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## NDA 21-107

# LOTRONEX<sup>®</sup> (alose tron hydrochloride) Tablets

Selective 5-HT<sub>3</sub> antagonist

Prometheus Laboratories Inc.  
9410 Carroll Park Drive  
San Diego, CA 92121  
(858) 410 2482

### RISK EVALUATION AND MITIGATION STRATEGY (REMS)

#### I. GOAL(S):

- To mitigate the risk of ischemic colitis (IC) and serious complications of constipation (CoC) associated with LOTRONEX (alose tron hydrochloride) by ensuring that LOTRONEX is used in only severely affected patients for whom benefits exceed the risks.
- To ensure that the risk of IC and serious CoC with the use of LOTRONEX are communicated to patients, pharmacists, and prescribers.

#### II. REMS ELEMENTS:

##### A. Medication Guide (MG)

A Medication Guide for LOTRONEX will be dispensed with each LOTRONEX prescription in accordance with 21 CFR 208.24.

A LOTRONEX prescription typically provides the patient with 30-day dosing which is divided into two cartons each containing a bottle with 30 tablets. A copy of the Medication Guide is affixed to each 30-tablet bottle. Copies of the Medication Guide will be available via the [lotronexppl.com](http://lotronexppl.com) website or by calling Prometheus Client Services at 1-888-423-5227.

Additionally, as part of the Prescribing Program for LOTRONEX, the LOTRONEX Medication Guide will be provided to certified prescribers who will provide a Medication Guide to each patient at the initiation of each new course of LOTRONEX therapy.

Please see appended Medication Guide.

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## B. Elements to Assure Safe Use

### 1. Healthcare providers who prescribe LOTRONEX will be specially certified.

- a. Prometheus will ensure that healthcare providers who prescribe LOTRONEX are specially certified in the Prescribing Program for LOTRONEX (PPL). To become certified, each prescriber enrolls into the Prescribing Program for LOTRONEX by submitting a completed Prescriber Enrollment Form and attesting to the following:
  - i. I request to participate in the Prescribing Program for LOTRONEX and acknowledge that I have read and understand the complete Prescribing Information and other enrollment materials for LOTRONEX. I understand the risks associated with its use and will follow the requirements of the Prescribing Program for LOTRONEX described below. I understand the importance of reporting all cases of ischemic colitis and serious complications of constipation to Prometheus at 1-888-423-5227.
  - ii. I understand that LOTRONEX is approved only for women with severe, diarrhea-predominant irritable bowel syndrome 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.

Diarrhea-predominant irritable bowel syndrome is severe if it includes diarrhea and one or more of the following:

- frequent and severe abdominal pain and discomfort,
  - frequent bowel urgency or fecal incontinence,
  - disability or restriction of daily activities due to irritable bowel syndrome.
- iii. I understand that if I prescribe LOTRONEX for my patient(s), I must be able to perform the following:
    - diagnose and manage irritable bowel syndrome, ischemic colitis, constipation, and complications of constipation or refer patients to a specialist as needed.
    - ensure that all patients under my care are educated by me or a healthcare provider in my practice about the benefits and risks of the drug.
  - iv. I agree to:

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- provide each of my patients with a copy of the LOTRONEX Medication Guide at initiation of LOTRONEX treatment.
  - review the content of the Medication Guide and encourage the patient to read it and ask questions.
  - have each patient sign the Patient Acknowledgement Form. The original signed form must be placed in the patient's medical record, and a copy given to the patient.
  - inform my patients about the Patient Follow-Up Survey, encourage them to participate and provide them with a Patient Follow-Up Survey Pre-Enrollment Form.
  - affix Prescribing Program for LOTRONEX program stickers to written prescriptions for LOTRONEX (i.e., the original and all subsequent prescriptions). Stickers will be provided as part of the Prescribing Program for LOTRONEX. Refills are permitted to be written on prescriptions.
  - ensure that all prescriptions for LOTRONEX are written and not transmitted by telephone, facsimile, or computer.
- b. PPL Enrollment materials can be requested via the [lotronexppl.com](http://lotronexppl.com) website or by phone at 1-888-423-5227.
- c. Prometheus will provide prescribers a PPL kit upon their enrollment.
- d. Prometheus will maintain a database of all certified enrolled prescribers.

