THE ALOSETRON REMS PROGRAM

Prescriber Education Slide Deck

Understanding the Benefits and Risks of Alosetron

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Important
Modified Alosetron REMS Program

The modified Alosetron REMS Program has changed from the previous program

❶ Prescribers are no longer required to affix prescribing program stickers to written prescriptions for alosetron

❷ Pharmacies are no longer required to only dispense alosetron for a paper prescription with an affixed prescribing program sticker. **Electronic prescriptions are now allowed.**

❸ Patients are no longer required to complete and submit a Patient Acknowledgement Form. Instead, a Patient Education Sheet is available for the prescriber to discuss with the patient.

Section 1:

Purpose

Purpose of the Prescriber Education Slide Deck for Alosetron

- By reviewing the information provided in this presentation, prescribers who prescribe alosetron hydrochloride (alosetron) will better understand the:

  - **Risks and benefits of alosetron;**

  - **Etiology of irritable bowel syndrome;**

  - **The Alosetron REMS Program**

Risk Evaluation and Mitigation Strategy (REMS)

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

Goals and Objectives

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

The goals and objectives of the Alosetron REMS Program are to mitigate the risks of ischemic colitis (IC) and serious complications of constipation (CoC) associated with alosetron hydrochloride (hereinafter, referred to as alosetron) by:

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

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.

Boxed Warning (cont'd)

- Alosetron is indicated only for women with severe diarrhea-predominant IBS who have not responded adequately to conventional therapy.

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

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.**

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.

Warnings and Precautions (cont'd)

Ischemic Colitis

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

Warnings and Precautions (cont'd)

Ischemic Colitis (cont'd)

- Alosetron should be discontinued immediately in patients with signs of ischemic colitis, e.g., rectal bleeding, bloody diarrhea, or new or worsening abdominal pain.

- Because ischemic colitis can be life threatening, patients with signs or symptoms of ischemic colitis should be evaluated promptly and have appropriate diagnostic testing performed.

- Treatment with alosetron should not be resumed in patients who develop ischemic colitis.

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)

- Concomitant administration of alosetron with fluvoxamine is contraindicated.

Drug Interactions

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

- Concomitant administration of alosetron and fluvoxamine is contraindicated.

- Concomitant administration of alosetron and moderate CYP1A2 inhibitors, including quinolone antibiotics and cimetidine, has not been evaluated, but should be avoided unless clinically necessary because of similar potential drug interactions.

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[a]

Gastrointestinal Adverse Reactions	Alosetron 1 mg BID (n=8,328[b])	Placebo (n=2,363)
Constipation[c]	29%	6%
Abdominal discomfort and pain	7%	4%
Nausea	6%	5%
GI discomfort and pain	5%	3%
Abdominal distention	2%	1%
Regurgitation and reflux	2%	2%
Hemorrhoids	2%	1%

[a] Reported in ≥1% of alosetron patients and occurring more frequently on alosetron 1 mg twice-a-day than on placebo.
[b] Data reported from 22 repeat-dose studies in patients with IBS treated for 8 to 24 weeks.
[c] *P<0.0001 vs placebo.*

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:

How to Prescribe Alosetron Tablets

Dosage and Administration

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

Dosage and Administration (cont'd)

- Usual Dose in Adults
  - **Alosetron should be started at a dosage of 0.5 mg twice-a-day. Patients controlled on this dose may be maintained on this regimen.**
  - If after 4 weeks, the 0.5 mg twice-a-day dosage is well tolerated but does not adequately control the IBS symptoms, then the dosage can be increased up to 1 mg twice-a-day.
  - **Alosetron should be discontinued in patients who have not had adequate control of IBS symptoms after 4 weeks of treatment with 1 mg twice-a-day.**
  - Alosetron should be discontinued immediately in patients who develop constipation or signs of ischemic colitis.
  - Alosetron should not be restarted in patients who develop ischemic colitis.

Dosage and Administration (cont'd)

- Clinical trial and postmarketing experience suggest that debilitated patients or patients taking additional medications that decrease GI motility may be at greater risk of serious complications of constipation.

- Therefore, appropriate caution and follow-up should be exercised if alosetron is prescribed for these patients.

- Alosetron can be taken with or without food.

Section 5:

Alosetron

REMS Program

Training in the Alosetron REMS Program

- Prescribers should read the Prescribing Information (PI) and other training materials to understand the benefits and risks of treatment with alosetron for severe diarrhea-predominant IBS.

- Prescribers can communicate the completion of training by filling out the Prescriber Completion of Alosetron REMS Program Training Form at www.AlosetronREMS.com or return it by mail or by fax.

- **The form must be completed and returned to the Alosetron REMS Program before a prescriber can be considered trained in the program.**

Training in the Alosetron REMS Program (cont'd)

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

Patient Education

- Once you have selected an appropriate patient for therapy:
  - provide the patient with the Alosetron Patient Education Sheet
  - review it together with the patient and explain the risks of therapy
  - answer any questions the patient may have.

- Instruct the patient to read the Medication Guide supplied with the product

Patient Responsibilities

Patients should be instructed to:

- read the Alosetron Patient Education Sheet before starting alosetron.
- read the Medication Guide before starting alosetron and each time they refill their prescription.
- not take alosetron if they are constipated.
- immediately discontinue alosetron and contact their prescriber if they become constipated or have symptoms of ischemic colitis such as new or worsening abdominal pain, bloody diarrhea, or blood in the stool.
- immediately contact their prescriber again if their constipation does not resolve after discontinuation of alosetron.

Patient Responsibilities(cont'd)

Patients should be instructed to:

- resume alosetron only if their constipation has resolved and after discussion with and the agreement of their treating prescriber.

- stop taking alosetron and contact their prescriber if alosetron does not adequately control IBS symptoms after 4 weeks of taking 1 mg twice-a-day.

- You have now reached the end of this Education Slide Deck.

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