetron REMS Program!

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

Training Confirmation: <Confirmation ID>

RESOURCES



For Patients

For Prescribers

Resources

Prescriber

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

Prescribing Information and Medication Guide

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

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

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



CONTACT US



For Patients

For Prescribers

Contact Us

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

Phone Number

1-844-267-8675

Fax Number

1-800-535-6805

Mailing Address

Alosetron REMS Program
PO BOX 29292
PHOENIX AZ 85038-9292

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

ANDA 200652Orig1s004

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

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

OSE RCM #	2016-2364
Reviewer Name	Jacqueline Sheppard, Pharm.D. Anahita Tavakoli, M.A.
Acting Deputy Division Director	Jamie Wilkins Parker, Pharm.D.
Review Completion Date	November 17, 2016
Subject	Evaluation of Proposed REMS modification
Established Name	Alosetron hydrochloride
Applicant/Application No.	Roxane Laboratories ANDA 200652/S-004
Therapeutic Class	Selective serotonin 5-HT3 antagonist
Formulation(s)	0.5 mg and 1 mg oral tablets
Dosing Regimen	One tablet twice a day
Proposed Indication(s)	Treatment of severe diarrhea-predominant irritable bowel syndrome in women with chronic IBS

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates the proposed risk evaluation and mitigation strategy (REMS) modification for Roxane Laboratories' (Roxane) alosetron hydrochloride (alosectron), ANDA 200652 (S-004), submitted on September 23, 2016 and amended on November 4, 2016. The modification provides an updated REMS document, REMS supporting document and REMS materials from that of the currently approved waiver-granted REMS for Alosetron. The proposed modified REMS was developed jointly by members of the Alosetron REMS Group (ARG) comprised of Roxane Laboratories, Amneal Pharmaceuticals and Par Pharmaceuticals.

This modification facilitates inclusion of the first additional ANDA into the approved alosetron shared system, and updates the REMS by removing completed requirements. The completed requirements include: 1) distribution of the REMS training kit to all prescribers who are likely to prescribe or who have prescribed alosetron in the 24 months preceding the first REMS modification approval (one-time requirement which occurred in January, 2016), and 2) distribution of the REMS letter for Professional Societies as these requirements have been completed by Roxane. The training kit will continue to be distributed to all prescribers identified as not having completed training. Finally, the modification allows for the addition of a CAPTCHA¹ as a new level of security under the Prescriber online Training Form of the alosetron REMS website. The ARG's proposed shared system (SS) REMS consists of elements to assure safe use (ETASU).

2 Background

2.1 PRODUCT BACKGROUND

Alosetron is an approved generic of the Reference Listed Drug (RLD) Lotronex (NDA 21107). The Lotronex REMS was approved with elements to assure safe use on September 2, 2010, to address the risk of ischemic colitis and serious complications of constipation. Alosetron was approved on May 4, 2015, with a REMS comparable to the Lotronex REMS, after the Agency granted Roxane a waiver for the requirement to form a single, shared system REMS with Lotronex. The REMS was last modified March 24, 2016 to provide for the provision of a text box to the prescriber online training form.

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

2.2 REGULATORY HISTORY

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

- 9/23/16: ANDA 200652 Suppl-04 received from Roxane. The proposal modifies the REMS and provides the proposed shared waiver-granted REMS, REMS supporting document and REMS materials in response to the inclusion of the first additional ANDA into the alosetron shared system.
- 10/27/16: Interim comments sent to ARG including edits to REMS document and website and the removal of the Letter to Professional Societies from the appended materials.
- 11/04/16: ANDA 200652 Suppl- 04 received from Roxane. The submission updated the REMS document and appended materials based upon interim comments sent on 10/27/16.

3 Proposed REMS Modifications

3.1 REMS DOCUMENT

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

3.2 REMS APPENDED MATERIALS

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

3.3 REMS SUPPORTING DOCUMENT AND REMS ASSESSMENT PLAN

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

4 Conclusion & Recommendations

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

5 Appendices

REMS Document

REMS Letter to Healthcare Providers

Alosetron REMS Program Prescriber Education Slide Deck

Alosetron REMS Program Safety Information Fact Sheet for Prescribers

Alosetron REMS Program Patient Education Sheet

Prescriber Completion of Alosetron REMS Program Training Form

Alosetron REMS Program website Prescriber Section screenshots

Alosetron REMS Program website Patients Section screenshots

5.1 REFERENCES

Roxane. Proposed REMS modification for Alosetron, <eCTD Sequence 0058>, Supplement 04, dated November 4, 2016.

