DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 206647

ANDA APPROVAL

Amneal Pharmaceuticals
50 Horseblock Road
Brookhaven, NY 11719
Attention: Alpesh Patel
Vice President, Global Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Alosetron Hydrochloride Tablets, 0.5 mg (base) and 1 mg (base).

Reference is made to your amendments dated September 10 and September 15, 2014; May 22, 2015; and February 25, April 22, September 23 and November 4, 2016.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. **Accordingly the ANDA is approved**, effective on the date of this letter. The Office of Bioequivalence has determined your Alosetron Hydrochloride Tablets, 0.5 mg (base) and 1 mg (base) to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug product (RLD), Lotronex Tablets, 0.5 mg and 1 mg, of Sebela Ireland Limited. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Section 505-1 of the FD&C Act authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. In accordance with section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA under section 505(j) is subject to certain elements of the REMS required for the applicable listed drug.

The details of the REMS requirements were outlined in our REMS notification letter dated January 22, 2015. In that letter, you were also notified that pursuant to section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA and the listed drug it references must use a single, shared system for elements to assure safe use (ETASU), unless FDA waives that requirement.

Your final proposed REMS, submitted on November 4, 2016, and appended to this letter, is approved. The REMS consists of ETASU.

The Alosetron REMS uses a waiver-granted shared system for the ETASU. This waiver-granted shared system REMS currently includes the products listed on the FDA REMS website available at http://www.fda.gov/rems. Other products may be added in the future if additional NDAs or ANDAs are approved.

Under section 505-1(g)(2)(C) of the FD&C Act, FDA can require the submission of a REMS assessment if FDA determines an assessment is needed to evaluate whether the REMS should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the REMS.

Additionally, the details for what should be included in your REMS assessments and the dates of the REMS assessments are listed in Appendix 1.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

> **ANDA 206647 REMS CORRESPONDENCE**
> **(insert concise description of content in bold capital letters, e.g.,**
> **UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY**

We remind you that you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FD&C Act.

We also remind you that section 505-1(f)(8) of the FD&C Act prohibits holders of an approved covered application from using any element to assure safe use to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

ANDA 206647 REMS ASSESSMENT

NEW SUPPLEMENT FOR ANDA 206647/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 206647/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 206647/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR ANDA 206647

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

OTHER

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at

http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Carol A. Holquist, RPh
Acting Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

ENCLOSURES:
Appendix 1
REMS

Appendix 1

Dates for submission of waiver-granted REMS assessments

The Alosetron Sponsors will submit REMS Assessments to FDA 18 months following the REMS modification approval on January 7, 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. The Alosetron Sponsors will submit each assessment so that it will be received by the FDA on or before the due date.

REMS Assessment Plan

The REMS Assessment Plan includes, but is not limited to, the following:

1. Results of an evaluation of whether patients received counseling from the prescriber, the patients' understanding of the serious risks of ischemic colitis and serious complications of constipation associated with alosetron, and the actions patients need to take should they experience early warning signs and symptoms of these risks.
2. Results of an evaluation of prescriber understanding of the appropriate patient population, the risks of ischemic colitis and serious complications of constipation associated with alosetron, and the importance of counseling patients about these risks. The evaluation will include a comparison of prescribers who completed training and prescribers who have not reported completion of training.
3. The number of prescribers and medical specialty of prescribers who reported that they completed training in the Alosetron REMS Program, including the number and medical specialty of prescribers contacted by Roxane to become trained after prescribing alosetron and the number and medical specialty contacted who completed training, during the reporting period and cumulative.
4. The number of prescribers who have not completed training and are writing prescriptions.
5. Numbers of prescriptions, by year for the last five years and annually thereafter.
6. Number of cases of the following events reported (from any source) during the reporting period and cumulative:
    - All reports of ischemic colitis;
    - All reports involving ischemic changes, ischemia, or necrosis of the colon
    - All reports involving constipation requiring hospitalization or emergency room visit;
    - All reports involving possible complications of constipation such as obstruction, perforation, intestinal ulceration, toxic megacolon, ileus, or impaction resulting in hospitalization or emergency room visit;
    - All reports of death, regardless of causality.
7. Summary and discussion of the above cases (received during the reporting period) and the clinical significance of these events.
8. An assessment of the extent to which the elements to assure safe use are meeting the goals or whether the goals or such elements should be modified.

Initial REMS Approved: 05/2015
Most recent modification: 11/2016

Risk Evaluation and Mitigation Strategy (REMS)

Shared System for Alosetron

Selective 5-HT_3 antagonist

I. GOAL(S):

The goals and objectives of the AlosetronREMS 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.

II. REMS ELEMENTS:

A. Elements to Assure Safe Use

1. **Training will be provided to healthcare providers who prescribe alosetron.**

   a. The Alosetron Sponsors will ensure that training provided to healthcare providers who prescribe alosetron includes information on the serious risks of IC and 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, and the importance of counseling patients about the risks of IC and serious CoC, using the Alosetron Prescribing Information and the following materials in the REMS Training Kit:

      i. REMS letter to Healthcare Providers
      ii. Alosetron REMS Program Prescriber Education Slide Deck
      iii. Alosetron REMS Program Safety Information Fact Sheet for Prescribers
      iv. Alosetron REMS Program Patient Education Sheet
      v. Prescriber Completion of Alosetron REMS Program Training Form

   b. In order to facilitate training, the Alosetron Sponsors will:

      i. Monitor distribution and prescription data monthly.
      ii. Contact all prescribers identified as not having completed training and provide training within 30 days of identification by mailing or emailing the REMS Training Kit. 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.
      iii. Ensure that prescribers can notify the Alosetron Sponsors when they have completed training via the Alosetron REMS Program website or by faxing or mailing a Prescriber Completion of 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 the Alosetron Sponsors have a presence.
      vi. Maintain an Alosetron REMS Program website [www.AlosetronREMS.com] and contact center (1-844-267-8675) to support prescribers.
      vii. Maintain a validated, secure database of healthcare providers who have notified the Alosetron Sponsors of completion of training, which will be defined as all training materials were reviewed independently by the healthcare provider.

viii. Ensure that the REMS materials listed below are available on the Alosetron REMS Program website or by calling the REMS contact center.

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

- REMS Training Kit
  - 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

- Other appended REMS materials:
  - Alosetron REMS Program website Prescriber Section screenshots
  - Alosetron REMS Program website Patients Section screenshots

FDA Required REMS Safety Information for Alosetron Tablets

Important Safety Update

The FDA has required this safety update as part of the Alosetron REMS Program to inform you that the Alosetron REMS Program **has changed** from the previous program.

ENROLLED Prescriber Actions:

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

NON-ENROLLED Prescriber Actions:

- Review the Alosetron REMS Program Training Kit and complete the Alosetron REMS Program Prescriber Completion Training Form which can be found at www.AlosetronREMS.com.
- You can also submit the enclosed form by fax to 1-800-535-6805.

You will find the Alosetron REMS Program Training Kit enclosed. The Training Kit is also available online at www.AlosetronREMS.com or you can request the Training Kit by calling the Alosetron REMS Program at 1-844-267-8675.

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

Summary of Changes to the REMS 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 Acknowledgment Form. Instead, a Patient Education Sheet is available for the prescriber to discuss with the patient.

Indication:

Alosetron 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.AlosetronREMS.com for more information.

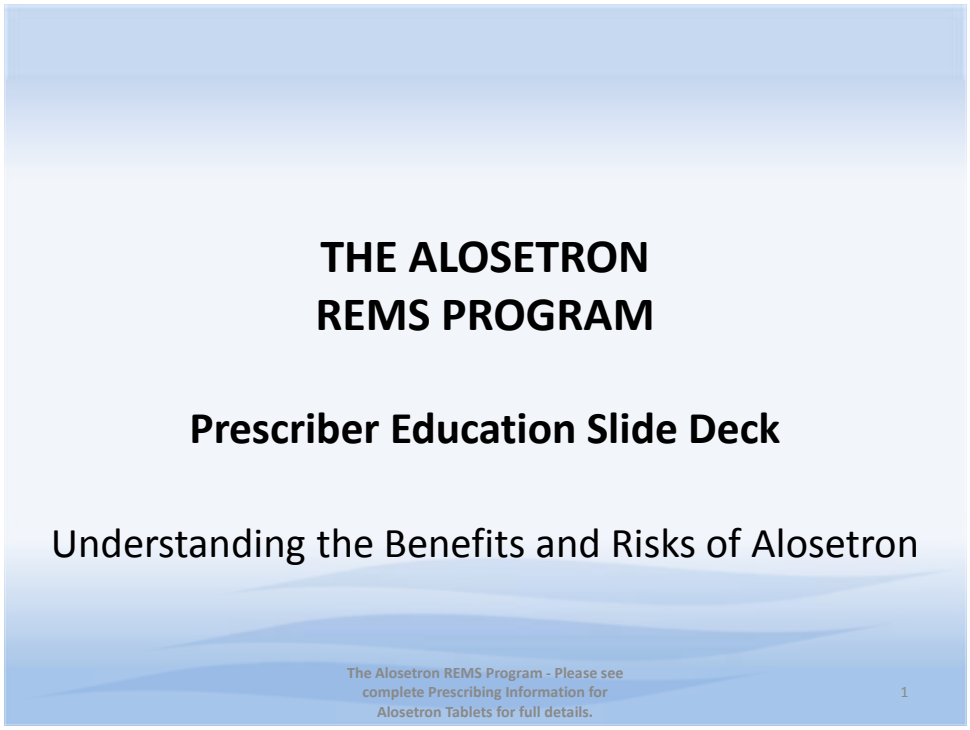
This letter does not contain the complete safety profile for alosetron. Please see the Prescribing Information and Medication Guide, enclosed.

Reporting Adverse Events

You are encouraged to report all suspected adverse events associated with alosetron to the FDA at www.fda.gov/medwatch, or 1-800-FDA-1088 or to the Alosetron REMS Program at 1-844-267-8675.

Sincerely,

The Alosetron REMS Program



THE ALOSETRON REMS PROGRAM

Prescriber Education Slide Deck

Understanding the Benefits and Risks of Alosetron

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

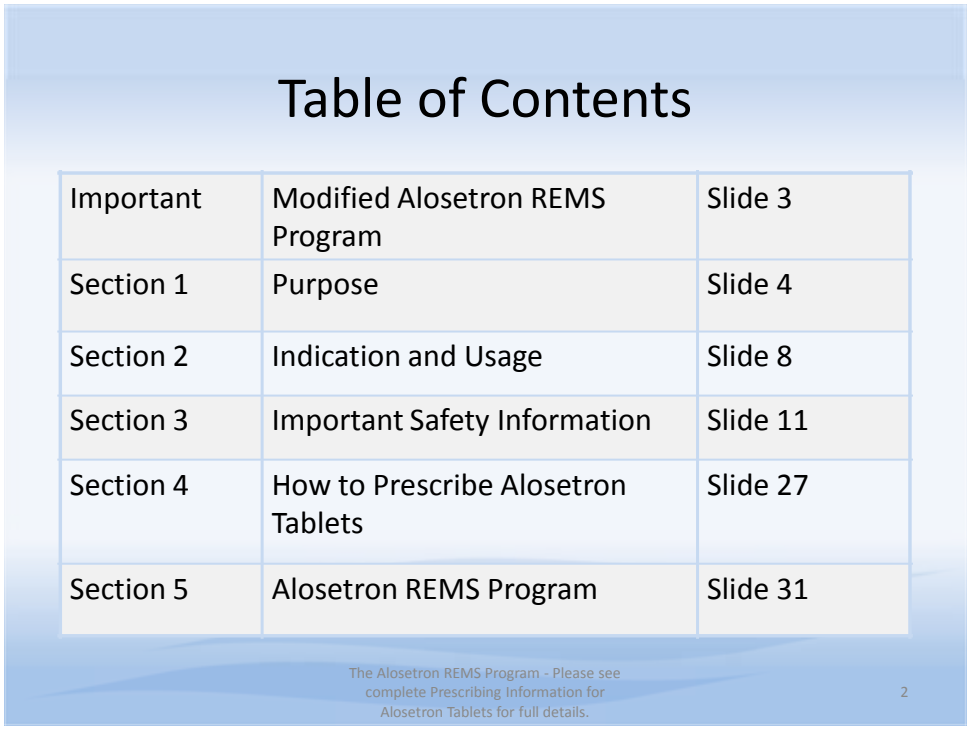
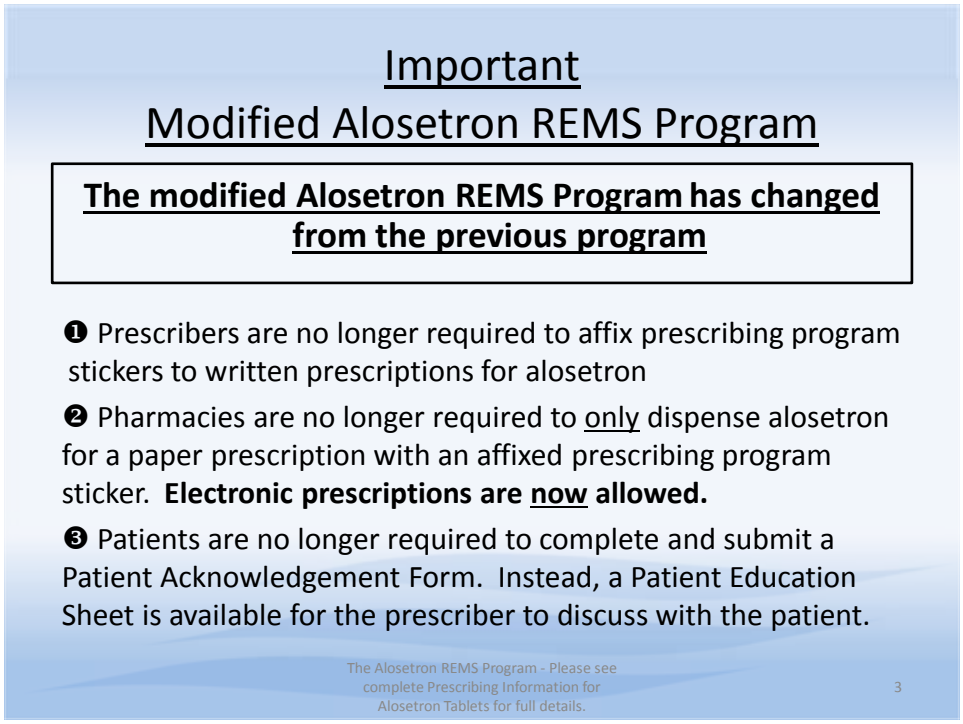


