THE ALOSETRON REMS PROGRAM

Pharmacist Education Slide Deck

Understanding the Benefits and Risks of Alosetron
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Section 1:

Purpose
Purpose of the Pharmacist Educational Slide Deck for Alosetron

- By reviewing the information provided in this presentation, pharmacists who dispense alosetron hydrochloride (alosetron) will better understand the:
  
  - Restricted distribution process for this product;
  
  - Risks and benefits of alosetron;
  
  - Etiology of irritable bowel syndrome;

- The Alosetron REMS Program
The Food and Drug Administration (FDA) has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for alosetron 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.
Goal of The Alosetron REMS Program and Key Elements

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

The Goals of the Alosetron REMS Program are:

• To mitigate the risk of ischemic colitis (IC) and serious complications of constipation (CoC) associated with alosetron hydrochloride (hereinafter, referred to as alosetron) by ensuring that alosetron is used in only severely affected patients in whom benefits exceed the risks.

• To ensure that the risk of IC and serious CoC with the use of alosetron are communicated to patients, pharmacists, and prescribers.
The Key Elements of the Alosetron REMS are:

- only prescribers who have enrolled in the Alosetron REMS Program, based on their understanding of the benefits and risks, can prescribe alosetron.

- pharmacists may only dispense alosetron from prescriptions with an Alosetron REMS sticker and written by prescribers participating in the Alosetron REMS Program.¹

¹ In the alternative, a prescription for alosetron may be dispensed in the presence of a Prescribing Program for LOTRONEX™ sticker, if generic substitution of alosetron is permitted pursuant to State substitution laws.
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.
Indication and Usage (cont’d)

- Diarrhea-predominant IBS is severe if it includes diarrhea and one or more of the following:
  - frequent and severe abdominal pain/discomfort,
  - frequent bowel urgency or fecal incontinence,
  - disability or restriction of daily activities due to IBS.

- Because of infrequent but serious GI adverse reactions associated with alosetron, the indication is restricted to those patients for whom the benefit-to-risk balance is most favorable.

- Clinical studies have not been performed to adequately confirm the benefits of alosetron in men.
Section 3: Important Safety Information
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 was implemented to help reduce risks of serious gastrointestinal adverse reactions. Only prescribers who have enrolled in the Alosetron REMS Program, based on their understanding of the benefits and risks, should prescribe alosetron.

The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.
Boxed Warning (cont’d)

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

• Alosetron should be discontinued immediately in patients who develop constipation or symptoms of ischemic colitis. Patients should immediately report constipation or symptoms of ischemic colitis to their prescriber. Alosetron should not be resumed in patients who develop ischemic colitis. Patients who have constipation should immediately contact their prescriber if the constipation does not resolve after alosetron is discontinued. Patients with resolved constipation should resume alosetron only on the advice of their treating prescriber.
Warnings and Precautions

Serious Complications of Constipation

- Some patients have experienced serious complications of constipation without warning. Examples include:

  - obstruction, ileus, impaction, toxic megacolon, and secondary bowel ischemia have been reported with use of alosetron during clinical trials.

  - in addition, rare cases of intestinal perforation and death have been reported from postmarketing clinical practice.

  - in some cases, complications of constipation required intestinal surgery, including colectomy.

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

• Alosetron should not be initiated in patients with constipation.

• Alosetron is contraindicated in patients with a history of:
  – chronic or severe constipation or sequelae from constipation;
  – intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforation, and/or adhesions;
  – ischemic colitis, impaired intestinal circulation, thrombophlebitis, or hypercoagulable state;
  – Crohn’s disease or ulcerative colitis;
  – diverticulitis;
  – severe hepatic impairment.
Contraindications (cont’d)

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

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

• Concomitant administration of alosetron and fluvoxamine is contraindicated.

• Concomitant administration of alosetron and moderate CYP1A2 inhibitors, including quinolone antibiotics and cimetidine, has not been evaluated, but should be avoided unless clinically necessary because of similar potential drug interactions.
Drug Interactions (cont’d)

• Caution should be used when alosetron and ketoconazole are administered concomitantly.

