

Initial REMS Approved: 09/2010
Last modified/revised: 04/2016

NDA 21-107

**LOTRONEX[®] (alosetron hydrochloride) Tablets
and Authorized Generic (alosetron hydrochloride) Tablets**

Selective 5-HT₃ antagonist

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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

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

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

II. REMS ELEMENTS:

A. Elements to Assure Safe Use

1. Training will be provided to healthcare providers who prescribe LOTRONEX and its authorized generic.

- a. Sebela will ensure that training provided to healthcare providers who prescribe LOTRONEX and its authorized generic includes information on the serious risks of IC and CoC associated with LOTRONEX/alosetron hydrochloride, the importance of understanding that LOTRONEX/alosetron hydrochloride should only be used in severely affected diarrhea-predominant irritable bowel syndrome patients for whom the benefits

exceed the risks, and the importance of counseling patients about the risks of IC and serious CoC, using the prescribing information and the following materials in the REMS Training Kit:

- i. REMS letter for Healthcare Providers
 - ii. LOTRONEX REMS Program Prescriber Education Slide Deck
 - iii. LOTRONEX REMS Program Safety Information Fact Sheet for Prescribers
 - iv. LOTRONEX REMS Program Patient Education Sheet
 - v. Prescriber Completion of LOTRONEX REMS Program Training Form
- b. In order to facilitate training, Sebela will:
- i. Ensure that training is provided to healthcare providers who prescribe LOTRONEX/alosetron hydrochloride by mailing or emailing the REMS Training Kit to healthcare providers who are likely to prescribe, or have prescribed LOTRONEX/alosetron hydrochloride in the 24 months preceding the REMS modification approval (01/2016). The REMS Training Kit will be distributed within 60 days after approval of the modified LOTRONEX REMS Program. Likely prescribers include, but are not limited to, general practitioners, family practitioners, internists, gastroenterologists, and nurse practitioners/physician assistants.
 - ii. Send a REMS letter for Professional Societies to the following professional societies and organizations, requesting that the letter or the content be provided to their membership within 6 and 12 months after approval of the modified LOTRONEX REMS Program.
 - American Academy of Family Physicians
 - American Academy of Nurse Practitioners
 - American Academy of Physicians Assistants
 - American College of Gastroenterology
 - American College of Physicians
 - American Gastroenterological Association
 - American Medical Association
 - iii. Ensure that prescribers can notify Sebela when they have completed training via the LOTRONEX REMS Program website or by faxing or mailing a Prescriber Completion of LOTRONEX REMS Program Training Form.
 - iv. Provide acknowledgement of completion of training electronically or by mail to prescribers upon receiving notification that training was completed.
 - v. Make REMS Training Materials available at professional society meetings and at medical educational venues where Sebela has a presence.
 - vi. Maintain a LOTRONEX REMS Program Website [www.lotronexrems.com] and call center (1-844-851-3395) 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 Sebela of completion of training, which will be defined as all training materials were reviewed independently by the healthcare provider.
- ix. Ensure that the REMS materials listed below are available on the LOTRONEX REMS Program Website or by calling the REMS Coordinating Center.

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

REMS Training Kit

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

Other appended REMS materials:

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

III. Timetable for Submission of Assessments

Sebela will submit REMS Assessments to the FDA 18 months after the date of approval of the modified REMS (01/2016) and every 12 months thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Sebela will submit each assessment so that it will be received by the FDA on or before the due date.

FDA Required REMS Safety Information for LOTRONEX[®] and its authorized generic alosetron hydrochloride

Important Safety Update

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

PPL-ENROLLED Prescriber Actions:

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

NON-ENROLLED Prescriber Actions:

- Review the LOTRONEX REMS Program Training Kit and complete the Prescriber Completion of LOTRONEX REMS Program Training Form which can be found at www.lotronexrems.com.
- You can also submit the enclosed form via e-mail to LotronexREMS@UBC.com or by fax to the Lotronex REMS Program Coordinating Center at 1-877-744-0361.

You will find the LOTRONEX REMS Program Training Kit enclosed. The Training Kit is also available online at www.lotronexrems.com or by calling the Lotronex REMS Program Coordinating Center at 1-844-851-3395, or via e-mail to LotronexREMS@UBC.com.

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

Summary of Changes to the REMS Program

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

Indication:

LOTRONEX/alosetron hydrochloride is a selective serotonin 5-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.lotronexrems.com for more information.