Table of Contents



Important

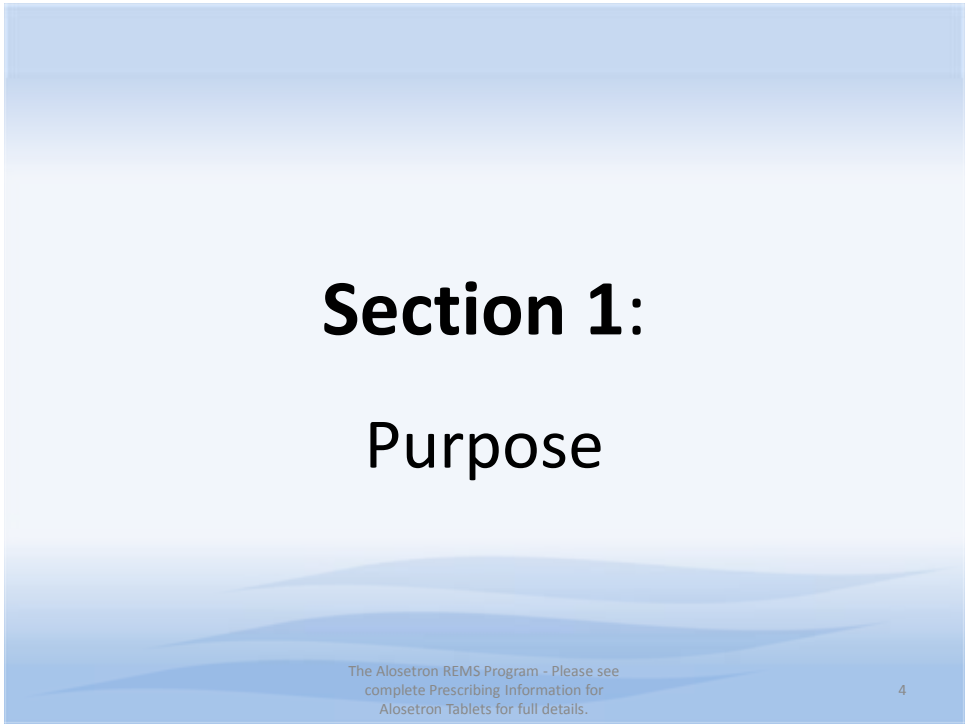
Modified Alosetron REMS Program

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

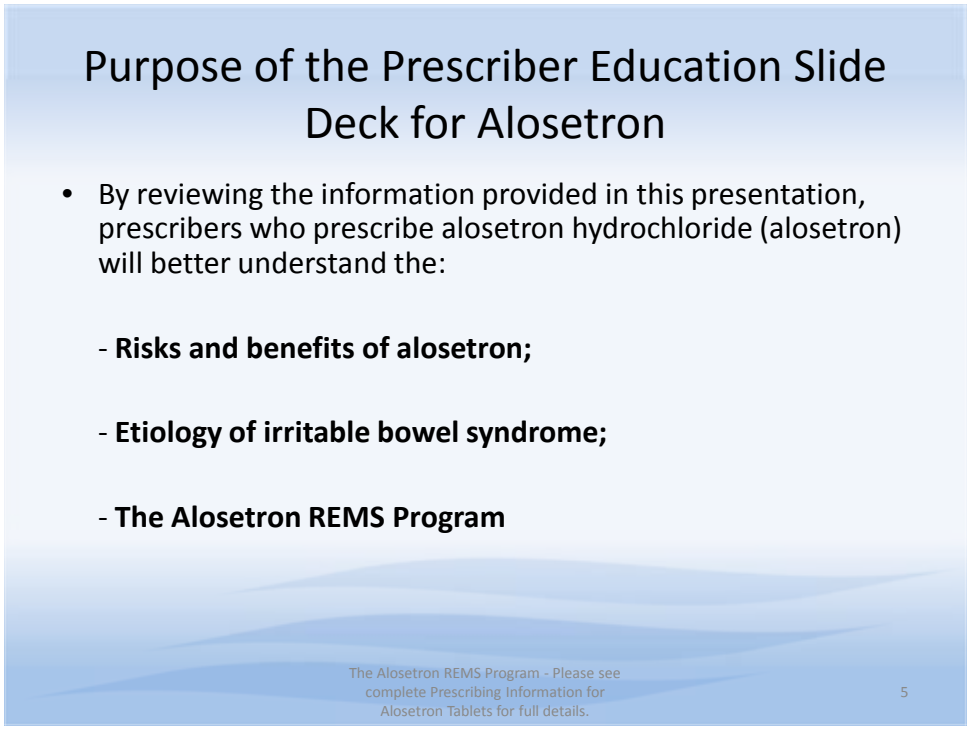
❷ Pharmacies are no longer required to only dispense alosetron for a paper prescription with an affixed prescribing program sticker. **Electronic prescriptions are now allowed.**

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



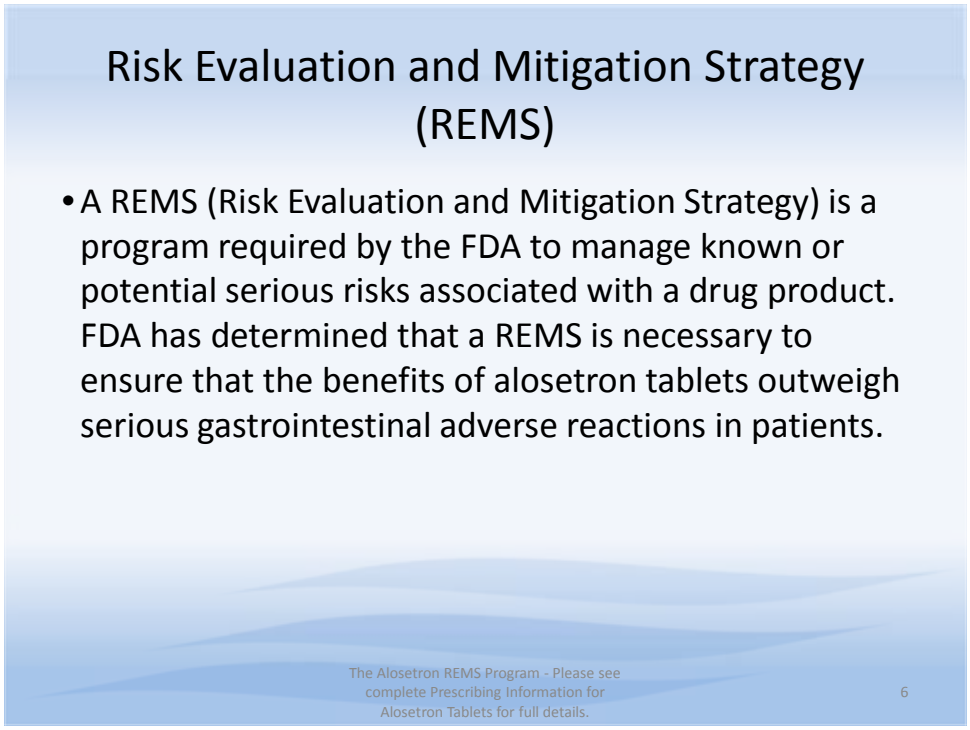
Purpose of the Prescriber Education Slide Deck for Alosetron

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

  - **Risks and benefits of alosetron;**

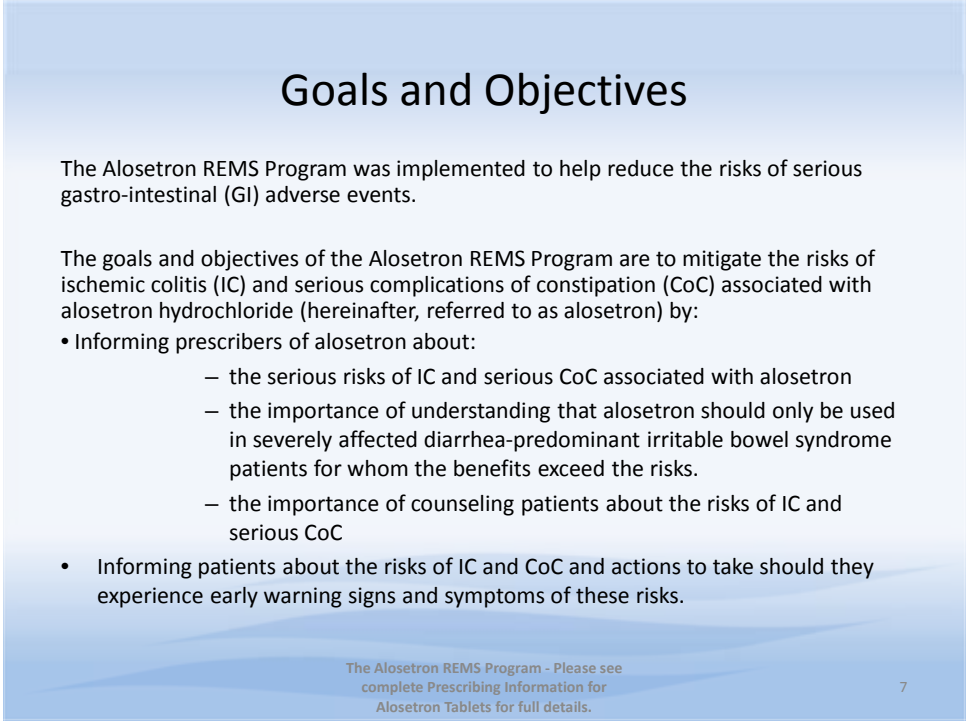
  - **Etiology of irritable bowel syndrome;**

  - **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.