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

- PPL Enrollment Materials
  - Prescriber Enrollment Form
  - PPL Enrollment Letter
  - PPL Prescriber Education Slide Deck
  - Prescribing Information
- LOTRONEXPPL Website For Prescriber Section webshots
- PPL Kit
  - PPL Kit Overview Letter
  - Patient Acknowledgement Form
  - Medication Guide
  - PPL stickers
  - Patient Follow-Up Survey Pre-Enrollment Form
- PPL Sticker Sheet
- Patient Follow-Up Survey Pre-Enrollment Form (included in the LOTRONEX Retail Pack)

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- 2. Each patient prescribed LOTRONEX must have signed a Patient Acknowledgement Form for documentation of safe-use conditions. By signing the Patient Acknowledgement Form the patient agrees to the following:**
- a. My doctor or healthcare provider under a doctor's direction, answered my questions about treatment with LOTRONEX. I have read and I understand the Medication Guide for LOTRONEX, including the section "Who should not take LOTRONEX?". I understand that about 1 out of every 1,000 women who take LOTRONEX may get serious complications of constipation. I understand that about 3 of every 1,000 women who take LOTRONEX over a 6-month period may get a serious problem where blood flow to parts of the large bowel is reduced (ischemic colitis). I understand that the serious condition of ischemic colitis, and other serious complications of constipation, can happen suddenly. These serious complications may lead to a hospital stay, and in rare cases, blood transfusions, surgery, and death.
  - b. I understand that certain people may be more likely to develop a serious bowel condition while taking LOTRONEX, including people who:
    - are older,
    - have other health problems,
    - take other medicines that may cause constipation.
  - c. I understand LOTRONEX is a medicine that should only be used for some women with severe chronic irritable bowel syndrome (IBS), whose main problem is diarrhea, and whose IBS symptoms have not been helped enough by other treatments.
  - d. I will follow instructions in the Medication Guide about:
    - **telling my doctor**, before taking LOTRONEX, about any illnesses I have, or other medicines I am taking or planning to take.
    - **taking LOTRONEX** exactly as my doctor prescribes it.
    - **stopping LOTRONEX** and calling my doctor right away if I get constipated, if I have new or worse pain in my stomach area (abdomen), or if I see blood in my bowel movements.
    - **calling my doctor** again if the constipation I called about before has not gotten better.
    - **not starting LOTRONEX again** unless my doctor tells me to do so, if I stopped taking it because I got constipated.
    - **talking with my doctor 4 weeks after starting LOTRONEX** to recheck my IBS symptoms.
    - **stopping LOTRONEX and calling my doctor** if my IBS symptoms have not improved after 4 weeks of taking 1 mg LOTRONEX 2 times a day.



e. If I see other doctors about my IBS or possible side effects from LOTRONEX, I will tell the doctor who prescribed LOTRONEX .

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

- Patient Acknowledgement Form
- LOTRONEXPPL Website for Patients Section
- LOTRONEX Medication Guide

**3. Pharmacists will only dispense LOTRONEX to patients with documentation of safe-use conditions:**

- a. The pharmacists will only dispense a prescription for LOTRONEX in the presence of a PPL sticker.
  - The PPL sticker provides verification to the pharmacist that the prescription is written by a certified prescriber enrolled in the PPL.
  - Pharmacists will not accept telephone, facsimile, or computerized prescriptions for LOTRONEX. The prescription may provide refills (30 day supplies).
- b. At the time of filling the prescription, pharmacists will dispense to the patient a 30-day supply which includes a copy of the Medication Guide.
- c. Prometheus will perform educational mailings twice-a-year (beginning no later than 3 months following the date of approval of this REMS) to pharmacists and retail pharmacies entitled “Important Information for Pharmacists” for a period of 2 years upon approval of the REMS and annually thereafter. The mailings will remind the pharmacists about their role within the PPL.
- d. Prometheus will direct pharmacists to review educational materials on the pharmacist section of the LOTRONEXPPL website. The educational materials will consist of a PPL Pharmacist Education Slide Deck [based on the approved PPL Prescriber Education Slide Deck] discussing the benefits and risks of LOTRONEX therapy and the pharmacist role in ensuring compliance with the PPL sticker program.