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

Reporting Adverse Events:

You are encouraged to report all suspected adverse events associated with LOTRONEX/alosetron hydrochloride to the FDA at www.fda.gov/medwatch, or 1-800-FDA-1088 or Sebelo Pharmaceuticals Inc. at 1-844-732-3521.

Sincerely,

Sebelo Pharmaceuticals Inc.

LOTRONEX[®] and its authorized generic alosetron hydrochloride:

Understanding the Benefits and Risks

The LOTRONEX REMS Program Prescriber Education Slide Deck

LOTRONEX is a registered trademark of Prometheus Laboratories Inc.

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LOT15049 03/16

Please see complete Prescribing Information for LOTRONEX/alosetron hydrochloride.

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Important

Modified LOTRONEX REMS Program

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

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

Section 1:

Purpose

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

Purpose

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

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

What is a REMS?

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

Goals and Objectives

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

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

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

Section 2:

Indication and Usage

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

Indication and Usage

- LOTRONEX[®]/alosetron hydrochloride is indicated **ONLY** for women with severe diarrhea-predominant IBS who have:
 - ✓ **chronic IBS symptoms (generally lasting 6 months or longer),**
 - ✓ **had anatomic or biochemical abnormalities of the GI tract excluded, and**
 - ✓ **not responded adequately to conventional therapy.**
- Diarrhea-predominant IBS is severe if it includes diarrhea and one or more of the following:
 - ✓ **frequent and severe abdominal pain/discomfort,**
 - ✓ **frequent bowel urgency or fecal incontinence,**
 - ✓ **disability or restriction of daily activities due to IBS.**
- Because of infrequent but serious GI adverse reactions associated with alosetron hydrochloride, the indication is restricted to those patients for whom the benefit-to-risk balance is most favorable.
- Clinical studies have not been performed to adequately confirm the benefits of alosetron hydrochloride in men.

Section 3:

Important Safety Information

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

Boxed Warning

WARNING: SERIOUS GASTROINTESTINAL ADVERSE REACTIONS

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

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

Boxed Warning (cont'd)

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

Please see complete Prescribing Information for LOTRONEX[®]/alosectron hydrochloride for full details about risks.

Warnings and Precautions

Serious Complications of Constipation

- Some patients have experienced serious complications of constipation without warning. Examples include:
 - ✓ **obstruction, ileus, impaction, toxic megacolon, and secondary bowel ischemia have been reported with use of alosetron hydrochloride during clinical trials**
 - ✓ **in addition, rare cases of intestinal perforation and death have been reported from post-marketing clinical practice**
 - ✓ **in some cases, complications of constipation required intestinal surgery, including colectomy**
- The incidence of serious complications of constipation was ~0.1%, or 1 per 1,000 patients, in women receiving either alosetron hydrochloride or placebo.
- Patients who are elderly, debilitated, or taking additional medications that decrease GI motility may be at greater risk for complications of constipation.
- Alosetron hydrochloride should be discontinued immediately in patients who develop constipation.

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

Warnings and Precautions (cont'd)

Ischemic Colitis

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

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

Warnings and Precautions (cont'd)

Ischemic Colitis

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

Please see complete Prescribing Information for LOTRONEX[®]/alosectron hydrochloride for full details about risks.

Contraindications

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

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

Drug Interactions

- In vivo data suggest that alosetron hydrochloride is primarily metabolized by cytochrome P450 (CYP) 1A2, with minor contributions from CYP3A4 and CYP2C9. Therefore, inducers or inhibitors of these enzymes may change the clearance of alosetron hydrochloride.
- Concomitant administration of alosetron hydrochloride and fluvoxamine is contraindicated.
- Concomitant administration of alosetron hydrochloride and moderate CYP1A2 inhibitors, including quinolone antibiotics and cimetidine, has not been evaluated, but should be avoided unless clinically necessary because of similar potential drug interactions.

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

Drug Interactions (cont'd)

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

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

Use in Specific Populations

- Pregnancy Category B.
- It is not known whether alosetron hydrochloride is excreted in human milk; caution should be exercised when alosetron hydrochloride is administered to a nursing woman.
- Safety and effectiveness in pediatric patients have not been established.
- Post-marketing experience suggests that elderly patients may be at greater risk for complications of constipation; therefore, appropriate caution and follow-up should be exercised if alosetron hydrochloride is prescribed for these patients.
- Increased exposure to alosetron hydrochloride and/or its metabolites is likely to occur in patients with hepatic impairment. Alosetron hydrochloride should not be used in patients with severe hepatic impairment and should be used with caution in patients with mild or moderate hepatic impairment.

