LOTRONEX® and its authorized generic alosetron hydrochloride:

Understanding the Benefits and Risks

The Prescribing Program for LOTRONEX™
Prescriber Education Slide Deck

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Please see complete Prescribing Information for LOTRONEX.
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Section 1:

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

- By reviewing the information provided in this presentation, prescribers who prescribe 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 risk of serious gastrointestinal adverse reactions. 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 the 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\(^a\)

<table>
<thead>
<tr>
<th>Gastrointestinal Adverse Reactions</th>
<th>LOTRONEX® (alosetron HCl) 1 mg BID (n=8,328(^b))</th>
<th>Placebo (n=2,363)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation(^c)</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>

\(^a\) 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 daily (n=9,316).

  - The effect was statistically significant compared with placebo ($P<0.0001$);

  - 11% of patients treated with LOTRONEX 1 mg twice daily withdrew from the studies due to constipation.

- Although the number of IBS patients treated with LOTRONEX 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 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:

How to Prescribe and Dispense LOTRONEX®
and its authorized generic alosetron hydrochloride

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

For safety reasons, only prescribers who enroll in the Prescribing Program for LOTRONEX™ (PPL) can prescribe LOTRONEX.

• Usual Dose in Adults

  - To lower the risk of constipation, LOTRONEX 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.

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

- Usual Dose in Adults

  - LOTRONEX 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.

  - LOTRONEX 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.

  - LOTRONEX should be discontinued immediately in patients who develop constipation or signs of ischemic colitis.

  - LOTRONEX should not be restarted in patients who develop ischemic colitis.

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

- LOTRONEX can be taken with or without food.

Please see complete Prescribing Information for LOTRONEX for full details about risks.
Section 5:

Prescribing Program
for LOTRONEX™ (PPL)
Enrolling 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 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 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™ (PPL)

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)
Inform Your Patients about the Requirements of the Prescribing Program for LOTRONEX™ (PPL)

• Once you have selected an appropriate patient for therapy, review the Medication Guide and explain the risks of therapy to the patient.

• Answer any questions the patient may have.

• Instruct the patient to complete the Patient Acknowledgement Form. Place a copy of the signed form in the patient’s medical record and give a copy to the patient.
The Prescribing Program for LOTRONEX™ (PPL)

- Affix the sticker to every prescription for LOTRONEX and its authorized generic:

![Sticker Image]

- Refills may be written on prescriptions.

- No telephone, facsimile, or computerized prescriptions are permitted with this program.
Patient Responsibilities

Patients should be instructed to:

- 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.
Patient Responsibilities

Patients should be instructed to (cont’d):

- 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.
Encourage Your Patients to Enroll in the Voluntary Follow-Up Survey for LOTRONEX® and its authorized generic alosetron hydrochloride

- Prometheus sponsors a patient survey to monitor the process of prescribing LOTRONEX and its authorized generic in clinical practice.

- The survey is important for monitoring the Prescribing Program for LOTRONEX™ (PPL).