Roxane. Proposed REMS modification for Alosetron, <eCTD Sequence 0057>, Supplement 04, dated September 23, 2016.

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

Risk Evaluation and Mitigation Strategy (REMS)

Shared System for Alosetron

Selective 5-HT₃ antagonist

I. GOAL(S):

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

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

II. REMS ELEMENTS:

A. Elements to Assure Safe Use

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

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

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

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

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

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

- Other appended REMS materials:
 - Alosetron REMS Program website Prescriber Section screenshots
 - Alosetron REMS Program website Patients Section screenshots

FDA Required REMS Safety Information for Alosetron Tablets

Important Safety Update

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

ENROLLED Prescriber Actions:

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

NON-ENROLLED Prescriber Actions:

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

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

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

Summary of Changes to the REMS Program

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

Electronic prescriptions are now allowed

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

Indication:

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

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

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

Please visit www.AlosetronREMS.com for more information.

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

Reporting Adverse Events

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

Sincerely,

The Alosetron REMS Program

THE ALOSETRON REMS PROGRAM

Prescriber Education Slide Deck

Understanding the Benefits and Risks of Alosetron

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

1

THE ALOSETRON REMS PROGRAM

Prescriber Education Slide Deck

Understanding the Benefits and Risks of Alosetron

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

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

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Important Modified Alosetron REMS Program

The modified Alosetron REMS Program has changed from the previous program

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

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

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Important

Modified Alosetron REMS Program

The modified Alosetron REMS Program has changed from the previous program

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

Section 1:

Purpose

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

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Section 1:

Purpose

Purpose of the Prescriber Education Slide Deck for Alosetron

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

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

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Purpose of the Prescriber Education Slide Deck for Alosetron

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

Risk Evaluation and Mitigation Strategy (REMS)

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

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

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Risk Evaluation and Mitigation Strategy (REMS)

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

Goals and Objectives

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

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

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

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

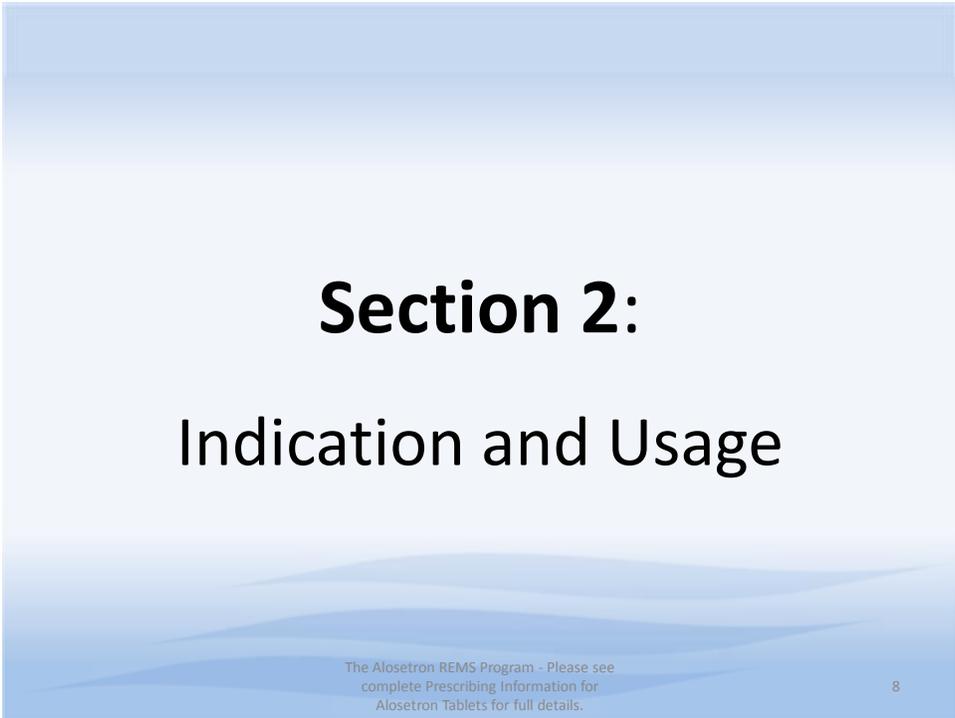
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Goals and Objectives