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

- Educational Mailing: Important Information for Pharmacists
- PPL Pharmacist Education Slide Deck
- LOTRONEXPPL Website For Pharmacists Section webshots

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### **C. Implementation System**

The implementation system for the LOTRONEX REMS includes the following:

- Prometheus will monitor compliance with completion of the Prescriber Enrollment Form and Patient Acknowledgement Form to help ensure LOTRONEX is prescribed by PPL-enrolled prescribers and that patients are only treated with LOTRONEX following documentation of safe use conditions by conducting surveys of prescribers and patients.
- Prometheus will monitor compliance with the PPL sticker program by conducting surveys of pharmacists, prescribers, and patients to help ensure LOTRONEX prescriptions are written by PPL-enrolled prescribers and dispensed by pharmacists in accordance with the requirements of the PPL.
- Based on monitoring and evaluation of the elements to assure safe use in section IIB, Prometheus will take reasonable steps to improve the implementation of these elements, if found to be inadequate, and to address non-compliance with the requirements of the PPL.

### **D. Timetable for Submission of Assessments**

Prometheus will submit REMS Assessments to the FDA every 6 months for the first year from the date of approval of the REMS and annually 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. Prometheus will submit each assessment so that it will be received by the FDA on or before the due date.

**MEDICATION GUIDE**  
**LOTRONEX® (LOW-trah-nex) Tablets**  
**(alose tron hydrochloride)**

**Before using LOTRONEX for the first time, you should:**

- Understand that LOTRONEX has serious risks for some people.
- Read and follow the directions in this Medication Guide.
- Sign a Patient Acknowledgement Form.

Read this Medication Guide carefully before you sign the Patient Acknowledgement Form. You must sign the Patient Acknowledgement Form before you start LOTRONEX. Read the Medication Guide you get with each refill for LOTRONEX. There may be new information. This Medication Guide does not take the place of talking with your doctor.

**1. What is the most important information I should know about LOTRONEX?**

**A. LOTRONEX is a medicine only for some women with severe chronic irritable bowel syndrome (IBS) whose:**

- main problem is diarrhea and
- IBS symptoms have not been helped enough by other treatments.

**B. Some patients have developed serious bowel side effects while taking LOTRONEX. Serious bowel (intestine) side effects can happen suddenly, including the following.**

- 1. Serious complications of constipation:** About 1 out of every 1,000 women who take LOTRONEX may get serious complications of constipation. These complications **may lead to a hospital stay and, in rare cases, blood transfusions, surgery, and death.** People who are older, who are weak from illness, or who take other constipating medicines may be more likely to have serious complications of constipation with LOTRONEX.

**To lower your chances of getting serious complications of constipation, do the following:**

- **If you are constipated,** do not start taking LOTRONEX.
- **If you get constipated while taking LOTRONEX,** stop taking it right away and call your doctor.
- **If your constipation does not get better after stopping LOTRONEX,** call your doctor again.
- **If you stopped taking LOTRONEX, do not start taking LOTRONEX again** unless your doctor tells you to do so.

- 2. Ischemic colitis (reduced blood flow to the bowel):** About 3 out of every 1,000 women who take LOTRONEX over a 6-month period may get a serious problem where blood flow to parts of the large bowel is reduced. This is called ischemic colitis. The chance of getting ischemic colitis when you take LOTRONEX for more

than 6 months is not known. **Ischemic colitis may lead to a hospital stay and, in rare cases, blood transfusions, surgery, and death.**

**To lower your chances of getting serious complications of ischemic colitis, stop taking LOTRONEX and call your doctor right away if you get:**

- new or worse pain in your stomach area (abdomen) or
- blood in your bowel movements.

### **C. Is LOTRONEX right for you?**

**LOTRONEX may be right for you if all of these things are true about you:**

- Your doctor has told you that your symptoms are due to IBS.
- Your IBS bowel problem is diarrhea.
- Your IBS has lasted for 6 months or longer.
- You tried other IBS treatments and they did not give you the relief you need.
- Your IBS is severe.

You can tell if your IBS is severe if **at least 1** of the following is true for you:

- You have lots of painful stomach cramps or bloating.
- You often cannot control the need to have a bowel movement, or you have “accidents” where your underwear gets dirty from diarrhea or bowel movements.
- You cannot lead a normal home or work life because you need to be near a bathroom.

Enough testing has not been done to confirm if LOTRONEX works in men or children under age 18.

