

Initial REMS Approved: 05/2015
Most recent modification: 03/2016

ANDA 200652

Alosetron Tablets

Selective 5-HT₃ antagonist

Roxane Laboratories, Inc.
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Columbus, OH 43228
Phone: (614) 276-4000

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

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.

II. REMS ELEMENTS:

A. Elements to Assure Safe Use

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

a. Roxane Laboratories (Roxane) 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, Roxane will:

- i. Ensure that training is provided to healthcare providers who prescribe alosetron by mailing or emailing the REMS Training Kit to healthcare providers who are likely to prescribe, or have prescribed alosetron in the 24 months preceding the REMS modification approval (MM/YYYY). The REMS Training Kit will be distributed within 60 days after approval of the modified Alosetron REMS Program. Likely prescribers include, but are not limited to, general practitioners, family practitioners, internists, gastroenterologists, and nurse practitioners/physician assistants.
- ii. Send a REMS letter for Professional Societies to the following professional societies and organizations, requesting that the letter or the content be provided to their membership within 6 and 12 months after approval of the modified Alosetron REMS Program.

American Academy of Family Physicians
American Academy of Nurse Practitioners
American Academy of Physicians Assistants
American College of Gastroenterology
American College of Physicians
American Gastroenterological Association
American Medical Association

- iii. Ensure that prescribers can notify Roxane 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 Roxane has a presence.
- vi. Maintain an Alosetron REMS Program website [www.AlosetronREMS.com] and contact center (1-844-267-8675) to support prescribers.
- vii. Monitor distribution and prescription data monthly. Contact all prescribers identified as not having completed training and provide training within 30 days of identification. Contact and provide training to all prescribers who do not report completion of training after the first contact up to two additional times, or until the prescriber reports completion, within 180 days of being first identified.
- viii. Maintain a validated, secure database of healthcare providers who have notified Roxane of completion of training, which will be defined as all training materials were reviewed independently by the healthcare provider.
- ix. Ensure that the REMS materials listed below are available on the 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
 - REMS letter for Professional Societies

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 Lotronex/alosetron hydrochloride 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,

Roxane Laboratories, Inc.

The Alosetron REMS Program sponsor

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

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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

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 - **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
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 - the importance of counseling patients about the risks of IC and serious CoC
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The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.

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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

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- **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:
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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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 - **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)

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Warnings and Precautions (cont'd)

Ischemic Colitis

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

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

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 - **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)

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- 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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 - 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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- 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.

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

^c $P < 0.0001$ vs placebo.

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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Adverse Reactions

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- 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 ($P<0.0001$);
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- 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.

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

- No specific antidote available for overdose of alosetron.
- 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.

28

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.

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.

29

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.

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 full 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

- Prescribers should read the full 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 Alosetron REMS Program.**

Training in the Alosetron REMS Program (cont'd)

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

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

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Training in the Alosetron REMS Program (cont'd)

- 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

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

- 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

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.
- 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.

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.

37

- 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.

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 Guide 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

V17

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](#)





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.

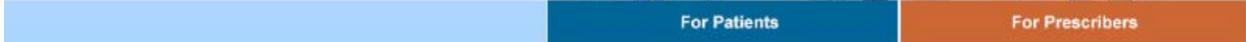
Resources

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



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



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="button" value="Submit"/>
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PRESCRIBER ONLINE TRAINING FORM – OTHER SPECIALTY SELECTED



For Patients

For Prescribers

Important Safety Information

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	-- Please select -- <input type="text"/>
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

Submit

Please consult the [Prescribing Information](#) and [Important Safety Information](#).

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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

-  [Prescribing Information](#)
-  [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](#)
-  [Medication Guide](#)



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

FDA Required REMS Safety Information

Alosetron tablets: Modified REMS

- **RISK OF 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.
- **INDICATED ONLY** for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have not responded adequately to conventional therapy
- **DISCONTINUE** immediately in patients who develop constipation or symptoms of ischemic colitis. Do not resume 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®)

Important Safety Notice

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

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.

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.

Healthcare providers who prescribe alosetron will be provided training to ensure the benefits of alosetron continue to outweigh the risks of ischemic colitis and serious complications of constipation. Training materials can be found at

www.AlosetronREMS.com or by calling 1-844-267-8675. By completing the Alosetron REMS Program Training Form a healthcare professional will be entered into a database for trained prescribers.

A non-promotional factsheet, reviewed by the FDA, with more detailed safety information on these risks, and a link to the Prescribing Information including the BOXED WARNING are available at www.AlosetronREMS.com.

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

This letter does not contain the complete safety profile for alosetron. Please visit www.AlosetronREMS.com for more information.

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,

Roxane Laboratories, Inc.

The Alosetron REMS Program sponsor

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
03/24/2016