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

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

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



Section 2:
Indication and Usage

Indication and Usage

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

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

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

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Indication and Usage

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

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

Indication and Usage (cont'd)

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

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

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Indication and Usage (cont'd)

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

Section 3:

Important Safety Information

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

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Section 3:
Important Safety Information

Boxed Warning

WARNING: SERIOUS GASTROINTESTINAL ADVERSE REACTIONS

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

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

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Boxed Warning

WARNING: SERIOUS GASTROINTESTINAL ADVERSE REACTIONS

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

Boxed Warning (cont'd)

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

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

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Boxed Warning (cont'd)

- Alosetron is indicated only for women with severe diarrhea-predominant IBS who have not responded adequately to conventional therapy.
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Warnings and Precautions

Serious Complications of Constipation

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

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

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Warnings and Precautions

Serious Complications of Constipation

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 - **in addition, rare cases of intestinal perforation and death have been reported from postmarketing clinical practice.**
 - **in some cases, complications of constipation required intestinal surgery, including colectomy.**

Warnings and Precautions (cont'd)

Serious Complications of Constipation (cont'd)

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

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

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Warnings and Precautions (cont'd)

Serious Complications of Constipation (cont'd)

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

Warnings and Precautions (cont'd)

Ischemic Colitis

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

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

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Warnings and Precautions (cont'd)

Ischemic Colitis

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 - cumulative incidence of ischemic colitis in women receiving alosetron was:
 - 0.2%, or 2 per 1,000 patients (95% CI 1 to 3), over 3 months
 - 0.3%, or 3 per 1,000 patients (95% CI 1 to 4), over 6 months
 - patient experience in controlled clinical trials is insufficient to estimate the incidence of ischemic colitis in patients taking alosetron for longer than 6 months

Warnings and Precautions (cont'd)

Ischemic Colitis (cont'd)

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

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

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Warnings and Precautions (cont'd)

Ischemic Colitis (cont'd)

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

Contraindications

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

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

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Contraindications

- Alosetron should not be initiated in patients with constipation.
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 - **ischemic colitis, impaired intestinal circulation, thrombophlebitis, or hypercoagulable state;**
 - **Crohn's disease or ulcerative colitis;**
 - **diverticulitis;**
 - **severe hepatic impairment.**

Contraindications (cont'd)

- Concomitant administration of alosetron with fluvoxamine is contraindicated.

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

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Contraindications (cont'd)

- Concomitant administration of alosetron with fluvoxamine is contraindicated.

Drug Interactions

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

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

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

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Drug Interactions

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

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

Drug Interactions (cont'd)

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

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

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Drug Interactions (cont'd)

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

Use in Specific populations

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

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

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Use in Specific populations

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

Use in Specific populations (cont'd)

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

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

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Use in Specific populations (cont'd)

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

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

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

^a Reported in ≥1% of alosetron patients and occurring more frequently on alosetron 1 mg twice-a-day than on placebo.
^b Data reported from 22 repeat-dose studies in patients with IBS treated for 8 to 24 weeks.
^c $P < 0.0001$ vs placebo.

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

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

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Adverse Reactions

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

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

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

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Overdosage

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

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

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Overdosage

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- Patients should be managed with appropriate supportive therapy.

Section 4:

How to Prescribe Alosetron Tablets

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

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Section 4:
How to Prescribe Alosetron Tablets

Dosage and Administration

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

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

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Dosage and Administration

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 - 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.

Dosage and Administration (cont'd)

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

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

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Dosage and Administration (cont'd)

- Usual Dose in Adults
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 - Alosetron should not be restarted in patients who develop ischemic colitis.