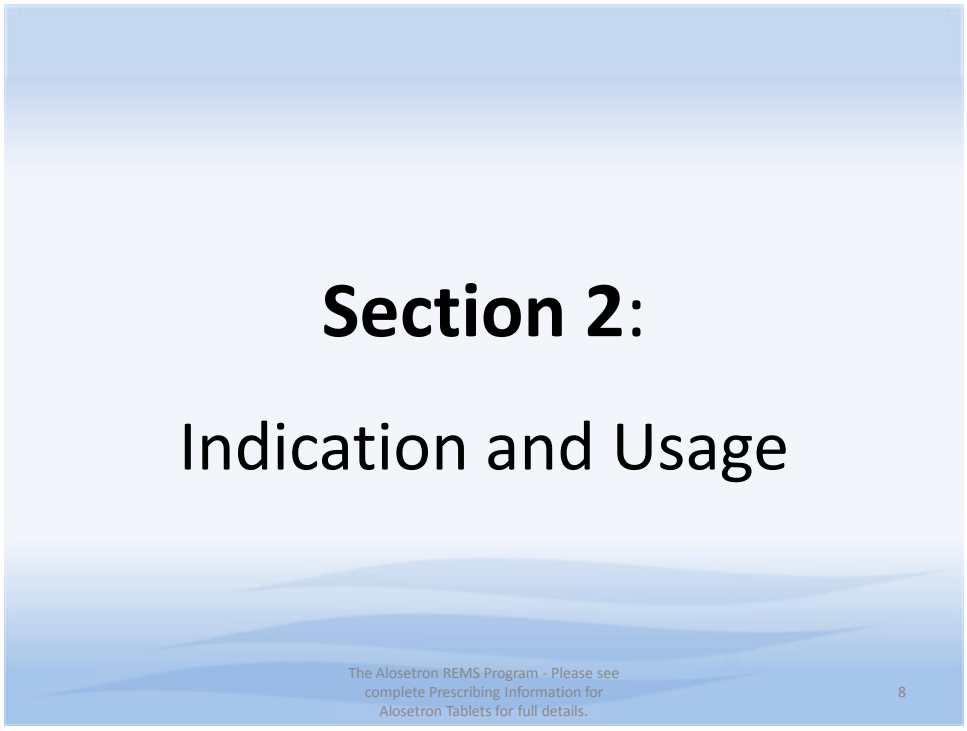


Goals and Objectives

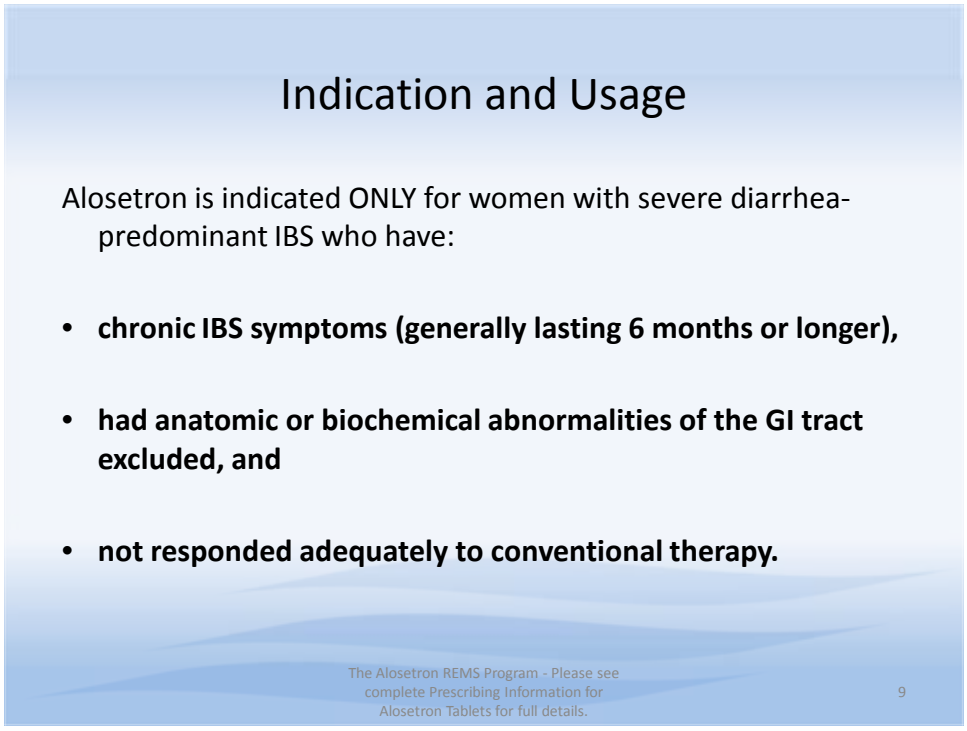
The Alosetron REMS Program was implemented to help reduce the risks of serious gastro-intestinal (GI) adverse events.

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.**



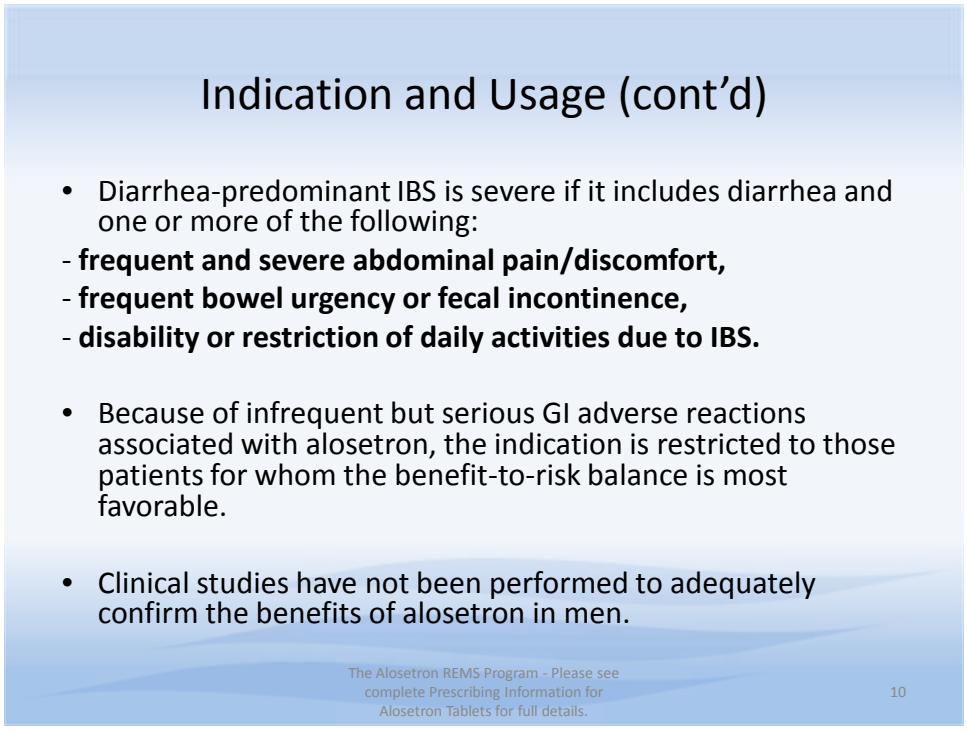
Section 2:
Indication and Usage



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:

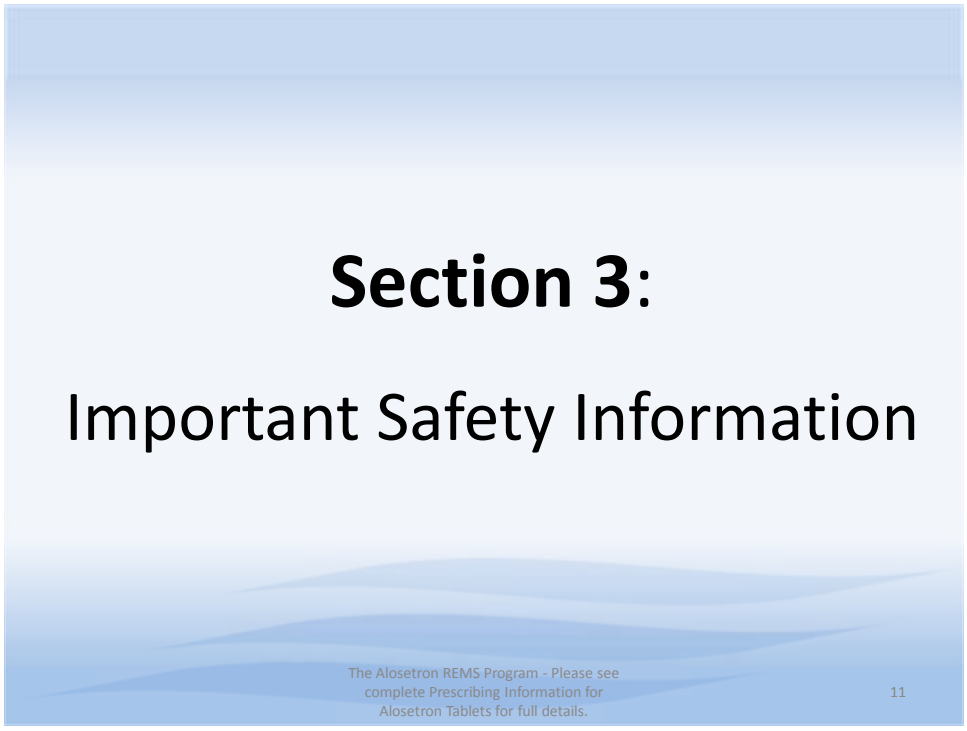
- **frequent and severe abdominal pain/discomfort,**

- **frequent bowel urgency or fecal incontinence,**

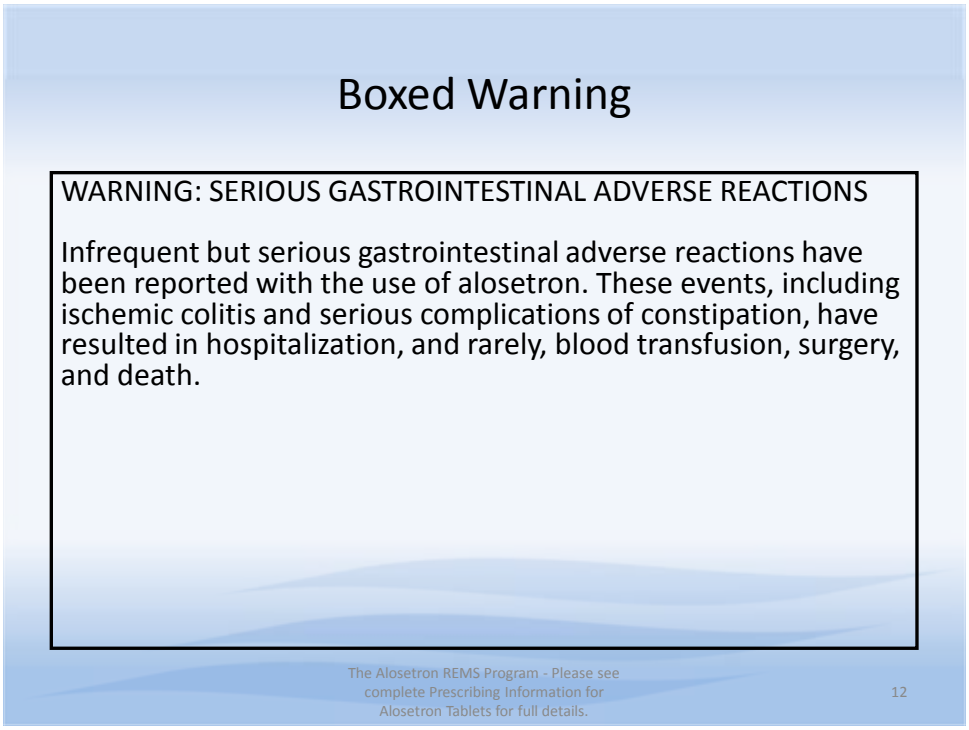
- **disability or restriction of daily activities due to IBS.**

- 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.



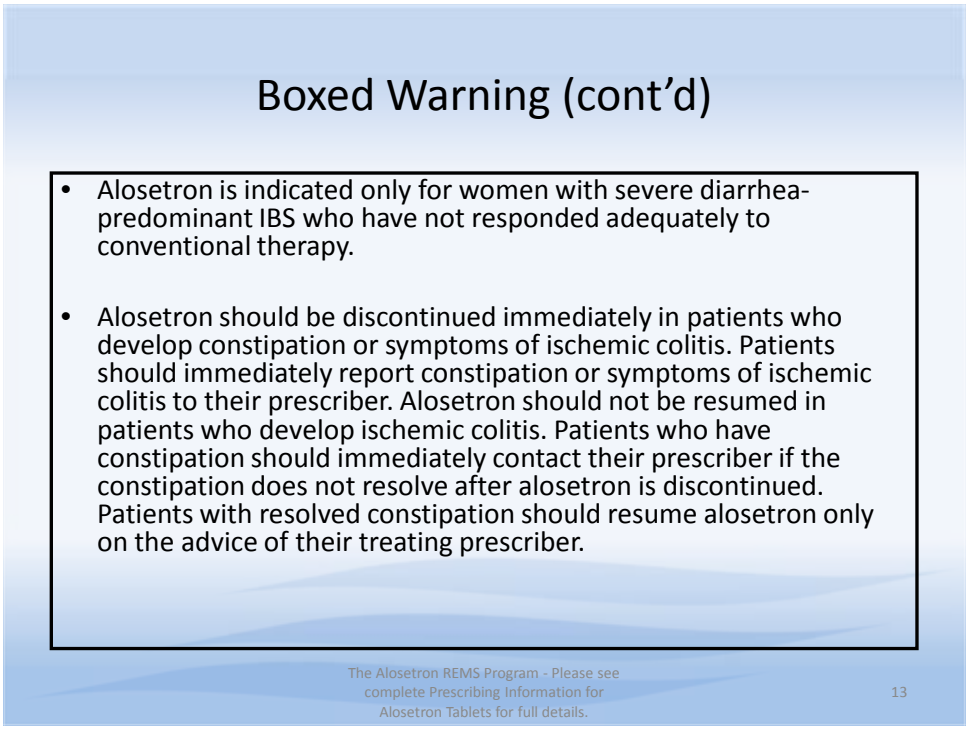
Section 3:
Important Safety Information



Boxed Warning

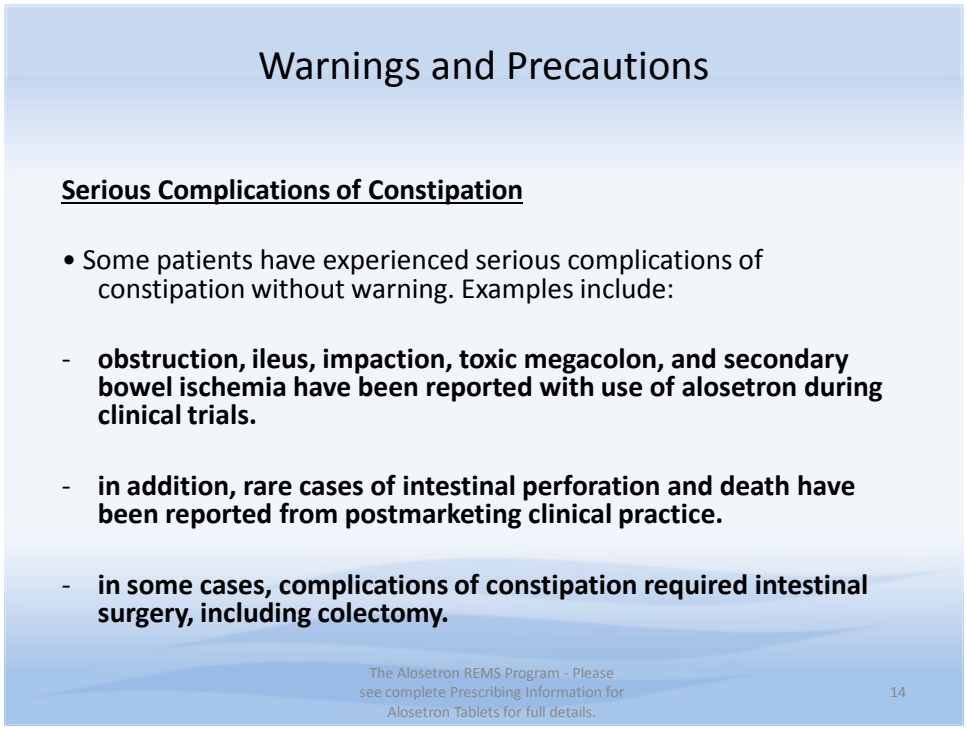
WARNING: SERIOUS GASTROINTESTINAL ADVERSE REACTIONS

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.