### **D. There is a special prescribing program for LOTRONEX.**

Only doctors who have signed up with the company that makes LOTRONEX should write prescriptions for LOTRONEX. As part of signing up, these doctors have said that they understand about IBS and the possible side effects of LOTRONEX. They have agreed to use a special sticker on **written** prescriptions for LOTRONEX, so the pharmacist will know that the doctors have signed up with the company. No telephone, facsimile, or computerized prescriptions are permitted with this program. Refills may be written on prescriptions. You may be taught about LOTRONEX by your doctor or healthcare provider under a doctor’s direction. Your doctor will ask you to sign a Patient Acknowledgement Form after you read this Medication Guide for the first time. Signing the Patient Acknowledgement Form means that you understand the benefits and risks of LOTRONEX and that you have read and understand this Medication Guide.

## **2. What is LOTRONEX?**

LOTRONEX is a medicine only for some women with severe chronic IBS whose:

- main problem is diarrhea and
- IBS symptoms have not been helped enough by other treatments.

LOTIRONEX does not cure IBS, and it may not help every person who takes it. For those who are helped, LOTIRONEX reduces lower stomach area (abdominal) pain and discomfort, the sudden need to have a bowel movement (bowel urgency), and diarrhea from IBS. If you stop taking LOTIRONEX, your IBS symptoms may return within 1 or 2 weeks to what they were before you started taking LOTIRONEX.

LOTIRONEX is not recommended for children.

### **3. Who should not take LOTIRONEX?**

LOTIRONEX is not right for everyone. **Do not take LOTIRONEX if any of the following apply to you:**

- Your main IBS problem is constipation or you are constipated most of the time.
- You have had a serious problem from constipation. **If you are constipated now, do not start taking LOTIRONEX.**
- You have had serious bowel blockages.
- You have had blood flow problems to your bowels, such as ischemic colitis.
- You have had blood clots.
- You have had Crohn's disease, ulcerative colitis, diverticulitis, or severe liver disease.
- You do not understand this Medication Guide or the Patient Acknowledgement Form, or you are not willing to follow them.
- You are taking fluvoxamine (LUVOX<sup>®</sup>).

### **4. What should I talk about with my doctor before taking LOTIRONEX?**

Talk with your doctor:

- about the possible benefits and risks of LOTIRONEX.
- about how much of a problem IBS is in your life and what treatments you have tried.
- about any other illnesses you have and medicines you take or plan to take. These include prescription and non-prescription medicines, supplements, and herbal remedies. Certain illnesses and medicines can increase your chance of getting serious side effects while taking LOTIRONEX. Other medicines may interact with how the body handles LOTIRONEX.
- about any allergies that you have. See the end of the Medication Guide for a complete list of ingredients in LOTIRONEX.
- if you are pregnant, planning to get pregnant, or breastfeeding.

### **5. How should I take LOTIRONEX?**

- Take LOTIRONEX exactly as your doctor prescribes it. You can take LOTIRONEX with or without food.
- Begin with 0.5 mg two times a day for 4 weeks to see how LOTIRONEX affects you. You and your doctor may decide that you should keep taking this dose if you are doing well.

- Check with your doctor 4 weeks after starting LOTRONEX:
  - If you try 0.5 mg two times a day for 4 weeks, it may not control your symptoms. If you do not get constipation or other side effects from LOTRONEX, your doctor may increase your dose up to 1 mg two times a day.
  - If 1 mg two times a day does not work after 4 weeks, LOTRONEX is not likely to help you. You should stop taking it and call your doctor.
- **If you miss a dose of LOTRONEX**, just skip that dose. Do **not** take 2 doses the next time. Wait until the next time you are supposed to take it and then take your normal dose.
- **Follow the important instructions in the section “What is the most important information I should know about LOTRONEX?”** about when you must stop taking the medicine and when you should call your doctor.
- **If you see other doctors** about your IBS or side effects from LOTRONEX, tell the doctor who prescribed LOTRONEX.

#### **6. What are the possible side effects of LOTRONEX?**

Constipation is the most common side effect among women with IBS who take LOTRONEX. **Some patients have developed serious bowel side effects while taking LOTRONEX.** Read the section **“What is the most important information I should know about LOTRONEX?”** at the beginning of this Medication Guide for information about the serious side effects you may get with LOTRONEX.