Dosage and Administration (cont'd)

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

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

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Dosage and Administration (cont'd)

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

Section 5:

Alosetron

REMS Program

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

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Section 5:
Alosetron REMS Program

Training in the Alosetron REMS Program

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

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

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Training in the Alosetron REMS Program

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Training in the Alosetron REMS Program (cont'd)

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

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

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Training in the Alosetron REMS Program (cont'd)

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 - REMS letter for Healthcare Providers
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 - Alosetron REMS Program Patient Education Sheet
 - Prescriber Completion of Alosetron REMS Program Training Form

Patient Education

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

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

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Patient Education

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

Patient Responsibilities

Patients should be instructed to:

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

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

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Patient Responsibilities

Patients should be instructed to:

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

Patient Responsibilities(cont'd)

Patients should be instructed to:

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

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

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Patient Responsibilities(cont'd)

Patients should be instructed to:

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

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

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

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

Safety Information Fact Sheet for Prescribers

FDA Required REMS* Safety Information

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

Risk of Serious Gastrointestinal Adverse Reactions

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

Appropriate Patient Selection

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

*What is the Alosetron REMS Program?

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

Indication

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

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

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

Reporting Adverse Events:

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

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

Alosetron REMS Program Patient Education Sheet

FDA Required Alosetron Safety Information

What is alosetron?

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

What is the most serious risk information about alosetron treatment?

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

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

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

How do I take alosetron?

- Take alosetron exactly as your doctor prescribes it.

When should I stop taking alosetron and call my doctor?

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

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

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

Please visit www.AlosetronREMS.com for further information.

Prescriber Completion of Alosetron REMS Program Training Form

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

***Indicates Required Field**

Name of Prescriber (print)*

(First) (Last)

Signature* Date*

NPI Number* _____

Specialty*

- Gastroenterology
- Colon & Rectal Surgery
- Family Medicine
- Obstetrics/Gynecology
- General Surgery
- Nurse Practitioner
- Cardiovascular Diseases
- Other (Please specify) _____
- Internal Medicine
- Nuclear Medicine
- Physician Assistant

Office Name _____

Office Address* _____

Office City* _____ State* _____ Zip Code* _____

Office Phone Number* _____ Office Fax Number* _____

Email* _____

Confirmation Correspondence Preference (please select one): Fax Email

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

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

Alosetron REMS

PO Box 29292, Phoenix, AZ 85038

Fax Number: 1-800-535-6805

Alosetron REMS Program

Risk Evaluation and Mitigation Strategy

Web Mockups

V19

FOOTER

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

Please consult the [Prescribing Information](#).

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



For Patients

For Prescribers

Alosetron REMS (Risk Evaluation and Mitigation Strategy)

What is the Alosetron REMS Program?

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

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

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

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

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

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



For Patients

For Prescribers

Patient Role in the Alosetron REMS Program

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

 [Alosetron REMS Program Patient Education Sheet](#)

Medication Guide

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

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

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





For Patients

For Prescribers

Prescriber Role in the Alosetron REMS Program

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

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

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

Prescriber Training

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

To train in the Alosetron REMS Program via web:

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

To train in the Alosetron REMS Program via fax:

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

Resources

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

Prescribing Information and Medication Guide

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

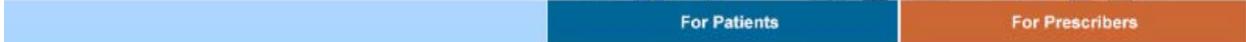
- [Alosetron Prescribing Information \(Par Pharmaceutical, Inc.\)](#)
- [Alosetron Medication Guide \(Par Pharmaceutical, Inc.\)](#)

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



Next

PRESCRIBER AGREEMENT



The Alosetron REMS Program – Prescriber Completion of Training

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

[Complete Training](#)

PRESCRIBER ONLINE TRAINING FORM



For Patients

For Prescribers

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

Prescriber Information

First Name	<input type="text"/>
Last Name	<input type="text"/>
Specialty	<input type="text" value="-- Please Select --"/>
National Provider Identifier (NPI)	<input type="text"/>
Office Name	<input type="text"/>
Address 1	<input type="text"/>
Address 2	<input type="text"/> (Optional)
City	<input type="text"/>
State	<input type="text" value="-- Please Select --"/>
Zip Code	<input type="text"/>
Phone	<input type="text"/>
Fax	<input type="text"/>
Email	<input type="text"/>
Correspondence Confirmation Preference	<input type="radio"/> Email <input type="radio"/> Fax