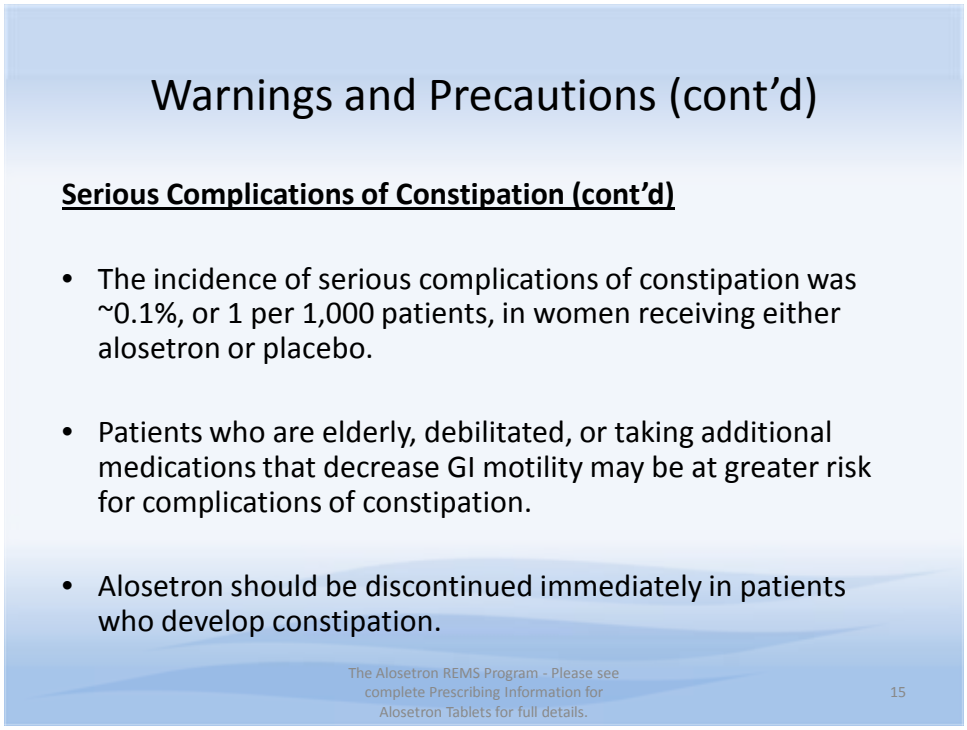


Warnings and Precautions

Serious Complications of Constipation

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

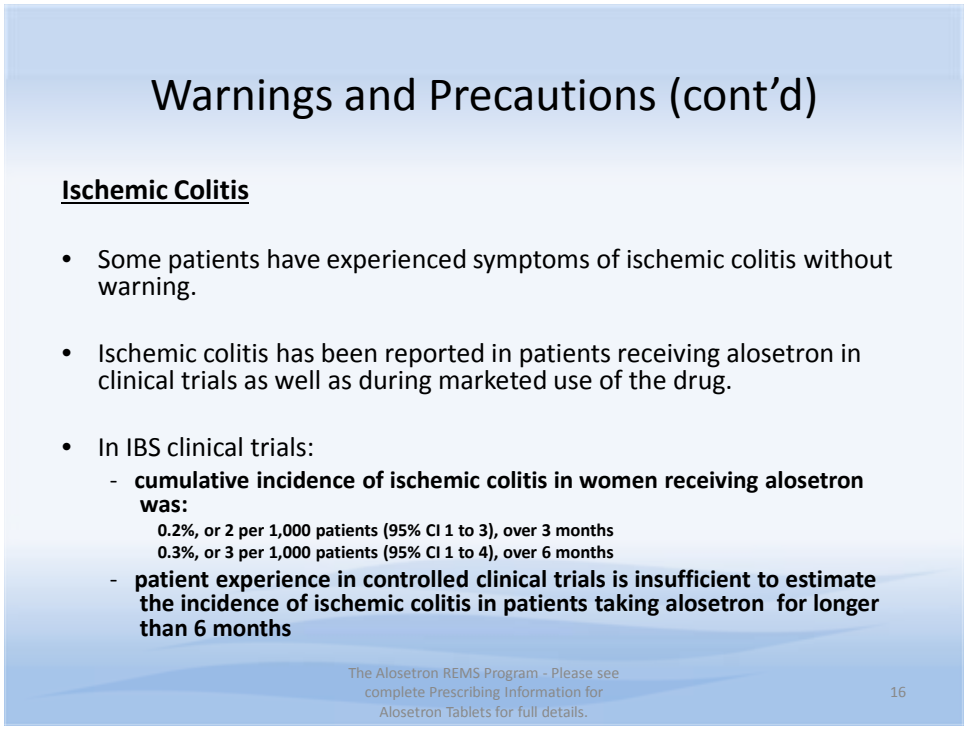
- **obstruction, ileus, impaction, toxic megacolon, and secondary bowel ischemia have been reported with use of alosetron during clinical trials.**
- **in addition, rare cases of intestinal perforation and death have been reported from postmarketing clinical practice.**
- **in some cases, complications 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

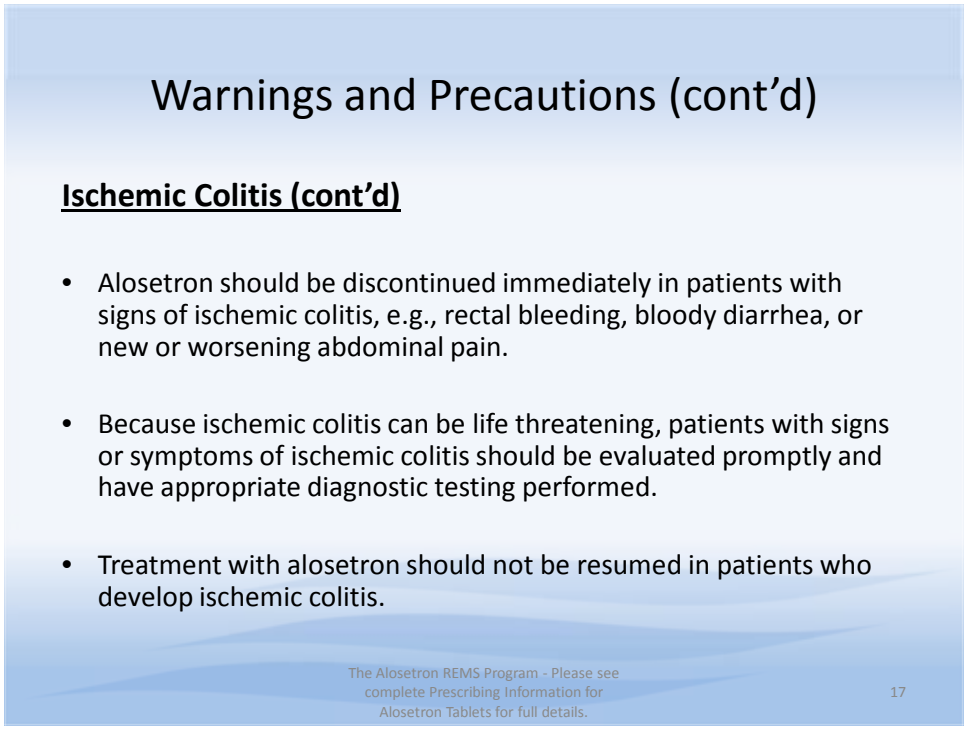
- Some patients have experienced symptoms of ischemic colitis without warning.
- Ischemic colitis has been reported in patients receiving alosetron in clinical trials as well as during marketed use of the drug.
- In IBS clinical trials:

- **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

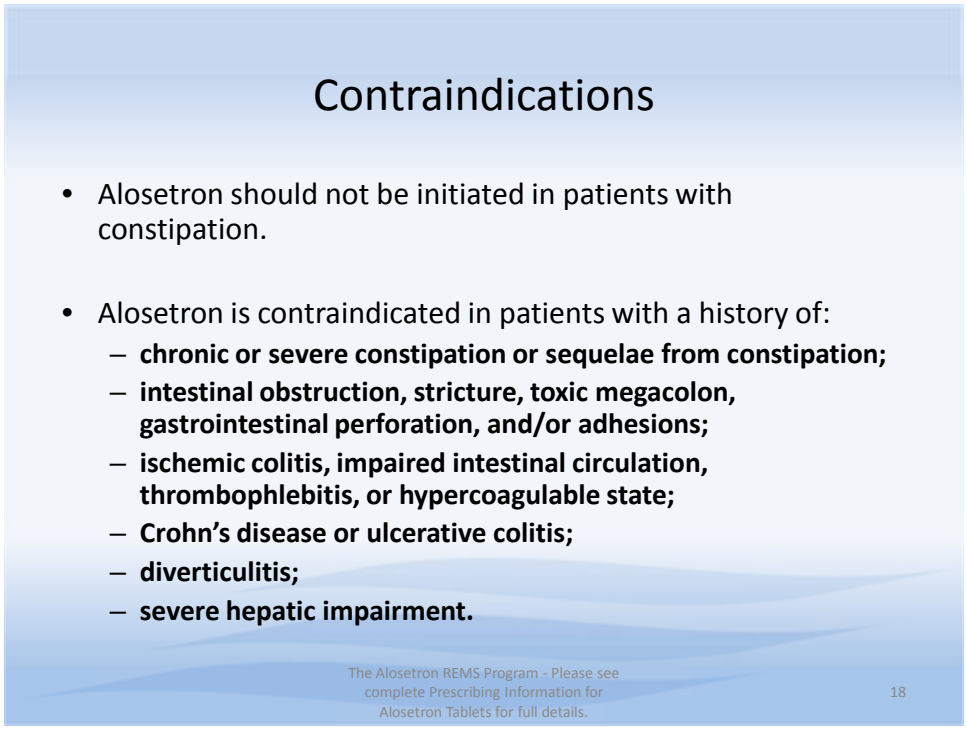
- **patient experience in controlled clinical trials is insufficient to estimate the incidence of ischemic colitis in patients taking alosetron for longer than 6 months**



Warnings and Precautions (cont'd)

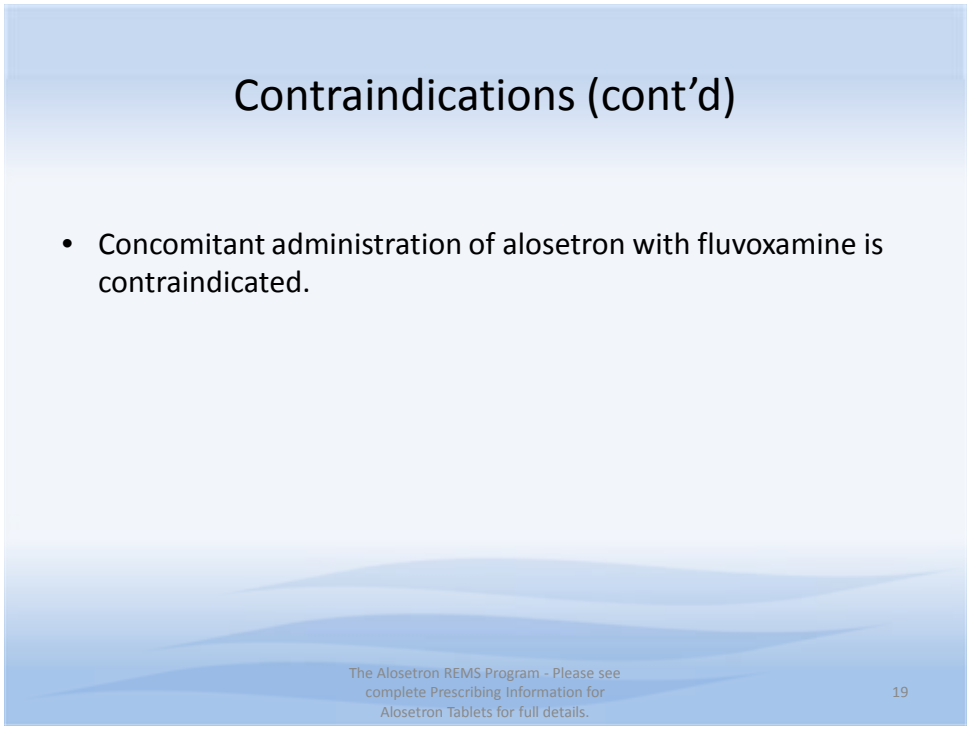
Ischemic Colitis (cont'd)

- 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.