This Medication Guide does not tell you about all the possible side effects of LOTRONEX. Your doctor or pharmacist can give you a more complete list.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

#### **7. How should I store LOTRONEX?**

- Store LOTRONEX between 59°F to 86°F (15°C to 30°C).
- Protect LOTRONEX from light and getting wet (moisture).

**Keep LOTRONEX and all medicines out of the reach of children.**

#### **8. General information about the safe and effective use of LOTRONEX**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you have any questions or concerns about LOTRONEX, ask your doctor. Do not use LOTRONEX for a condition for which it was not prescribed. Do not share your medicine with other people. It may harm them.

Your doctor or pharmacist can give you more information about LOTRONEX that was written for healthcare professionals. You can also contact the company that makes LOTRONEX (toll free) at 1-888-423-5227 or at [www.lotronexpl.com](http://www.lotronexpl.com).

#### **9. What are the ingredients of LOTRONEX?**

**Active Ingredient:** alosetron hydrochloride.

**Inactive Ingredients:** lactose (anhydrous), magnesium stearate, microcrystalline cellulose, and

pregelatinized starch. The white film-coat for the 0.5 mg tablet contains hypromellose, titanium dioxide, and triacetin. The blue film-coat for the 1 mg tablet contains hypromellose, titanium dioxide, triacetin, and indigo carmine.

Manufactured for:  
Prometheus Laboratories Inc.  
9410 Carroll Park Drive  
San Diego, CA 92121

*This Medication Guide has been approved by the U.S. Food and Drug Administration.*

Revised September 2010

LX002D

## **PRESCRIBING PROGRAM FOR LOTRONEX™ PRESCRIBER ENROLLMENT FORM**

*Prometheus will ensure that healthcare providers who prescribe LOTRONEX are specially certified in the Prescribing Program for LOTRONEX (PPL). To become certified, each prescriber enrolls into the Prescribing Program for LOTRONEX by submitting a completed Prescriber Enrollment Form and attesting to the following:*

I request to participate in the Prescribing Program for LOTRONEX and acknowledge that I have read and understand the complete Prescribing Information and other enrollment materials for LOTRONEX. I understand the risks associated with its use and will follow the requirements of the Prescribing Program for LOTRONEX described below. I understand the importance of reporting all cases of ischemic colitis and serious complications of constipation to Prometheus at 1-888-423-5227.

I understand that LOTRONEX is approved only for women with severe, diarrhea-predominant irritable bowel syndrome 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.

Diarrhea-predominant irritable bowel syndrome 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 irritable bowel syndrome.

I understand that if I prescribe LOTRONEX for my patient(s), I must be able to perform the following:

- diagnose and manage irritable bowel syndrome, ischemic colitis, constipation, and complications of constipation, or refer patients to a specialist as needed.
- ensure that all patients under my care are educated by me or a healthcare provider in my practice about the benefits and risks of the drug.

I agree to:

- provide each of my patients with a copy of the LOTRONEX Medication Guide at initiation of LOTRONEX treatment.
- review the content of the Medication Guide and encourage the patient to read it and ask questions.
- have each patient sign the Patient Acknowledgement Form. The original signed form must be placed in the patient's medical record, and a copy given to the patient.



- inform my patients about the Patient Follow-Up Survey, encourage them to participate and provide them with a Patient Follow-Up Survey Pre-Enrollment Form.
- affix Prescribing Program for LOTRONEX program stickers to written prescriptions for LOTRONEX (i.e., the original and all subsequent prescriptions). Stickers will be provided as part of the Prescribing Program for LOTRONEX. Refills are permitted to be written on prescriptions.
- ensure that all prescriptions for LOTRONEX are written and not transmitted by telephone, facsimile, or computer.

\_\_\_\_\_  
Name of Prescriber (print)

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

DEA Number \_\_\_\_\_

Office Address: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

Office Phone Number: \_\_\_\_\_

Office Fax Number: \_\_\_\_\_

Upon enrollment, you will receive a prescribing kit for LOTRONEX with the complete Prescribing Information, Prescribing Program for LOTRONEX stickers, multiple copies of the Medication Guide and Patient Acknowledgement Form for LOTRONEX, and instructions for ordering additional supplies of Program materials.

You only need to enroll once, and you are under no obligation to prescribe LOTRONEX.

If you have any questions, please call the Prescribing Program for LOTRONEX at 1-888-423-5227 or visit [www.lotronexppl.com](http://www.lotronexppl.com).