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

Signature (First and Last Name as typed above)

Date MM/DD/YYYY

I'm not a robot



Submit

PRESCRIBER ONLINE TRAINING FORM – OTHER SPECIALTY SELECTED



For Patients

For Prescribers

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

Prescriber Information

First Name	<input type="text"/>
Last Name	<input type="text"/>
Specialty	Other <input type="text" value="-- Please Specify --"/>
National Provider Identifier (NPI)	<input type="text"/>
Office Name	<input type="text"/>
Address 1	<input type="text"/>
Address 2	<input type="text"/> (Optional)
City	<input type="text"/>
State	<input type="text" value="-- Please Select --"/>
Zip Code	<input type="text"/>
Phone	<input type="text"/>
Fax	<input type="text"/>
Email	<input type="text"/>
Correspondence Confirmation Preference	<input type="radio"/> Email <input type="radio"/> Fax

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

<input type="text" value="Signature (First and Last Name as typed above)"/>	<input type="text" value="Date MM/DD/YYYY"/>	<input type="checkbox"/> I'm not a robot	
---	--	--	--

Submit

PRESCRIBER TRAINING CONFIRMATION



For Patients

For Prescribers

Congratulations!

You have successfully trained in the Alosetron REMS Program!

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

Training Confirmation: <Confirmation ID>

RESOURCES



For Patients

For Prescribers

Resources

Prescriber

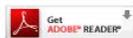
-  [Alosetron REMS Program Prescriber Education Slide Deck](#)
-  [Prescriber Completion of Alosetron REMS Program Training Form](#)
-  [Alosetron REMS Program Patient Education Sheet](#)
-  [Alosetron REMS Program Safety Information Fact Sheet for Prescribers](#)
-  [REMS Letter to Healthcare Providers](#)

Prescribing Information and Medication Guide

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

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

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



CONTACT US



For Patients

For Prescribers

Contact Us

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

Phone Number

1-844-267-8675

Fax Number

1-800-535-6805

Mailing Address

Alosetron REMS Program
PO BOX 29292
PHOENIX AZ 85038-9292

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/s/

JACQUELINE E SHEPPARD
11/17/2016

JAMIE C WILKINS PARKER
11/18/2016

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

OSE RCM #	2016-2364
Reviewer Name	Jacqueline Sheppard, Pharm.D. Anahita Tavakoli, M.A.
DRISK Acting Team Leader	Robert Pratt, Pharm.D.
Acting Deputy Division Director	Jamie Wilkins Parker, Pharm.D.
Review Completion Date	October 26, 2016
Subject	Evaluation of Proposed REMS modification
Established Name	Alosetron hydrochloride
Applicant/Application No.	Roxane Laboratories ANDA 200652/S-004
Therapeutic Class	Selective serotonin 5-HT ₃ antagonist
Formulation(s)	0.5 mg and 1 mg oral tablets
Dosing Regimen	One tablet twice a day
Proposed Indication(s)	Treatment of severe diarrhea-predominant irritable bowel syndrome in women with chronic IBS

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

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates the proposed risk evaluation and mitigation strategy (REMS) modification for Roxane Laboratories' (Roxane) alosetron hydrochloride (alosetron), ANDA 200652 (S-004), submitted on September 23, 2016. The modification provides the proposed shared waiver-granted REMS, REMS supporting document and REMS materials that were developed jointly by members of the Alosetron REMS Group (ARG) comprised of Roxane Laboratories, Amneal Pharmaceuticals and Par Pharmaceuticals.

This modification was submitted in response to the inclusion of the first additional ANDA into the alosetron shared system. Additionally, the modification will allow for the removal of the requirements: 1) to distribute the REMS training kit to all prescribers who are likely to prescribe or who have prescribed alosetron in the 24 months preceding the first REMS approval and 2) for the distribution of the REMS letter for Professional Societies as these requirements have been completed by Roxane. Furthermore, the modification will allow for the removal of the REMS letter for Professional Societies from the REMS materials. Finally, the modification allows for the addition of a CAPTCHA¹ as a new level of security under the Prescriber online Training Form of the alosetron REMS website. The ARG's proposed shared system (SS) REMS consists of elements to assure safe use (ETASU).