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

Adverse Reactions Reported in $\geq 1\%$ of IBS Patients^a

Gastrointestinal Adverse Reactions	Alosetron hydrochloride 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 $\geq 1\%$ of alosetron hydrochloride patients and occurring more frequently on alosetron hydrochloride 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.

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

Adverse Reactions

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

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

Overdosage

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

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

Section 4:

How to Prescribe LOTRONEX[®]/alosetron hydrochloride

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

Dosage and Administration

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

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

Dosage and Administration (cont'd)

- Usual Dose in Adults (cont't):
 - ✓ **Alosetron hydrochloride should be discontinued in patients who have not had adequate control of IBS symptoms after 4 weeks of treatment with 1 mg twice-a-day.**
 - ✓ **Alosetron hydrochloride should be discontinued immediately in patients who develop constipation or signs of ischemic colitis.**
 - ✓ **Alosetron hydrochloride should not be restarted in patients who develop ischemic colitis.**
- Clinical trial and post-marketing experience suggest that debilitated patients or patients taking additional medications that decrease GI motility may be at greater risk of serious complications of constipation.
- Therefore, appropriate caution and follow-up should be exercised if alosetron hydrochloride is prescribed for these patients.
- Alosetron hydrochloride can be taken with or without food.

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

Section 5:

LOTRONEX REMS ProgramTM

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

LOTRONEX REMS Program™

Prescriber Training

- Prescribers should read the full Prescribing Information (PI) and other training materials to understand the benefits and risks of treatment with LOTRONEX®/alosetron hydrochloride for severe diarrhea-predominant IBS.
- Prescribers can communicate the completion of training by filling out the Prescriber Completion of LOTRONEX REMS Program™ Training Form:
 - online at www.lotronexrems.com, or
 - via e-mail at LotronexREMS@UBC.com, or
 - by fax to the Lotronex REMS Program Coordinating Center at 1-877-744-0361.

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

LOTRONEX REMS Program™

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

LOTRONEX REMS Program™

Patient Education

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

LOTRONEX REMS Program™

Patient Responsibilities

Patients should be instructed to:

- read the LOTRONEX REMS Program Patient Education Sheet before starting LOTRONEX®/alosetron hydrochloride .
- read the Medication Guide before starting LOTRONEX®/alosetron hydrochloride and each time they refill their prescription.
- not take LOTRONEX®/alosetron hydrochloride if they are constipated.
- immediately discontinue LOTRONEX®/alosetron hydrochloride and contact their prescriber if they become constipated or have symptoms of ischemic colitis such as new or worsening abdominal pain, bloody diarrhea, or blood in the stool.
- immediately contact their prescriber again if their constipation does not resolve after discontinuation of LOTRONEX®/alosetron hydrochloride.
- resume LOTRONEX®/alosetron hydrochloride only if their constipation has resolved and after discussion with and the agreement of their treating prescriber.
- stop taking LOTRONEX®/alosetron hydrochloride and contact their prescriber if LOTRONEX®/alosetron hydrochloride does not adequately control IBS symptoms after 4 weeks of taking 1 mg twice-a-day.

LOTRONEX[®] REMS Program
Safety Information Fact Sheet for Prescribers

FDA Required REMS* Safety Information

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

Risk of Serious Gastrointestinal Adverse Reactions

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

Appropriate Patient Selection

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

***What is the Lotronex REMS Program?**

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

Indication:

LOTRONEX/alosetron hydrochloride 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 Lotronex/alosetron hydrochloride to the FDA at www.fda.gov/medwatch, or 1-800-FDA-1088 or Sebela Pharmaceuticals Inc. at 1-844-732-3521.

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

LOT15050 03/16

FDA Required Lotronex/alosetron hydrochloride Safety Information

What is LOTRONEX/alosetron hydrochloride?

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

What is the most serious risk information about LOTRONEX/alosetron hydrochloride treatment?

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

What should I tell my doctor before I start taking LOTRONEX/alosetron hydrochloride?

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

How do I take LOTRONEX/alosetron hydrochloride?