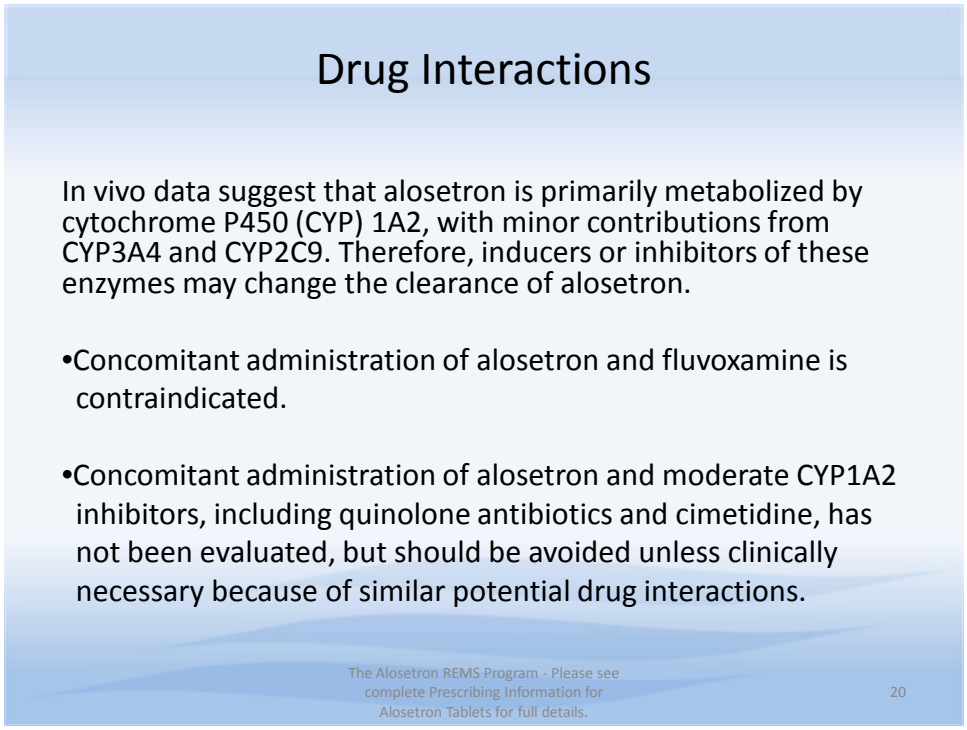
Contraindications

- 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)

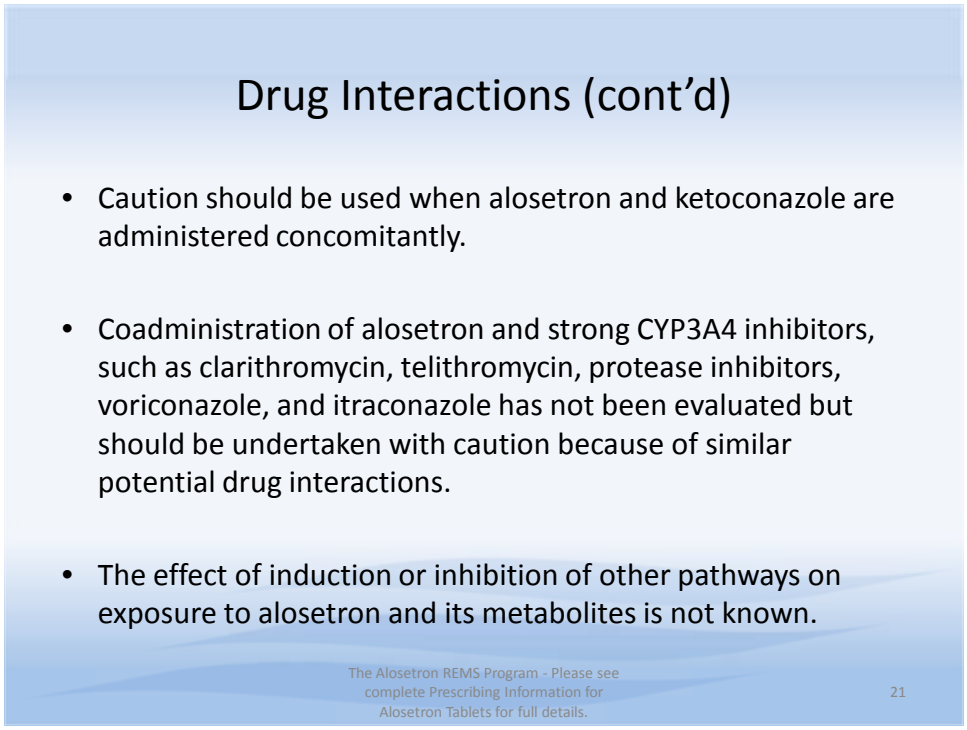
- Concomitant administration of alosetron with fluvoxamine is contraindicated.



Drug Interactions

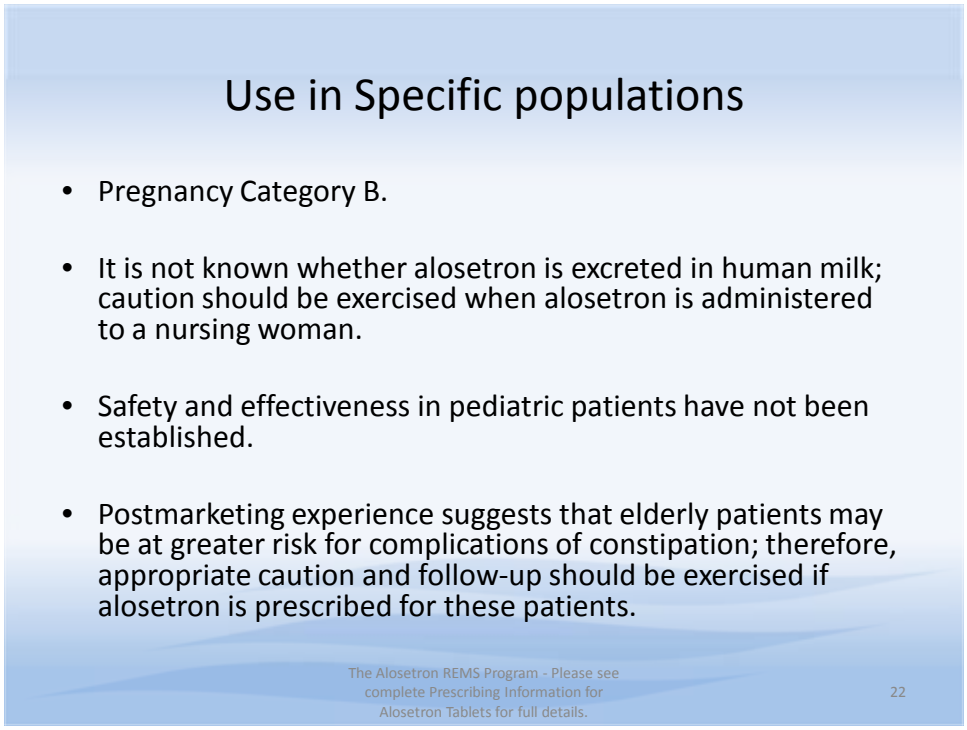
In vivo data suggest that alosetron is primarily metabolized by cytochrome P450 (CYP) 1A2, with minor contributions from CYP3A4 and CYP2C9. Therefore, inducers or inhibitors of these enzymes may change the clearance of alosetron.

- 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.



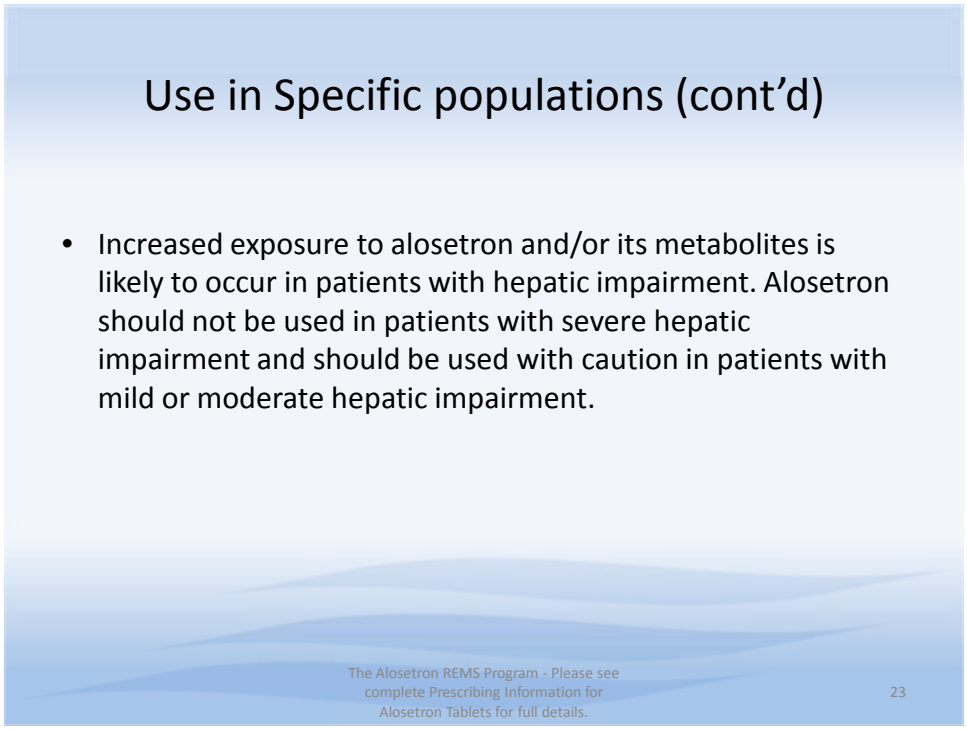
Drug Interactions (cont'd)

- 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.



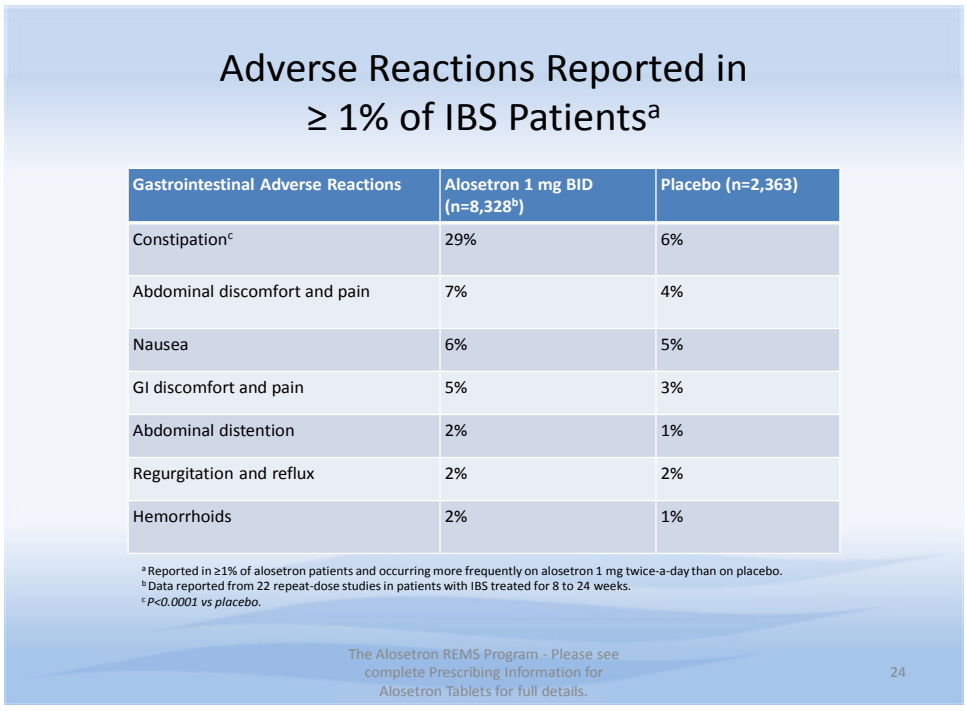
Use in Specific populations

- 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.