TO ENROLL, VISIT [WWW.LOTRONEXPPL.COM](http://WWW.LOTRONEXPPL.COM) OR PHONE 1-888-423-5227 OR COMPLETE THIS FORM IN ITS ENTIRETY AND MAIL OR FAX TO THE FOLLOWING ADDRESS:

**Prescribing Program for LOTRONEX**

Prometheus Client Services

9410 Carroll Park Drive

San Diego, CA 92121

1-888-423-5227

Fax Number: 1-888-824-0896

## Prescribing Program for LOTRONEX™

### Prescriber Enrollment Form



Prometheus will ensure that healthcare providers who prescribe LOTRONEX are specially certified in the Prescribing Program for LOTRONEX (PPL). To become certified, each prescriber enrolls into the Prescribing Program for LOTRONEX by submitting a completed Prescriber Enrollment Form and attesting to the following:

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I agree to:

- provide each of my patients with a copy of the LOTRONEX Medication Guide at initiation of LOTRONEX treatment.
- review the content of the Medication Guide and encourage the patient to read it and ask questions.
- have each patient sign the Patient Acknowledgement Form. The original signed form must be placed in the patient's medical record, and a copy given to the patient.
- inform my patients about the Patient Follow-Up Survey, encourage them to participate and provide them with a Patient Follow-Up Survey Pre-Enrollment Form.
- affix Prescribing Program for LOTRONEX program stickers to written prescriptions for LOTRONEX (i.e., the original and all subsequent prescriptions). Stickers will be provided as part of the Prescribing Program for LOTRONEX. Refills are permitted to be written on prescriptions.
- ensure that all prescriptions for LOTRONEX are written and not transmitted by telephone, facsimile, or computer.

Name of Prescriber (print)

Signature

Date

DEA Number

Office Address:

Office Phone Number:

Office Fax Number:

Upon enrollment, you will receive a prescribing kit for LOTRONEX with the complete Prescribing Information, Prescribing Program for LOTRONEX stickers, multiple copies of the Medication Guide and Patient Acknowledgement Form for LOTRONEX, and instructions for ordering additional supplies of Program materials.

You only need to enroll once, and you are under no obligation to prescribe LOTRONEX.

If you have any questions, please call the Prescribing Program for LOTRONEX at 1-888-423-5227 or visit [www.lotronexppl.com](http://www.lotronexppl.com).

**TO ENROLL, VISIT [WWW.LOTRONEXPPL.COM](http://WWW.LOTRONEXPPL.COM) OR PHONE 1-888-423-5227 OR COMPLETE THIS FORM IN ITS ENTIRETY AND MAIL OR FAX TO THE FOLLOWING ADDRESS:**

#### Prescribing Program for LOTRONEX

Prometheus Client Services  
9410 Carroll Park Drive  
San Diego, CA 92121

1-888-423-5227  
Fax Number: 1-888-824-0896



**PROMETHEUS®**  
Therapeutics & Diagnostics  
*For the person in every patient®*

9410 Carroll Park Drive  
San Diego, CA 92121  
888-423-5227  
888-824-0896 fax

[www.prometheuslabs.com](http://www.prometheuslabs.com)

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XX Month 20XX

Dear Prescriber:

Thank you for your interest in prescribing LOTRONEX<sup>®</sup> (alosetron hydrochloride) tablets.

Enclosed you will find:

- LOTRONEX Prescribing Information
- LOTRONEX Prescribing Program for LOTRONEX (PPL) Prescriber Education Slide Deck (on CD-ROM)
- LOTRONEX Prescriber Enrollment Form
- LOTRONEX Medication Guide

The instructions and requirements for enrolling in the Prescribing Program for LOTRONEX<sup>™</sup> (PPL) are included in the Prescriber Enrollment Form enclosed. A completed Prescriber Enrollment Form should be faxed to Prometheus Client Services at 1-888-824-0896.

Once we have received your enrollment form, a Prescribing Program for LOTRONEX kit will be mailed to you.

If you have any questions regarding the information, materials received, or if your packet is missing any of the above listed items, please contact Prometheus Client Services at 1-888-423-5227.

Sincerely,

Client Services  
Prometheus Laboratories Inc.