• Coadministration of alosetron and strong CYP3A4 inhibitors, such as clarithromycin, telithromycin, protease inhibitors, voriconazole, and itraconazole has not been evaluated but should be undertaken with caution because of similar potential drug interactions.

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

<table>
<thead>
<tr>
<th>Gastrointestinal Adverse Reactions</th>
<th>Alosetron 1 mg BID (n=8,328)</th>
<th>Placebo (n=2,363)</th>
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<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>

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.

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.
Overdosage

- No specific antidote available for overdose of alosetron.

- Patients should be managed with appropriate supportive therapy.
Section 4:
Alosetron
REMS Program
Prescriber Enrollment in the Alosetron REMS Program

• Prescribers must read the full PI and understand the benefits and risks of treatment with alosetron for severe diarrhea-predominant IBS.

• Prescribers then complete the Prescriber Enrollment Form at www.AlosetronREMS.com or return it by mail or by fax.

• The form must be returned to the sponsor before a prescriber can be considered enrolled in the Alosetron REMS Program.

• Alosetron REMS Program Kits, including Medication Guides and stickers that need to be affixed to every prescription, are provided after enrollment.
Prescriber Requirements in the Alosetron REMS Program

- Once an appropriate patient has been selected for therapy, the Medication Guide and risks of alosetron 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

Step 1: Review and provide Medication Guide to the patient.

Step 2: Have the patient complete the Patient Acknowledgment Form. Place the original in the patient’s medical record and give a copy to the patient.

Step 3: Provide patient with written prescription with affixed Alosetron REMS sticker. Refills are permitted on written prescription.

The Alosetron REMS Program - Please see complete Prescribing Information for Alosetron Tablets for full details.
Section 5:
Role of the Pharmacist in the Alosetron REMS Program
Pharmacist Responsibilities

• Learn about the Alosetron REMS Program.

• Understand the benefits and risks of treatment with alosetron for severe diarrhea-predominant IBS, which are described in 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 alosetron by ensuring that the Alosetron REMS sticker is present on the prescription prior to dispensing alosetron to a patient.
Pharmacist Responsibilities (cont’d)

• If an Alosetron REMS sticker is not present on the prescription, call 1-844-267-8675 to confirm that the prescriber is enrolled in the Alosetron REMS.¹

• Provide each patient with their prescribed treatment of alosetron and a copy of the alosetron Medication Guide.

¹ In the alternative, a prescription for alosetron may be dispensed in the presence of a Prescribing Program for LOTRONEX™ sticker, if generic substitution of alosetron is permitted pursuant to State substitution laws.
The Alosetron REMS Program

• To prescribe alosetron, prescribers must be enrolled in the Alosetron REMS Program

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

• Pharmacists should also learn about and understand the benefits and risks associated with alosetron treatment.
The Alosetron REMS Sticker

- Upon enrollment in the Alosetron REMS Program, stickers for prescriptions are provided to prescribers.

Alosetron Tablets
The sticker indicates that this prescription is in compliance with the Alosetron REMS
REFILL PERMITTED
The Alosetron REMS Sticker (cont’d)

• Stickers affixed to a prescription of alosetron indicate the following:
  – Certifies participation of a prescriber in the Alosetron REMS;
  – Alosetron 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

Step 1: Verify the validity of Alosetron prescription by checking for the Alosetron REMS sticker (refills are permitted on written prescriptions)

Step 2: Dispense Alosetron to the patient, including the Alosetron Medication Guide

Note to Pharmacist: If an Alosetron REMS sticker is not present on the prescription, call 1-844-267-8675 to confirm that the prescriber is enrolled in the Alosetron REMS Program. In the alternative, a prescription for alosetron may be dispensed in the presence of a Prescribing Program for LOTRONEX™ sticker, if generic substitute of alosetron is permitted pursuant to State substitution laws.
• You have now reached the end of this Education Slide Deck.

• If you have questions regarding the Alosetron REMS Program, please call 1-844-267-8675 or visit www.AlosetronREMS.com.