LOTRONEX®
and its authorized generic
alosetron hydrochloride:

Understanding the Benefits
and Risks

The Prescribing Program for LOTRONEX™
Pharmacist Education Slide Deck

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Please see complete Prescribing Information for LOTRONEX.
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Section 1:

Purpose
Purpose of the Pharmacist Educational Slide Deck for LOTRONEX® (alosetron HCl)

• By reviewing the information provided in this presentation, pharmacists who dispense LOTRONEX and its authorized generic will better understand the:

  –Restricted distribution process for this product;
  –Risks and benefits of LOTRONEX;
  –Etiology of irritable bowel syndrome;
  –Prescribing Program for LOTRONEX™(PPL).
Risk Evaluation and Mitigation Strategy (REMS)

The Food and Drug Administration (FDA) has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for LOTRONEX® and its authorized generic to ensure the benefits of the drug outweigh the risks of serious gastrointestinal adverse events. A REMS is a strategy to address the serious risks associated with a drug. The REMS can range from periodic assessment of a product’s postmarketing safety profile to strict limitations on the way a drug is prescribed, distributed, or dispensed.
Goals of the Prescribing Program for LOTRONEX™ and Key Elements

The Prescribing Program for LOTRONEX™ (PPL) was implemented to help reduce the risks of serious GI adverse events.

The Goals of the LOTRONEX® REMS Program are:

- To mitigate the risk of ischemic colitis (IC) and serious complications of constipation (CoC) associated with alosetron hydrochloride by ensuring that LOTRONEX and its authorized generic are used in only severely affected patients in whom the benefits exceed the risks.

- To ensure that the risk of IC and serious CoC with use of LOTRONEX and its authorized generic are communicated to patients, pharmacists, and prescribers.
Goals of the Prescribing Program for LOTRONEX™ and Key Elements (cont’d)

The Key Elements of the LOTRONEX® REMS are:

- only prescribers who have enrolled in the Prometheus Prescribing Program for LOTRONEX™ (PPL), based on their understanding of the benefits and risks, can prescribe LOTRONEX or its authorized generic.
- pharmacists may only dispense LOTRONEX and its authorized generic from prescriptions with a sticker and written by prescribers participating in the PPL.
Section 2:

Indication and Usage

Please see complete Prescribing Information for LOTRONEX for full details about risks.
LOTRONEX® (alosetron HCl): Indication and Usage

LOTRONEX® (alosetron HCl) 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.

Please see complete Prescribing Information for LOTRONEX for full details about risks.
LOTRONEX® (alosetron HCl):
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 LOTRONEX, the indication is restricted to those patients for whom the benefit-to-risk balance is most favorable.

• Clinical studies have not been performed to adequately confirm the benefits of LOTRONEX in men.

Please see complete Prescribing Information for LOTRONEX for full details about risks.
Section 3:

Important Safety Information

Please see complete Prescribing Information for LOTRONEX for full details about risks.
LOTRONEX® (alosetron HCl):
Boxed Warning

WARNING: SERIOUS GASTROINTESTINAL ADVERSE REACTIONS

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

- The Prescribing Program for LOTRONEX™ was implemented to help reduce risks of serious gastrointestinal adverse reactions. Only prescribers who have enrolled in the Prometheus Prescribing Program for LOTRONEX, based on their understanding of the benefits and risks, should prescribe LOTRONEX.

Please see complete Prescribing Information for LOTRONEX for full details about risks.
LOTRONEX® (alosetron HCl):  
Boxed Warning (cont’d)

- LOTRONEX is indicated only for women with severe diarrhea-predominant IBS who have not responded adequately to conventional therapy. Before receiving the initial prescription for LOTRONEX, the patient must read and sign the Patient Acknowledgement Form for LOTRONEX.

- LOTRONEX 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. LOTRONEX 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 LOTRONEX is discontinued. Patients with resolved constipation should resume LOTRONEX only on the advice of their treating prescriber.

Please see complete Prescribing Information for LOTRONEX for full details about risks.
LOTRONEX® (alosetron HCl):
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 LOTRONEX 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.

Please see complete Prescribing Information for LOTRONEX for full details about risks.
LOTRONEX® (alosetron HCl): 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 LOTRONEX or placebo.