**LOTRONEX<sup>®</sup>  
(alosetron HCl) Tablets:**

Understanding the Benefits  
and Risks

**The Prescribing Program for LOTRONEX<sup>™</sup>  
Prescriber Education Slide Deck**

PROMETHEUS, LOTRONEX, the LOTRONEX design mark, and the Prescribing Program for LOTRONEX are trademarks or registered trademarks of Prometheus Laboratories Inc.

Please see complete Prescribing Information for LOTRONEX.

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**LOTRONEX<sup>®</sup>  
(alosetron HCl) Tablets:**

Understanding the Benefits  
and Risks

**The Prescribing Program for  
LOTRONEX<sup>™</sup>  
Prescriber Education Slide Deck**

**PROMETHEUS, LOTRONEX, the LOTRONEX design mark, and the Prescribing Program for LOTRONEX are trademarks or registered trademarks of Prometheus Laboratories Inc.**

**Please see complete Prescribing Information for LOTRONEX.**

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# Section 1: Purpose



## Section 1: Purpose



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

- By reviewing the information provided in this presentation, prescribers who prescribe LOTRONEX 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).**

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

- By reviewing the information provided in this presentation, prescribers who prescribe LOTRONEX 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<sup>®</sup> 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.

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## Goal 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 LOTRONEX (alosetron hydrochloride) by ensuring that LOTRONEX is 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 are communicated to patients, pharmacists, and prescribers.**

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- **To ensure that the risk of IC and serious CoC with the use of LOTRONEX are communicated to patients, pharmacists, and prescribers.**



## Goal 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.
- **pharmacists may only dispense LOTRONEX from prescriptions with a sticker and written by prescribers participating in the PPL.**

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## Goals of the Prescribing Program for LOTRONEX™ and Key Elements (cont'd)

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## **Section 2: Indication and Usage**



## Section 2: Indication and Usage



## LOTRONEX<sup>®</sup> (alosetron HCl): Indication and Usage

LOTRONEX<sup>®</sup> (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.

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Please see complete Prescribing Information for LOTRONEX for full details.





## LOTRONEX<sup>®</sup> (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.

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## LOTRONEX<sup>®</sup> (alosetron HCl): Indication and Usage (cont'd)

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**Please see complete Prescribing Information for LOTRONEX for full details.**

## **Section 3: Important Safety Information**

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

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## LOTRONEX<sup>®</sup> (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<sup>™</sup> 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.

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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.

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## 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.**

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**Please see complete Prescribing Information for LOTRONEX for full details about risks.**



## LOTRONEX<sup>®</sup> (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.

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## LOTRONEX<sup>®</sup> (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**

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## LOTRONEX<sup>®</sup> (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.

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## LOTRONEX<sup>®</sup> (alosetron HCl): Warnings and Precautions (cont'd)

### Ischemic Colitis (cont'd)

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## 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.**

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## LOTRONEX<sup>®</sup> (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.

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### 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.

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### 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.

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## LOTRONEX<sup>®</sup> (alose tron HCl):

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## LOTRONEX<sup>®</sup> (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.

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## LOTRONEX<sup>®</sup> (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.

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### Use in Specific Populations (cont'd)

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## Adverse Reactions Reported in >1% of IBS Patients<sup>a</sup>

Gastrointestinal Adverse Reactions	LOTROXEX® (alosetron HCl) 1 mg BID (n=8,328 <sup>b</sup> )	Placebo (n=2,363)
Constipation <sup>c</sup>	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%

<sup>a</sup> Reported in ≥1% of LOTROXEX patients and occurring more frequently on LOTROXEX 1mg twice-a-day than on placebo.

<sup>b</sup> Data reported from 22 repeat-dose studies in patients with IBS treated for 8 to 24 weeks.

<sup>c</sup> P<0.0001 vs placebo.

Please see complete Prescribing Information for LOTROXEX for full details about risks.

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<sup>b</sup> Data reported from 22 repeat-dose studies in patients with IBS treated for 8 to 24 weeks.

<sup>c</sup>  $P < 0.0001$  vs placebo.

**Please see complete Prescribing Information for LOTRONEX for full details about risks.**





## LOTRONEX<sup>®</sup> (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 patients with IBS 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.

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## LOTRONEX<sup>®</sup> (alosetron HCl): Overdosage

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

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## **Section 4:**

### **How to Prescribe and Dispense LOTRONEX<sup>®</sup> (alose tron HCl) Tablets**

Please see complete Prescribing Information for LOTRONEX for full details.