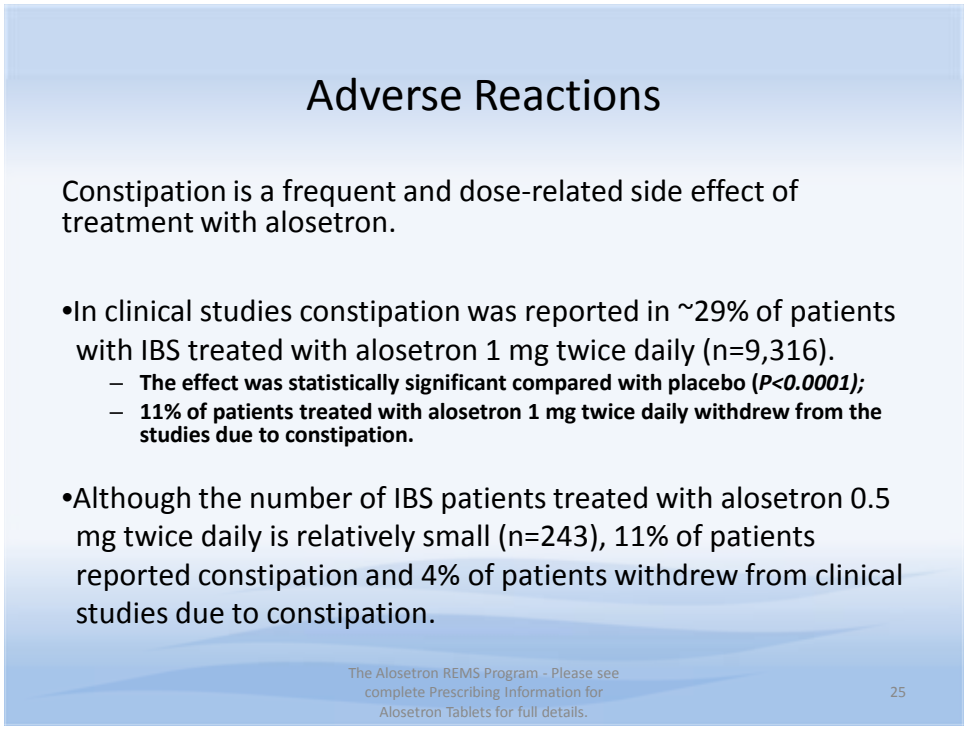
Adverse Reactions Reported in ≥ 1% of IBS Patients[a]

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.

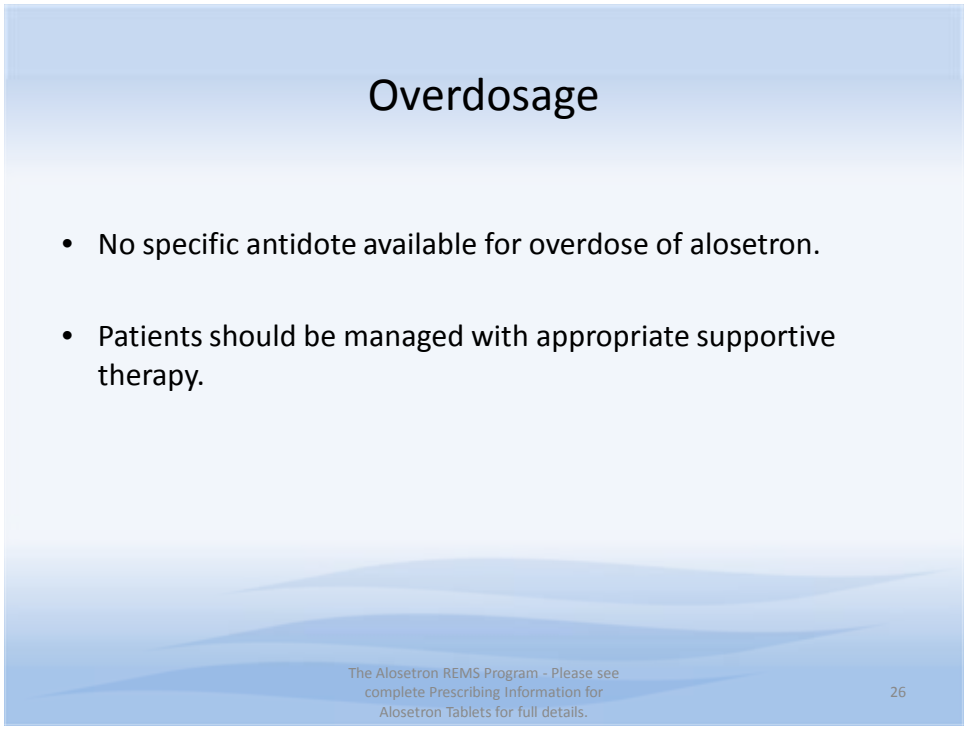
[c] *P<0.0001 vs placebo.*



Adverse Reactions

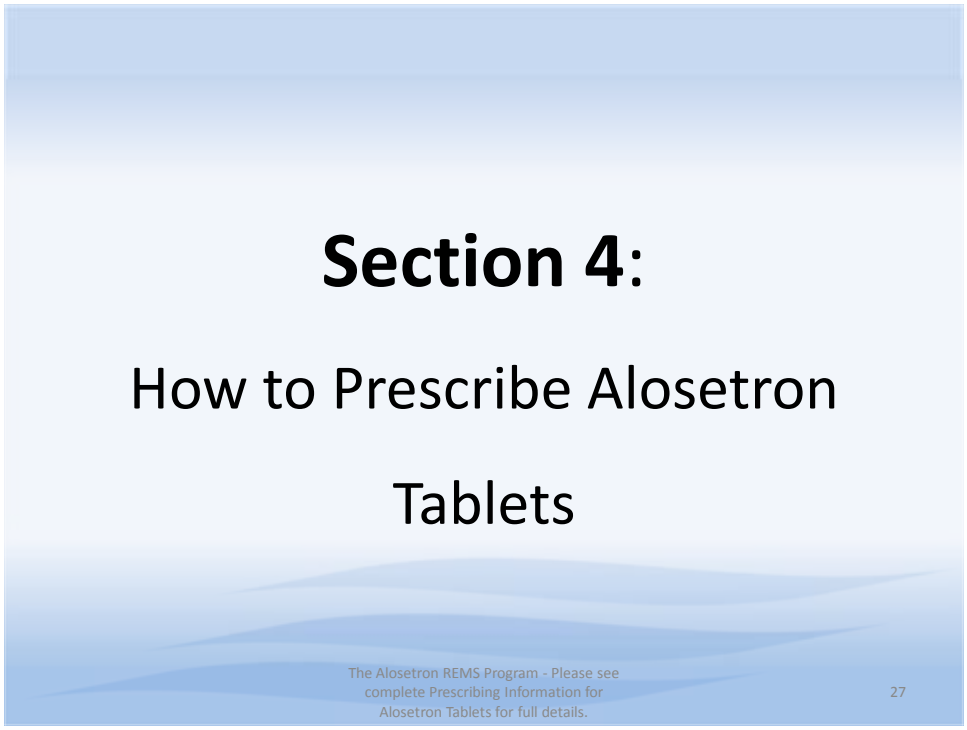
Constipation is a frequent and dose-related side effect of treatment with alosetron.

- 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.