- Patients who are elderly, debilitated, or taking additional medications that decrease GI motility may be at greater risk for complications of constipation.

- LOTRONEX should be discontinued immediately in patients who develop constipation.

Please see complete Prescribing Information for LOTRONEX for full details about risks.
LOTRONEX® (alosetron HCl):
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 LOTRONEX in clinical trials as well as during marketed use of the drug.

• In IBS clinical trials:
  – cumulative incidence of ischemic colitis in women receiving LOTRONEX 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 LOTRONEX for longer than 6 months.

Please see complete Prescribing Information for LOTRONEX for full details about risks.
LOTRONEX® (alosetron HCl): Warnings and Precautions (cont’d)

Ischemic Colitis (cont’d)

• LOTRONEX 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 LOTRONEX should not be resumed in patients who develop ischemic colitis.

Please see complete Prescribing Information for LOTRONEX for full details about risks.
LOTRONEX® (alosetron HCl):
Contraindications

• LOTRONEX should not be initiated in patients with constipation.

• LOTRONEX 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.

Please see complete Prescribing Information for LOTRONEX for full details about risks.
LOTRONEX® (alosetron HCl):
Contraindications (cont’d)

• LOTRONEX should not be used by patients who are unable to understand or comply with the Patient Acknowledgement Form.

• Concomitant administration of LOTRONEX with fluvoxamine is contraindicated.

Please see complete Prescribing Information for LOTRONEX for full details about risks.
LOTRONEX® (alosetron HCl):

Drug Interactions

In vivo data suggest that LOTRONEX 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 LOTRONEX

- Concomitant administration of LOTRONEX and fluvoxamine is contraindicated.
- Concomitant administration of LOTRONEX 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 for full details about risks.
LOTRONEX® (alosetron HCl):

Drug Interactions (cont’d)

- Caution should be used when LOTRONEX and ketoconazole are administered concomitantly.

- Coadministration of LOTRONEX 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 LOTRONEX and its metabolites is not known.

Please see complete Prescribing Information for LOTRONEX for full details about risks.
LOTRONEX® (alosetron HCl):

Use in Specific Populations

- Pregnancy Category B.

- It is not known whether LOTRONEX is excreted in human milk; caution should be exercised when LOTRONEX 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 LOTRONEX is prescribed for these patients.

Please see complete Prescribing Information for LOTRONEX for full details about risks.
LOTRONEX® (alosetron HCl):
Use in Specific Populations (cont’d)

• Increased exposure to LOTRONEX and/or its metabolites is likely to occur in patients with hepatic impairment. LOTRONEX 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 for full details about risks.
## Adverse Reactions Reported in ≥ 1% of IBS Patients

<table>
<thead>
<tr>
<th>Gastrointestinal Adverse Reactions</th>
<th>LOTRONEX&lt;sup&gt;a&lt;/sup&gt; (alosetron HCl) 1 mg BID</th>
<th>Placebo (n=2,363)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>29%</td>
<td>6%</td>
</tr>
<tr>
<td>Abdominal discomfort and pain</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>GI discomfort and pain</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Regurgitation and reflux</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Hemorrhoids</td>
<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>

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**Notes:**

- **a** Reported in ≥1% of LOTRONEX patients and occurring more frequently on LOTRONEX 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 for full details about risks.
LOTRONEX® (alosetron HCl):
Adverse Reactions

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

• In clinical studies constipation was reported in ~29% of patients with IBS treated with LOTRONEX 1 mg twice-a-day (n=9,316):
  – The effect was statistically significant compared with placebo ($P<0.0001$).
  – 11% of patients treated with LOTRONEX 1 mg twice-a-day withdrew from the studies due to constipation.

• Although the number of IBS patients treated with LOTRONEX 0.5 mg twice-a-day 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 for full details about risks.
LOTRONEX® (alosetron HCl): Overdosage

- No specific antidote available for overdose of LOTRONEX.

- Patients should be managed with appropriate supportive therapy.