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

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

- Stop taking LOTRONEX/alosetron hydrochloride and call your doctor right away if you get constipated, if you have new or worse pain in your stomach area (abdomen), or if you see blood in your bowel movements.
- Call your doctor again if the constipation you called about before has not gotten better.
- Do not start taking LOTRONEX/alosetron hydrochloride again unless your doctor tells you to do so, if you stopped taking it because you got constipated.
- Talk with your doctor 4 weeks after starting LOTRONEX/alosetron hydrochloride to recheck your IBS symptoms.
- Stop taking LOTRONEX/alosetron hydrochloride and call your doctor if your IBS symptoms have not improved after 4 weeks of taking 1 mg of LOTRONEX/alosetron hydrochloride 2 times a day.
- If you see other doctors about your IBS or possible side effects from LOTRONEX/alosetron hydrochloride, tell the doctor who prescribed LOTRONEX/alosetron hydrochloride.

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

Please visit www.LotronexREMS.com for further information.

PRESCRIBER COMPLETION OF LOTRONEX[®] REMS PROGRAM TRAINING FORM

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

** Required fields*

Prescriber's Information:

*First Name: _____ Middle Name: _____

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

*Signature: _____ *Date: _____

*NPI #: _____

Prescriber's Office Address:

*Address 1: _____

Address 2: _____

*City: _____ *State: _____ Zip code: _____

*Phone #: _____

Fax #: _____

*E-mail: _____

E-MAIL TO: LotronexREMS@UBC.com

FAX TO: Lotronex REMS Program Coordinating Center 1-877-744-0361

MAIL TO: Lotronex REMS
200 Pinecrest Plaza
Morgantown, WV 26505

FDA Required REMS Safety Information

LOTRONEX[®] and its authorized generic alosetron hydrochloride tablets: Modified REMS

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

Important Safety Notice

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

Risk of Serious Gastrointestinal Adverse Reactions

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

Changes to the REMS Program

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

Healthcare providers who prescribe LOTRONEX/alosetron hydrochloride will be provided training to ensure the benefits of LOTRONEX/alosetron hydrochloride continue to outweigh the risks of ischemic colitis and serious complications of constipation. Training materials can be found at www.lotronexREMS.com or by calling 1-844-851-3395. By completing the LOTRONEX REMS Program Training Form a healthcare professional will be entered into a database for trained prescribers.

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

Indication:

LOTRONEX/alosetron hydrochloride 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 LOTRONEX/alosetron hydrochloride. Please visit www.lotronexREMS.com for more information.

Reporting Adverse Events:

You are encouraged to report all suspected adverse events associated with LOTRONEX/alosetron hydrochloride to the FDA at www.fda.gov/medwatch, or 1-800-FDA-1088 or Sebelo Pharmaceuticals Inc. at 1-844-732-3521.

Sincerely,

Sebelo Pharmaceuticals, Inc.

LOT15056 03/16

Rx Prescriber Information

What is my role in the LOTRONEX REMS Program?

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

Step 1: Complete the LOTRONEX REMS Program Prescriber Training

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

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

Step 2: Educate Patients

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

Program Resources and Education Materials

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

There are two ways to obtain program materials:

1. VIEW, PRINT, OR SAVE ON YOUR COMPUTER –You can view, print, or save the materials to your computer. Select items from the list below.
2. BY PHONE – you can order materials by calling the LOTRONEX REMS Program Coordinating Center at 1-844-851-3395.

- [REMS letter Healthcare Providers](#)
- [LOTRONEX REMS Program Prescriber Education Slide Deck](#)
- [LOTRONEX REMS Program Safety Information Fact Sheet for Prescribers](#)
- [LOTRONEX REMS Program Patient Education Sheet](#)
- [LOTRONEX REMS Program Professional Societies Letter](#)
- [LOTRONEX Prescribing Information](#)
- [alose tron hydrochloride Prescribing Information](#)

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645 Hembree Parkway, Suite I
Roswell, Georgia 30076
Toll Free 1-844-732-3521

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Patient Information

INFORMATION FOR PATIENTS

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

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

Important safety Information about LOTRONEX/alose tron hydrochloride:

Serious bowel (intestine) side effects can happen suddenly including

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

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

Stop taking LOTRONEX/alose tron hydrochloride and call your doctor right away if you get:

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

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

LOTROX/alose tron hydrochloride is:

A medicine only for some women with severe chronic irritable bowel syndrome (IBS) whose main problem is diarrhea and IBS symptoms have not been helped enough by other treatments.