2 Background

2.1 PRODUCT BACKGROUND

Alosetron is an approved generic of the Reference Listed Drug (RLD) Lotronex (NDA 21107). The Lotronex REMS was approved with elements to assure safe use on September 2, 2010, to address the risk of ischemic colitis and serious complications of constipation. Alosetron was approved on May 4, 2015, with a REMS comparable to the Lotronex REMS, after the Agency granted Roxane a waiver for the requirement to form a single, shared system REMS with Lotronex. The REMS was last modified March 24, 2016 to provide for the provision of a text box to the prescriber online training form.

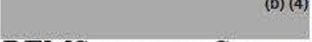
¹ A CAPTCHA is a type of challenge-response test used in computing to determine whether or not the user is human.

2.2 REGULATORY HISTORY

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

- 5/04/15: ANDA 200652 approved after the requirement for a single, shared system REMS program for alosetron hydrochloride products waived. The new program is named the Alosetron REMS Program.
-  (b) (4)
- 7/10/15: ANDA 200652 Suppl-02 received from Roxane. The proposal includes modified REMS goals, removal of the Medication Guide from the REMS elements, and modifications to the ETASU.
- 1/07/16: ANDA 200652 Suppl-02 which provided for modified goals, removal of the Medication Guide, and modifications to the ETASU approved.
- 2/03/16: ANDA 200652 Suppl-03 received from Roxane. The proposal includes a modification to the Website interface.
- 3/24/16: ANDA 200652 Suppl-03 received from Roxane. The proposal provides for the provision of a text box to the prescriber online training form approved.
- 9/23/16: ANDA 200652 Suppl-04 received from Roxane. The proposal modifies the REMS and provides the proposed shared waiver-granted REMS, REMS supporting document and REMS materials in response to the inclusion of the first additional ANDA into the alosetron shared system.

3 Proposed REMS Modifications

The ARG proposes to change the name of the stakeholders from Roxane laboratories (Roxane) to the  (b) (4). While the sponsor name should be updated to reflect the shared system, the name of the stakeholders should be Alosetron Sponsors instead of  (b) (4)  (b) (4). This is in line with the Agency's current thinking on the naming of REMS program Sponsors. The sponsor name should be changed throughout all the materials. This will not affect the name of the REMS program (Alosetron REMS Program) but used only when referring to the Sponsors (Alosetron Sponsors).

3.1 REMS DOCUMENT

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

Goals

There are no proposed changes to the Alosetron goals.

Elements to Assure Safe Use

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

- The requirement to distribute the REMS training kit to all prescribers who are likely to prescribe or who have prescribed alosetron in the 24 months preceding the first REMS approval was removed from the REMS document.

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

- The requirement to send a REMS letter for Professional Societies was removed from the REMS document.

Reviewer Comment: We agree with this proposal. The REMS letter for Professional Societies was distributed by Roxane on February 23, 2016 and the requirements are now complete. See comments in Section 4.

3.2 REMS APPENDED MATERIALS

REMS Letter to Healthcare Providers

- Reference to the RLD was removed from the Reporting Adverse Events section.

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

- Reference to the salt was removed from the Reporting Adverse Events section.

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

Alosetron REMS Program Patient Education Sheet

- The Alosetron Sponsors made a minor grammar and punctuation that did not change the risk messaging

Review Comment: We agree with this modification.

Alosetron REMS Website

- The single sponsor “Medication Guide” PDF link was removed under the patient heading and a new section was added entitled “Medication Guide” with PDF links to each sponsors’ alosetron Medication Guides.

Reviewer Comment: We agree with this modification.

- The single sponsor “Prescribing Information and Medication Guide” PDF links were removed under both the Prescriber Heading and Resource Heading and new sections were added entitled (b) (4) Prescribing Information and Medication Guide” with PDF links to each sponsors’ alosetron (b) (4) Prescribing Information and Medication Guides.

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

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

Reviewer Comment: We agree with this modification.

Letter for Professional Societies

- Reference to Roxane Laboratories, Inc., The Alosetron REMS Program sponsor was removed and replaced with (b) (4)

Reviewer Comment: As the requirement for a letter for Professional Societies was removed from the ETASU of the REMS program, this letter should be removed from the appended materials of the Alosetron REMS. See comments in Section 4.