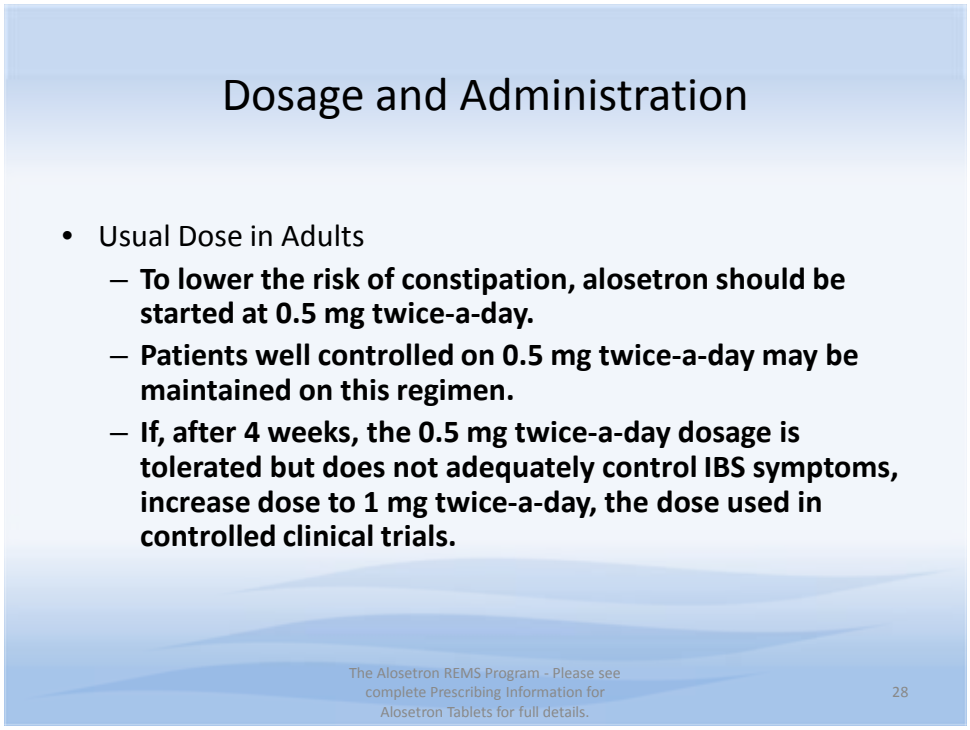


Overdosage

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

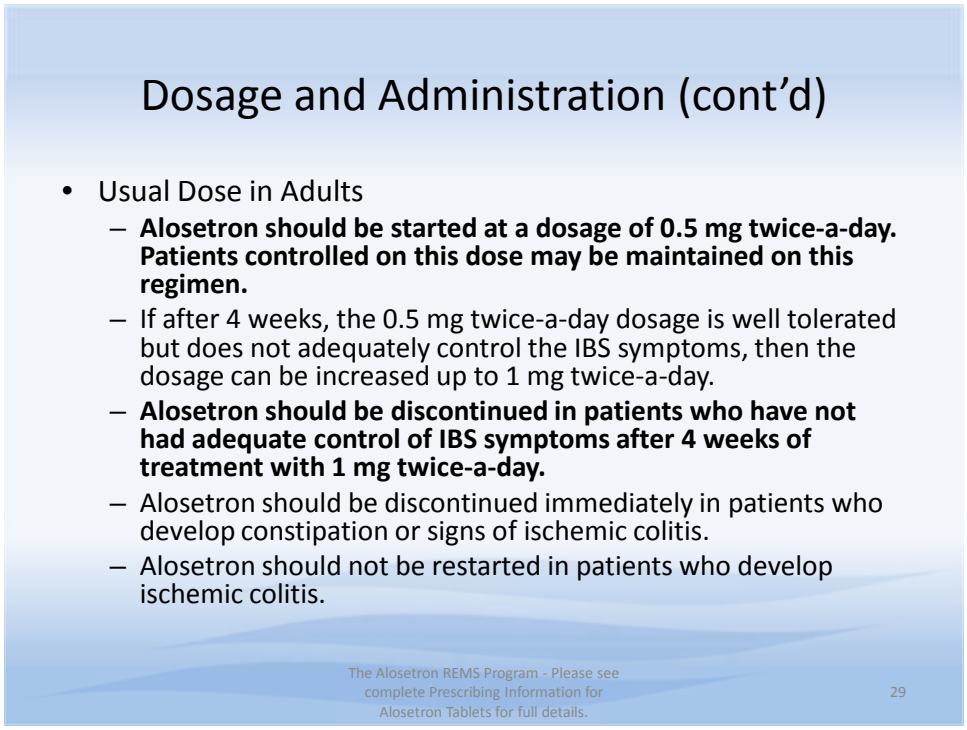


Section 4:
How to Prescribe Alosetron Tablets



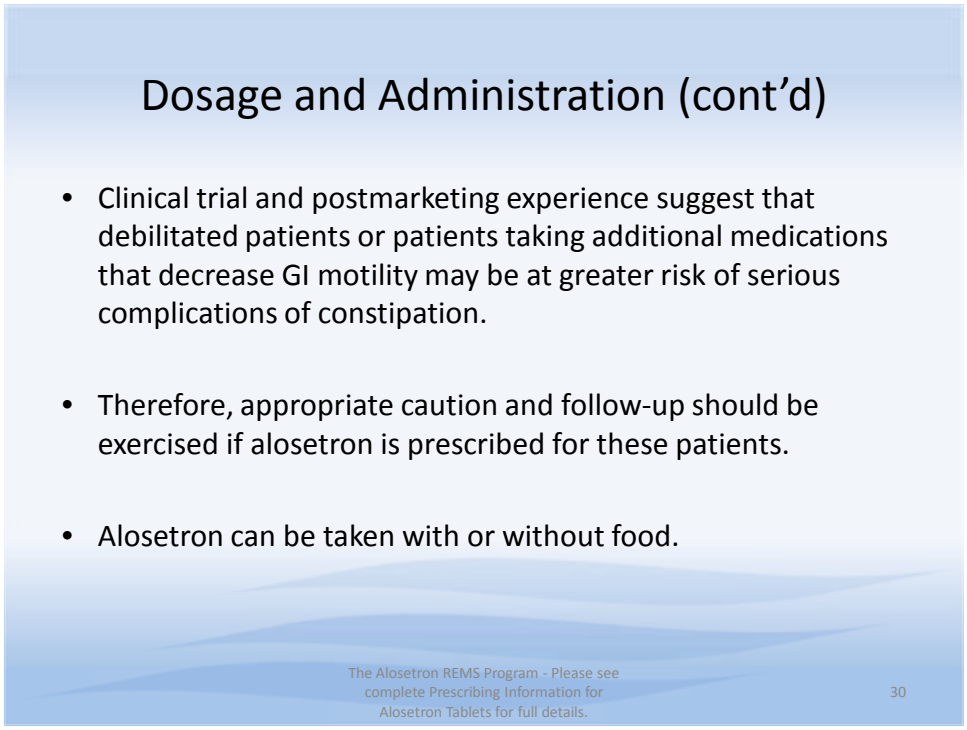
Dosage and Administration

- 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.**



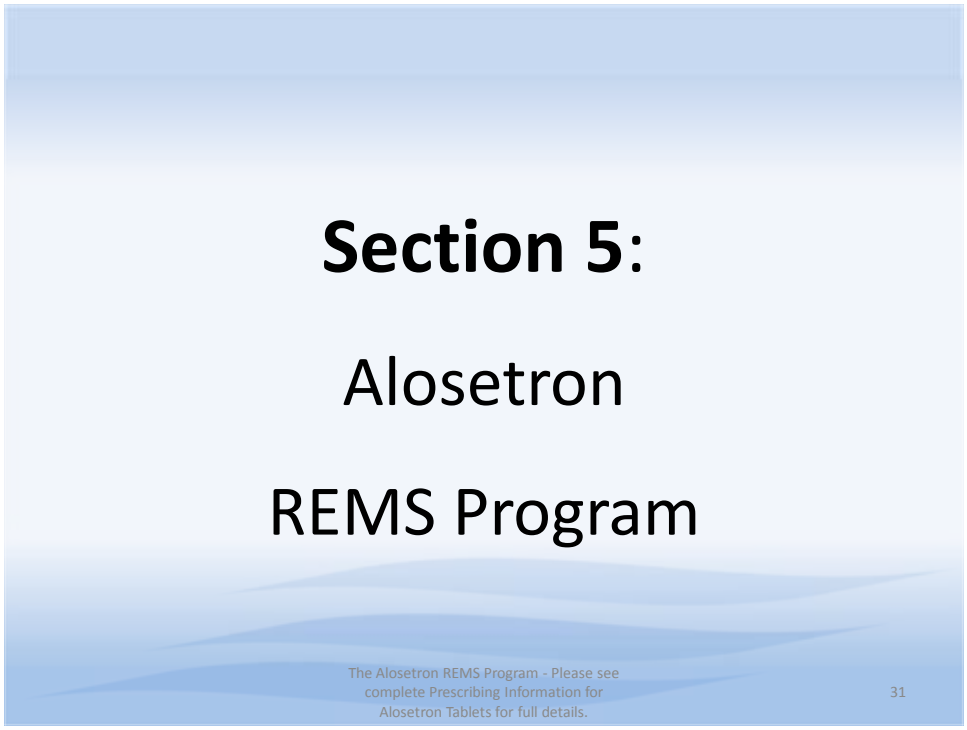
Dosage and Administration (cont'd)

- 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.

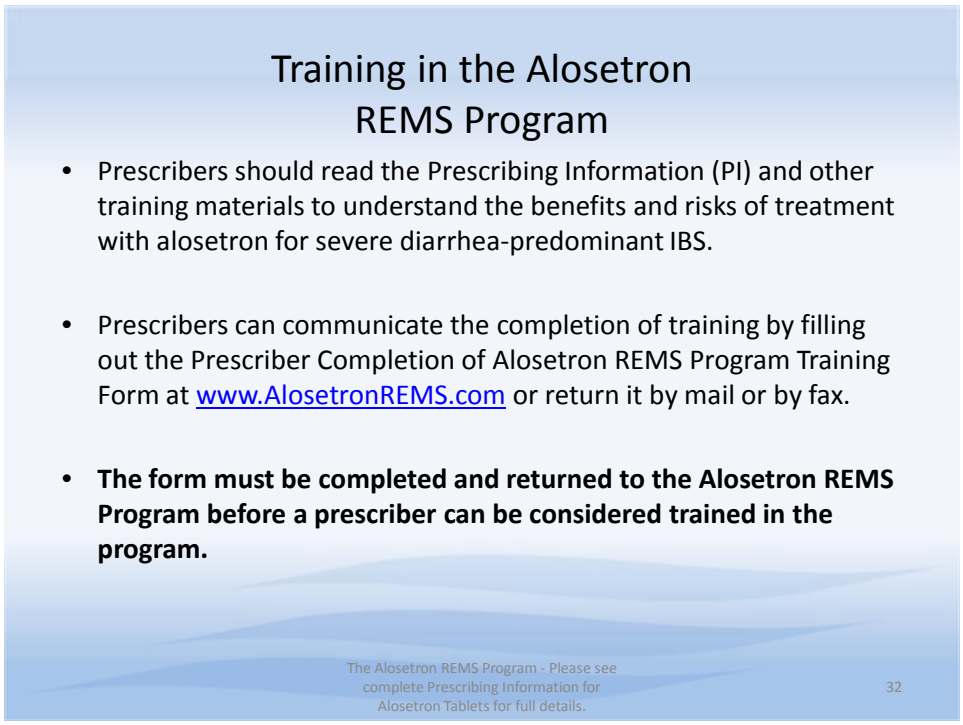


Dosage and Administration (cont'd)

- 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.

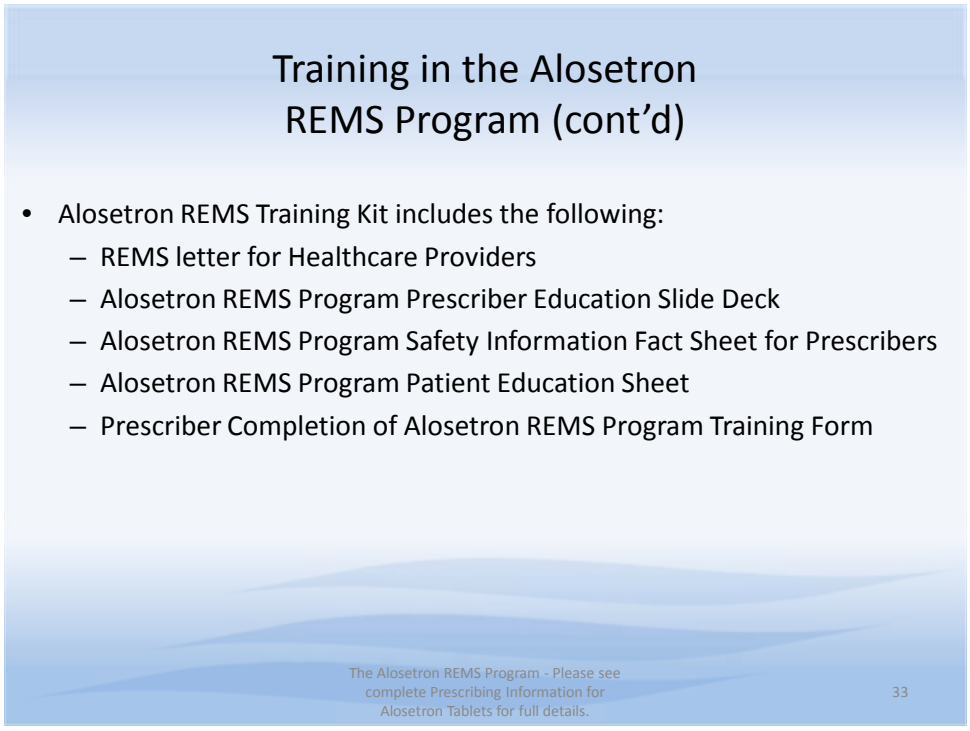


Section 5:
Alosetron REMS Program



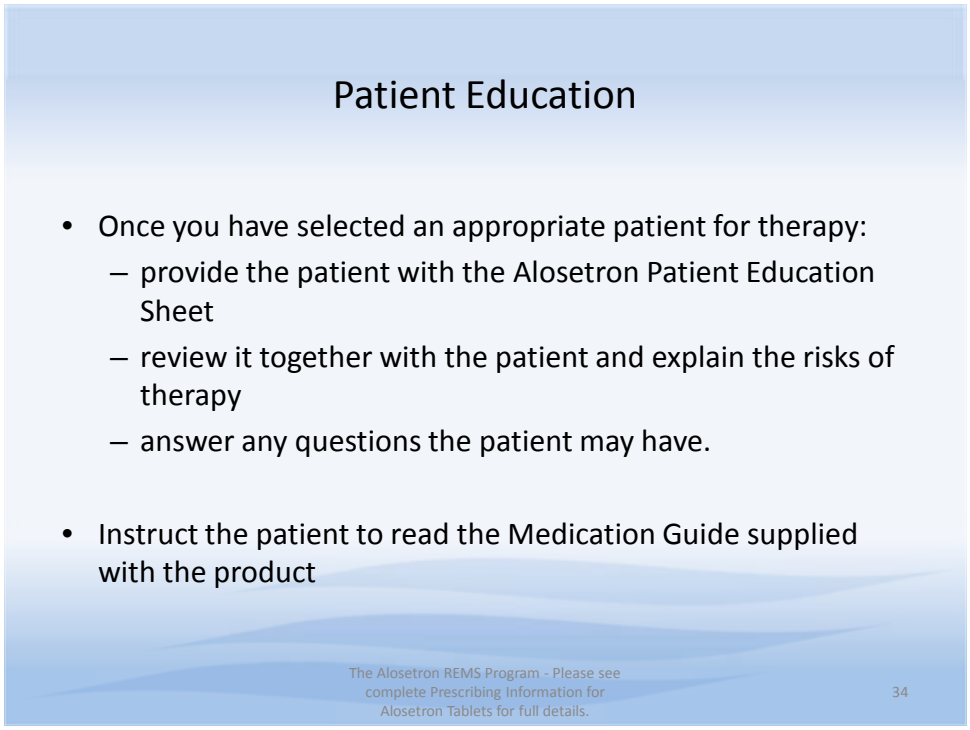
Training in the Alosetron REMS Program

- 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 Alosetron REMS Program.**



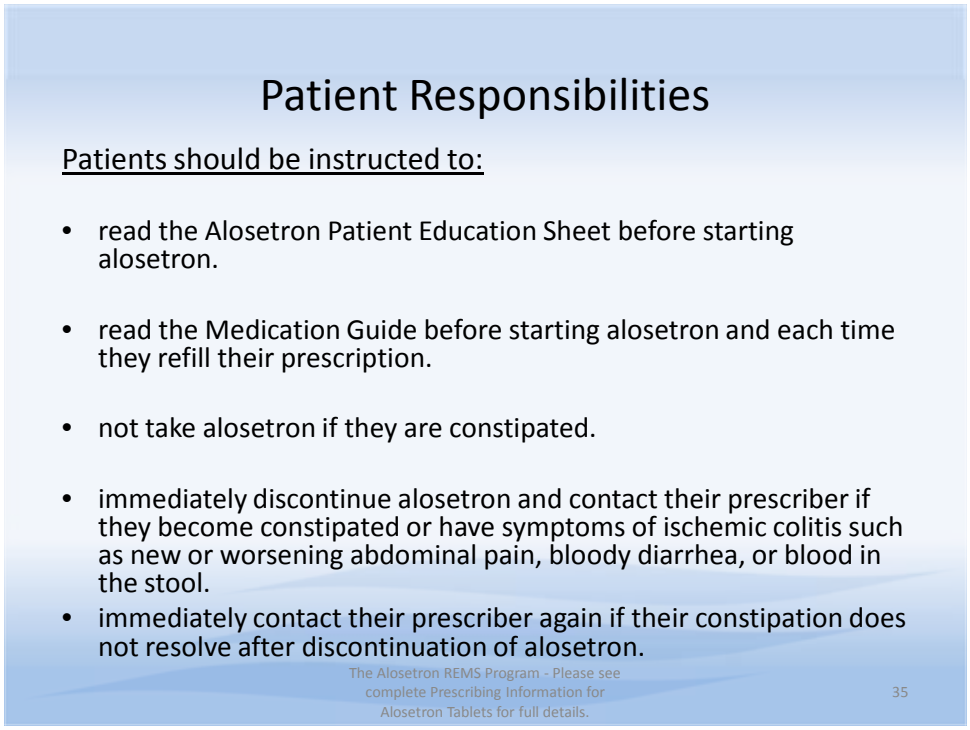
Training in the Alosetron REMS Program (cont'd)

- 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

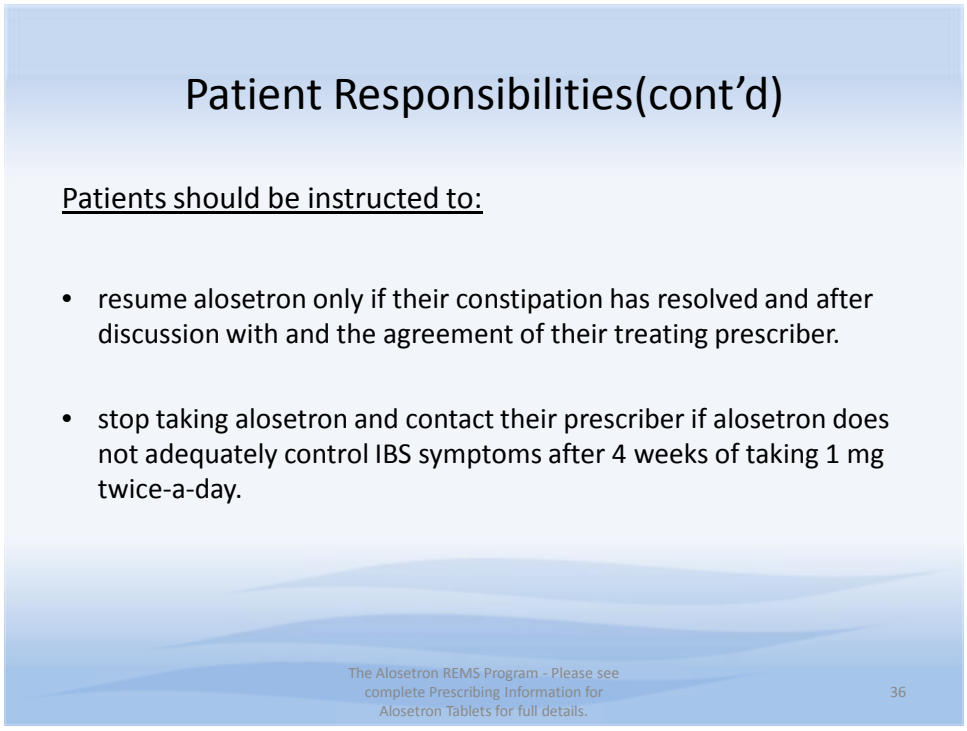
- Once you have selected an appropriate patient for therapy:
  - provide the patient with the Alosetron Patient Education Sheet
  - review it together with the patient and explain the risks of therapy
  - answer any questions the patient may have.
- Instruct the patient to read the Medication Guide supplied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