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

Download the:

[LOTROX REMS Program Patient Education Sheet](#)



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LOTTRONEX REMS (Risk Evaluation and Mitigation Strategy) Program

LOTTRONEX and its authorized generic alosetron hydrochloride are available by prescription as:
LOTTRONEX[®] (alose tron hydrochloride) Tablets.

What is the LOTTRONEX REMS Program?

A REMS is a strategy to manage known or potential serious risks associated with a drug product and is required by the FDA to ensure the benefits of a drug outweigh the risks. The purpose of the LOTTRONEX REMS Program is to inform prescribers about the risks of:
Serious Gastrointestinal Adverse Reactions, including ischemic colitis and serious complications of constipation, which have resulted in hospitalization and, rarely, blood transfusion, surgery, and death.

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

- [LOTTRONEX[®] \(alose tron hydrochloride\) Tablets](#)
- [Alose tron hydrochloride](#)

INDICATION: LOTTRONEX/alose tron hydrochloride is indicated only for women with severe diarrhea-predominant irritable bowel syndrome who have: chronic irritable bowel syndrome symptoms (generally lasting 6 months or longer), had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and not responded adequately to conventional therapy. Diarrhea-predominant irritable bowel syndrome is severe if it includes diarrhea and one or more of the following: frequent and severe abdominal pain/discomfort, frequent bowel urgency or fecal incontinence, disability or restriction of daily activities due to irritable bowel syndrome. Because of infrequent but serious gastrointestinal adverse events associated with LOTTRONEX/alose tron hydrochloride, the indication is restricted to those patients for whom the benefit-to-risk balance is most favorable. Clinical studies have not been performed to adequately confirm the benefits of LOTTRONEX/alose tron hydrochloride in men.



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Medication Guide

LOTROX® (LOW-trah-nex) Tablets (alosetron hydrochloride)

Before using LOTROX for the first time, you should:

- Understand that LOTROX has serious risks for some people.
- Read and follow the directions in this Medication Guide.

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

1. What is the most important information I should know about LOTROX?

A. LOTROX is a medicine only for some women with severe chronic irritable bowel syndrome (IBS) whose:

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

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

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

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

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

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

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

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

C. Is LOTROX right for you?

LOTROX may be right for you if **all** of these things are true about you:

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

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

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

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

2. What is LOTROX?

LOTROX is a medicine only for some women with severe chronic IBS whose:

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

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

LOTROX is not recommended for children.

3. Who should not take LOTROX?

LOTROX is not right for everyone. Do not take LOTROX if **any** of the following apply to you:

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

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

Talk with your doctor:

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

5. How should I take LOTROX?

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

6. What are the possible side effects of LOTROX?

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

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

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

7. How should I store LOTROX?

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

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

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

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you have any questions or concerns about LOTROX, ask your doctor. Do not use LOTROX for a condition for which it was not prescribed. Do not share your medicine with other people. It may harm them. Your doctor or pharmacist can give you more information about LOTROX that was written for healthcare professionals. You can also contact the company that makes LOTROX (toll free) at 1-844-732-3521 or at www.lotrox.com.

9. What are the ingredients of LOTROX?

Active Ingredient: alosetron hydrochloride.

Inactive Ingredients: lactose (anhydrous), magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The white film-coat for the 0.5 mg tablet contains hypromellose, titanium dioxide, and triacetin. The blue film-coat for the 1 mg tablet contains hypromellose, titanium dioxide, triacetin, and indigo carmine.

Manufactured for:
Sebela Ireland Ltd.

Distributed By:
Sebela Pharmaceuticals Inc.
645 Hembree Parkway, Suite I
Roswell, Georgia 30076

Toll Free 1-844-732-3521

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

Revised January 2016 MDG 89503 0116

INDICATION: LOTROX/alosetron hydrochloride is indicated only for women with severe diarrhea-predominant irritable bowel syndrome who have: chronic irritable bowel syndrome symptoms (generally lasting 6 months or longer), had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and not responded adequately to conventional therapy. Diarrhea-predominant irritable bowel syndrome is severe if it includes diarrhea and one or more of the following: frequent and severe abdominal pain/discomfort, frequent bowel urgency or fecal incontinence, disability or restriction of daily activities due to irritable bowel syndrome. Because of infrequent but serious gastrointestinal adverse events associated with LOTROX/alosetron hydrochloride, the indication is restricted to those patients for whom the benefit-to-risk balance is most favorable. Clinical studies have not been performed to adequately confirm the benefits of LOTROX/alosetron hydrochloride in men.



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