3.3 REMS SUPPORTING DOCUMENT AND ASSESSMENT PLAN

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

4 Discussion

The ARG modified the REMS document in response to the inclusion of the first additional ANDAs, PAR and Amneal, into the alosetron shared system. The name of the stakeholders was changed from Roxane laboratories (Roxane) to the (b) (4) throughout the REMS document and supporting materials. We disagree with this proposed name change. The name of the stakeholders should be “Alosetron Sponsors” instead of (b) (4) (b) (4). This is in line with the Agency’s current thinking on the naming of REMS program Sponsors. The sponsor name should be changed throughout all the materials. This will not affect the name of the REMS program (Alosetron REMS Program) but only when referring to the Sponsors (Alosetron Sponsors). For example in the REMS document, the term Alosetron REMS Program was added in place of Roxane when referring to the program. This is appropriate usage and we agree with this change.

The ARG have also proposed changes to the ETASU of the REMS document. The requirements to distribute the REMS training kit to all prescribers who are likely to prescribe or who have prescribed alosetron in the 24 months preceding the first REMS approval, and the requirements to distribute a REMS letter for Professional Societies were removed as these requirements have been completed by Roxane. DRISK agrees with the removal of these elements from the shared system REMS document. The REMS Letter for Professional Societies was distributed by Roxane on February 23, 2016 and the REMS training kit was sent by Roxane on March 7, 2016. As the requirements have been completed, they are no longer pertinent to the shared system REMS and do not need to be included in the modified REMS document. However, while the REMS training kit no longer has to be distributed in bulk mailing, the REMS training kit is still required to be distributed to prescribers who have prescribed alosetron and have not been identified as having completed training. In addition, the Letter for Professional Societies should be removed from the REMS document and appended materials because it will be no longer distributed as part of the REMS.

The REMS Letter to Healthcare Providers was modified so that the reference to the RLD was removed from the Reporting Adverse Events section. Additionally, reference to the salt of alosetron was removed. DRISK agrees with this modification. This modification will align the presentation of alosetron in the REMS Letter to Healthcare Providers with the other appended materials.

We are in agreement with the ARG’s proposal to remove the single sponsor “Medication Guide” PDF link under the patient heading and add a new section entitled “Medication Guide” with PDF links to each sponsors’ alosetron Medication Guides on the alosetron website. We are also in agreement with the plan to remove the single sponsor “Prescribing Information and Medication

Guide” PDF links under both the Prescriber Heading and Resource Heading and the addition of new sections with PDF links to each sponsors’ alosetron Prescribing Information and Medication Guides. However, we disagree with entitling the new sections (b) (4) Prescribing Information and Medication Guide.” The use of the term (b) (4) when describing the Prescribing Information is not necessary. The section should be entitled “Prescribing Information and Medication Guide.” Furthermore, we agree with the addition of the added CAPTCHA as a new level of security under the Prescriber online Training Form to require users to check a box stating they are not a robot prior to submission.

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

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

5 Conclusion & Recommendations

DRISK does not agree with all of the proposed modifications to the alosetron REMS program. Comments for Roxane are provided in Section 6.

6 Comments for the Sponsor

The comments in the attached red-lined documents are based on the Agency’s review of the proposed REMS modification for alosetron submitted under ANDA 200652. In order to facilitate further review, we ask that you respond to these comments within 7 business days.

A. General Comments

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

B. REMS Document

ETASU A

1. Letter for Professional Societies should be removed from the REMS document and appended materials because it will be no longer distributed as part of the REMS.

C. Website

1. Under both the Prescriber Heading and Resource Headings of the website, the new sections encompassing PDF links to each sponsors' alosetron Prescribing Information and Medication Guides should be entitled "Prescribing Information and Medication Guide." It is not necessary to use the term (b) (4) when describing the Prescribing Information.

7 Appendices

REMS Document

7.1 REFERENCES

Roxane. Proposed REMS modification for Alosetron, <eCTD Sequence 0057>, Supplement 04, dated September 23, 2016.