Please see complete Prescribing Information for LOTRONEX for full details about risks.
Section 4:

The Prescribing Program
for LOTRONEX™
Prescriber Enrollment in the Prescribing Program for LOTRONEX™ (PPL)

• Prescribers must read the full PI and understand the benefits and risks of treatment with LOTRONEX and its authorized generic for women with severe diarrhea-predominant IBS.

• Prescribers then complete the Prescriber Enrollment Form at www.lotronexppl.com or call 1-888-423-5227 or ask a Prometheus representative for enrollment materials:
  
  – The form must be returned to Prometheus before a prescriber can be considered enrolled in the PPL.

• Starter PPL kits including Medication Guides and stickers that need to be affixed to every prescription are provided after enrollment.
The Prescribing Program for LOTRONEX™

• Once an appropriate patient has been selected for therapy, the Medication Guide and risks of therapy must be discussed with the patient.

• Any questions from the patient should be initially addressed by the prescriber or a healthcare provider under the prescriber’s direction.

• Instruct the patient to complete the Patient Acknowledgement Form. The original signed form should be placed in the patient’s medical record and another copy should be given to the patient.
Overview of Prescriber Responsibilities for the Prescribing Program for LOTRONEX™

1. Review and provide Medication Guide to patient

2. Have the patient complete the Patient Acknowledgement Form, place the original in the patient’s medical record, and give a copy to the patient

3. Provide patient with written prescription with affixed PPL sticker (refills are permitted on written prescriptions)
Section 5:

Role of the Pharmacist in the Prescribing Program for LOTRONEX™
Pharmacist Responsibilities

- Learn about the Prescribing Program for LOTRONEX™ (PPL).

- Understand the benefits and risks of treatment with LOTRONEX® and its authorized generic for severe diarrhea-predominant IBS, including the information in the Retail Pack for LOTRONEX and its authorized generic, which contains the Prescribing Information, the Medication Guide, and the Patient Follow-Up Survey Pre-Enrollment Form.

- To ensure documentation of safe-use conditions, pharmacists must confirm the validity of every prescription of LOTRONEX and its authorized generic by ensuring that the PPL sticker is present on the prescription prior to dispensing LOTRONEX or its authorized generic to a patient.
Pharmacist Responsibilities (cont’d)

- If a PPL sticker is not present on the prescription, call Prometheus Client Services at 1-888-423-5227 to confirm that the prescriber is enrolled in the Prescribing Program for LOTRONEX.

- Provide each patient with their prescribed treatment of LOTRONEX® or the authorized generic and the Retail Pack. The Retail Pack includes a copy of the Medication Guide.
The Prescribing Program for LOTRONEX™

- To prescribe LOTRONEX® and its authorized generic, prescribers (physicians) must be enrolled in the Prescribing Program for LOTRONEX™ (PPL).

- To enroll, prescribers must understand the benefits and risks of treatment with LOTRONEX and its authorized generic for women with severe diarrhea-predominant IBS, including the information in the Prescribing Information, the Medication Guide, and the Patient Acknowledgement Form for LOTRONEX and its authorized generic.

- Pharmacists should also learn about and understand the benefits and risks associated with LOTRONEX/alosetron hydrochloride treatment.
The Prescribing Program for LOTRONEX™ (cont’d)

- Upon enrollment in the Prescribing Program for LOTRONEX™ (PPL), stickers for prescriptions are provided to prescribers.

- Stickers affixed to a prescription of LOTRONEX® and its authorized generic indicate the following:
  
  - Certifies participation of a prescriber in the PPL;
  
  - LOTRONEX and its authorized generic prescription is valid and may be filled by a pharmacist;
  
  - Prescription may include refills.

- Telephone, faxed, or computerized prescriptions are NOT valid under the program.
Overview of Pharmacist Responsibilities
A Simple 2-Step Process

1. Verify validity of LOTRONEX or its authorized generic prescription by checking for the PPL sticker (refills are permitted on written prescriptions)
2. Dispense a Retail Pack for LOTRONEX or its authorized generic, which includes Medication Guide, Prescribing Information, Medicine, and Patient Follow-Up Survey Pre-Enrollment Form

Note to Pharmacist:
If a PPL sticker is not present on the prescription, call Prometheus Client Services at 1-888-423-5227 to confirm that the prescriber is enrolled in the PPL.