Patient Responsibilities

Patients should be instructed to:

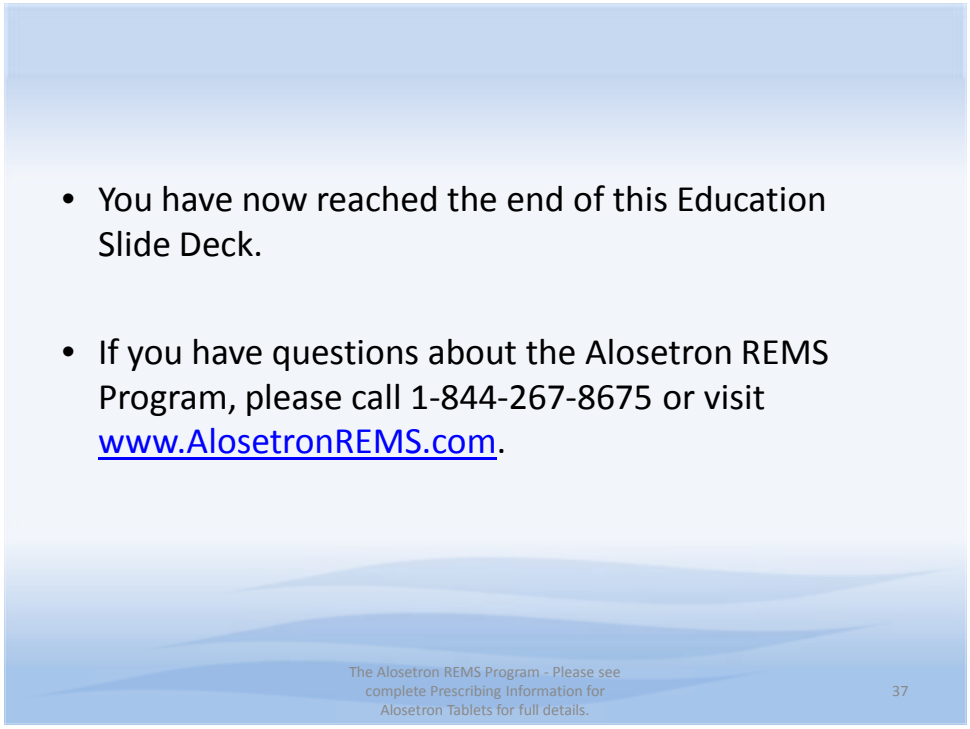
- read the Alosetron Patient Education Sheet before starting alosetron.
- read the Medication Guide before starting alosetron and each time they refill their prescription.
- not take alosetron if they are constipated.
- immediately discontinue alosetron and contact their prescriber if they become constipated 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.

Alosetron 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 alosetron hydrochloride tablets (alosetron). 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** alosetron immediately in patients who develop constipation or symptoms of ischemic colitis. Do not resume alosetron 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 alosetron 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** alosetron 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 alosetron in accordance with the approved indication. Alosetron 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 Alosetron 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 alosetron tablets outweigh serious gastrointestinal adverse reactions in patients. This factsheet is required by the FDA as part of the Alosetron REMS Program. Please visit www.AlosetronREMS.com for further information.

Indication

Alosetron 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 alosetron to the FDA at www.fda.gov/medwatch, or 1-800-FDA-1088 or to the Alosetron REMS Program at 1-844-267-8675.

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

Alosetron REMS Program Patient Education Sheet

FDA Required Alosetron Safety Information

What is alosetron?

- Alosetron 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. Alosetron 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 alosetron treatment?

- About 1 out of every 1,000 women who take alosetron may get serious complications of constipation. About 3 out of every 1,000 women who take alosetron 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 alosetron. 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 alosetron?

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

How do I take alosetron?

- Take alosetron exactly as your doctor prescribes it.

When should I stop taking alosetron and call my doctor?

- Stop taking alosetron 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 alosetron 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 alosetron to recheck your IBS symptoms.
- Stop taking alosetron and call your doctor if your IBS symptoms have not improved after 4 weeks of taking 1 mg of alosetron 2 times a day.
- If you see other doctors about your IBS or possible side effects from alosetron, tell the doctor who prescribed alosetron.

This education sheet only discusses the most serious risk information of alosetron. For more safety information about alosetron please see the alosetron medication guides available at www.AlosetronREMS.com

Please visit www.AlosetronREMS.com for further information.

Prescriber Completion of Alosetron REMS Program Training Form

Thank you for completing the Alosetron 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.

***Indicates Required Field**

Name of Prescriber (print)*

_____

(First) (Last)

_____ _____

Signature* Date*

NPI Number* _____

Specialty*

☐ Gastroenterology ☐ General Surgery ☐ Internal Medicine
☐ Colon & Rectal Surgery ☐ Nurse Practitioner ☐ Nuclear Medicine
☐ Family Medicine ☐Cardiovascular Diseases ☐ Physician Assistant
☐ Obstetrics/Gynecology ☐ Other (Please specify) _____

Office Name _____

Office Address* _____

Office City* _____ State*_____Zip Code* _____

Office Phone Number* _____Office Fax Number*_____

Email* _____

Confirmation Correspondence Preference (please select one): ☐ Fax ☐ Email

If you have any questions regarding the Alosetron REMS Program, please call 1-844-267-8675.

To complete training, visit www.AlosetronREMS.com or complete this form in its entirety and mail or fax it to the Alosetron REMS Program to the following address:

Alosetron REMS

PO Box 29292, Phoenix, AZ 85038

Fax Number: 1-800-535-6805

Alosetron REMS Program

Risk Evaluation and Mitigation Strategy

Web Mockups

V19

FOOTER

Footer is included on every web page. To reduce the length of the document, the screenshot is included once.

HOME PAGE

alosetron REMS

For Patients | For Prescribers

Alosetron REMS (Risk Evaluation and Mitigation Strategy)

What is the Alosetron REMS Program?

A REMS (**R**isk **E**valuation and **M**itigation **S**trategy) is a program required by the Food and Drug Administration (FDA) to manage known or potential serious risks associated with a drug product. The FDA has determined that a REMS is necessary for alosetron to ensure the benefits of the drug outweigh the risk of serious gastrointestinal (GI) adverse reactions.

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

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.

Alosetron is indicated ONLY for women with severe diarrhea-predominant IBS who have:

- Chronic irritable bowel syndrome symptoms (generally lasting for 6 months or longer),
- had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and
- not responded adequately to conventional therapy.

alosetron REMS

For Patients | For Prescribers

Patient Role in the Alosetron REMS Program

Only patients who are counseled on the safe use of alosetron by their prescriber should be prescribed alosetron. Patients will be counseled on the Alosetron REMS Program by trained prescribers. Patients will have the opportunity to discuss any questions or concerns they have with their prescriber. The prescriber will provide and review the Alosetron REMS Program Patient Education Sheet with the patient at the beginning of treatment. Please use the links below to review the Alosetron REMS Program Patient Education Sheet and Medication Guide.

Alosetron REMS Program Patient Education Sheet

Medication Guide

Alosetron Medication Guide (Amneal Pharmaceuticals LLC)

Alosetron Medication Guide (Par Pharmaceutical, Inc.)

Alosetron Medication Guide (Roxane Laboratories, Inc.)

Get ADOBE READER

PRESCRIBERS

Prescriber Role in the Alosetron REMS Program

Only prescribers who train in the Alosetron REMS Program, based on their understanding of the benefits and risks, should prescribe alosetron. The Alosetron REMS Program facilitates patients safety. The program requires patients and prescribers to understand the appropriate use of alosetron and its potential risks, as well as potential adverse events and how to handle them.

Prescribers should comply with the following requirements of the Alosetron REMS Program:

- Review the Alosetron REMS Program Prescriber Education Slide Deck
- Fill out and submit the Prescriber Completion of Alosetron REMS Program Training Form.

Prescriber Training

Prescribers should train in the Alosetron REMS Program prior to prescribing alosetron.

To train in the Alosetron REMS Program via web:

1. Review the Alosetron REMS Program Prescriber Education Slide Deck located in the Resources section below.
2. Press **Next** to begin the completion of training process.

To train in the Alosetron REMS Program via fax:

1. Review the Alosetron REMS Program Prescriber Education Slide Deck located in the Resources section below.
2. Complete the Prescriber Completion of Alosetron REMS Program Training Form located in the Resources section below.
3. Fax the completed Prescriber Completion of Alosetron REMS Program Training Form to the Alosetron REMS Program at 1-800-535-6805.

Resources

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

Prescribing Information and Medication Guide

- Alosetron Prescribing Information (Amneal Pharmaceuticals LLC)
- Alosetron Medication Guide (Amneal Pharmaceuticals LLC)

- Alosetron Prescribing Information (Par Pharmaceutical, Inc.)
- Alosetron Medication Guide (Par Pharmaceutical, Inc.)

- Alosetron Prescribing Information (Roxane Laboratories, Inc.)
- Alosetron Medication Guide (Roxane Laboratories, Inc.)

Get ADOBE READER

Next

PRESCRIBER AGREEMENT

The Alosetron REMS Program – Prescriber Completion of Training

Thank you for completing the Alosetron REMS Program training. As a confirmation that you independently reviewed the program training materials, please press the **Complete Training** button and provide your details on the following form.

Complete Training

PRESCRIBER ONLINE TRAINING FORM

alosetron REMS

For Patients | For Prescribers

Please complete the fields below and press **Submit** to complete training in the Alosetron REMS Program. All fields below are required unless otherwise indicated.

Prescriber Information

First Name	
Last Name	
Specialty	-- Please Select --
National Provider Identifier (NPI)	
Office Name	
Address 1	
Address 2	(Optional)
City	
State	-- Please Select --
Zip Code	
Phone	
Fax	
Email	
Correspondence Confirmation Preference	○ Email ○ Fax

Your signature and date are required to complete your training. Please type your exact first and last name along with today's date in the spaces provided below. This will serve as your electronic signature and will certify that you have read and agreed to the terms provided for the program.

Signature (First and Last Name as typed above) | Date MM/DD/YYYY | ☐ I'm not a robot reCAPTCHA Privacy - Terms

Submit

PRESCRIBER ONLINE TRAINING FORM – OTHER SPECIALTY SELECTED

Please complete the fields below and press **Submit** to complete training in the Alosetron REMS Program. All fields below are required unless otherwise indicated.

Prescriber Information

First Name

Last Name

Specialty: Other

-- Please Specify --

National Provider Identifier (NPI)

Office Name

Address 1

Address 2 (Optional)

City

State: -- Please Select --

Zip Code

Phone

Fax

Email

Correspondence Confirmation Preference: Email Fax

Your signature and date are required to complete your training. Please type your exact first and last name along with today's date in the spaces provided below. This will serve as your electronic signature and will certify that you have read and agreed to the terms provided for the program.

Signature (First and Last Name as typed above)

Date MM/DD/YYYY

I'm not a robot reCAPTCHA Privacy - Terms

Submit

PRESCRIBER TRAINING CONFIRMATION

Congratulations!

You have successfully trained in the Alosetron REMS Program!

Below is your Alosetron REMS Program Training Confirmation. Please note, you will receive acknowledgement of completion of training via your correspondence confirmation preference. Please retain this information for your records.

Training Confirmation: <Confirmation ID>

RESOURCES

Resources

Prescriber

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

Prescribing Information and Medication Guide

- Alosetron Prescribing Information (Amneal Pharmaceuticals LLC)
- Alosetron Medication Guide (Amneal Pharmaceuticals LLC)

- Alosetron Prescribing Information (Par Pharmaceutical, Inc.)
- Alosetron Medication Guide (Par Pharmaceutical, Inc.)

- Alosetron Prescribing Information (Roxane Laboratories, Inc.)
- Alosetron Medication Guide (Roxane Laboratories, Inc.)

Get ADOBE READER

CONTACT US

For Patients | For Prescribers

Contact Us

If you have any questions or require additional information, please contact the Alosetron REMS Program utilizing the information provided below.

Phone Number
1-844-267-8675

Fax Number
1-800-535-6805

Mailing Address
Alosetron REMS Program
PO BOX 29292
PHOENIX AZ 85038-9292

Carol Holquist

Digitally signed by Carol Holquist
Date: 12/22/2016 09:03:06AM
GUID: 508da712000293e0f6d8acfd3c5e67fe