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

/s/

JACQUELINE E SHEPPARD
10/26/2016

CYNTHIA L LACIVITA
10/26/2016
Concur

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

ANDA 200652Orig1s004

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

From: Barley, Stacy
To: "vmiller@west-ward.com"; Sasmith@west-ward.com
Subject: ANDA 200652/S-004 alosetron: REMS information request
Date: Thursday, October 27, 2016 2:59:00 PM
Attachments: 2016_10_25_Alosetron_SS_rems-doc-redline-20160923.docx

Hello,

Please refer to your supplemental Abbreviated New Drug Application (sANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for alosetron.

We are reviewing your September 23, 2016 REMS supplement submission and have the following comments and information request:

The comments in the attached red-lined documents are based on the Agency's review of the proposed REMS modification for alosetron submitted under ANDAs 200652/S-004. In order to facilitate further review, we ask that you respond to these comments within 7 business days (November 4, 2016).

A. General Comments

1. We have provided a revised REMS document for the alosetron REMS program. A complete REMS including the REMS document, all appended materials and REMS Supporting Document should be submitted to each application. Submit both a Word tracked changes version and a Word clean version of each of these documents, as well as a pdf version of each of the previously mentioned documents and appended materials. We ask that you respond to these comments and re-submit all documents by November 4, 2016.

2. Revise the name of the stakeholders to Alosetron Sponsors instead of (b) (4). The sponsor name should be changed throughout all the materials. This is in line with the Agency's current thinking on the naming of REMS program Sponsors. This will not affect the name of the REMS program (Alosetron REMS Program) but used only when referring to the Sponsors (Alosetron Sponsors). For example, the "Alosetron Sponsors will ensure training..." and "Alosetron REMS Program Patient Education Sheet" are correct usages.

B. REMS Document

ETASU A

1. Letter for Professional Societies should be removed from the REMS document and appended materials because it will be no longer distributed as part of the REMS.

C. Website

1. Under both the Prescriber Heading and Resource Headings of the website, the new sections encompassing PDF links to each sponsors' alosetron Prescribing Information and Medication Guides should be entitled "Prescribing Information and Medication Guide." It is not necessary to use the term (b) (4) when describing the Prescribing Information.

Please continue to communicate with the Alosetron REMS group to ensure the REMS revisions are in alignment.

Contact me if you have any questions.

Regards,

Stacy

*Stacy Barley, RN, M.S.N., M.S.H.A.
CDR (CAPT sel), USPHS Commissioned Corps
Senior Program Management Officer Consultant
REMS Coordinator
Office of Bioequivalence
OGD/CDER/FDA*

*WO 75, Room 2642
10903 New Hampshire Avenue*

Silver Spring, MD 20993

*(301) 796-2137 (office)
stacy.barley@fda.hhs.gov*

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Following this page, 3 Pages of Draft REMS have been Withheld in Full as (b)(4)

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/s/

STACY R BARLEY
10/27/2016

REQUEST FOR CONSULTATION

TO (Division/Office):

Mail: OSE

FROM: Stacy Barley, REMS Coordinator

OB/OGD, 301-796-2137

DATE
10/11/16

IND NO.
N/A

ANDA NO.
200652 Supplement
4

TYPE OF DOCUMENT
REMS modification (minor)

DATE OF DOCUMENT
9/23/16

NAME OF DRUG
Alosetron hydrochloride

PRIORITY CONSIDERATION
high

CLASSIFICATION OF DRUG
alosetron

DESIRED COMPLETION DATE
11/21/16

NAME OF FIRM: Roxane Laboratories Inc.

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
 BIOAVAILABILTY STUDIES
 PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
 PROTOCOL-BIOPHARMACEUTICS
 IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
 CASE REPORTS OF SPECIFIC REACTIONS (List below)
 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
 SUMMARY OF ADVERSE EXPERIENCE
 POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

This consult is in follow-up to the email I issued to DRISK on 9/30/16 notifying you that the Office of Generic Drugs received the minor modification for the REMS of ANDA 200652 alosetron. This REMS proposes changes that will allow the REMS to be more generic to accommodate other alosetron products to joining the waived REMS program. Please review the proposed changes in the submission.

SIGNATURE OF REQUESTER
Stacy Barley

METHOD OF DELIVERY (Check all that apply)
 MAIL DARRTS HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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

/s/

STACY R BARLEY
10/11/2016