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### How to Prescribe and Dispense LOTRONEX<sup>®</sup> (alose tron HCl) Tablets

Please see complete Prescribing Information for LOTRONEX for full details.



## LOTRONEX<sup>®</sup> (alosetron HCl): Dosage and Administration

For safety reasons, only prescribers who enroll in the Prescribing Program for LOTRONEX<sup>™</sup> (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 daily, the dose used in controlled clinical trials.

Please see complete Prescribing Information for LOTRONEX for full details.

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## LOTRONEX<sup>®</sup> (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.

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## LOTRONEX<sup>®</sup> (alosetron HCl): Dosage and Administration (cont'd)

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## LOTRONEX<sup>®</sup> (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.

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# **Section 5:**

## **Prescribing Program for LOTRONEX™ (PPL)**



# 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® for severe diarrhea-predominant IBS.
- Prescribers then complete the Prescriber Enrollment Form at [www.lotronexppl.com](http://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.

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## 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) 33

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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™

- Once you have selected an appropriate patient for therapy, review the Medication Guide and explain the risks of LOTRONEX® 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.

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## Inform Your Patients about the Requirements of the Prescribing Program for LOTRONEX™

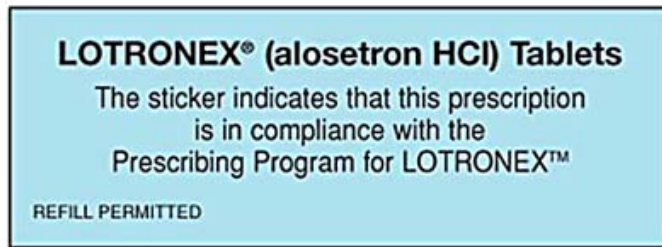
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- Answer any questions the patient may have.
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## The Prescribing Program for LOTRONEX™

- Affix sticker to every prescription:

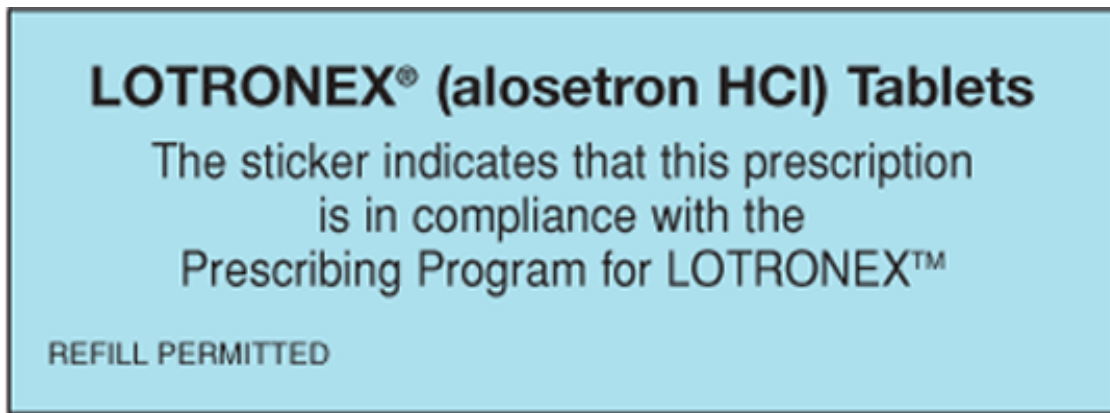


- Refills may be written on prescriptions.
- No telephone, facsimile, or computerized prescriptions are permitted with this program.

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## The Prescribing Program for LOTRONEX™ (PPL)

- Affix the sticker to every prescription:



- 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<sup>®</sup> and each time they refill their prescription.
- not take LOTRONEX if they are constipated.
- immediately discontinue LOTRONEX 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.

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## Patient Responsibilities

### Patients should be instructed to:

- read the Medication Guide before starting LOTRONEX<sup>®</sup> and each time they refill their prescription.
- not take LOTRONEX if they are constipated.
- immediately discontinue LOTRONEX 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.

Patients should be instructed to (cont'd):

- resume LOTRONEX<sup>®</sup> only if their constipation has resolved and after discussion with and the agreement of their treating prescriber.
- stop taking LOTRONEX and contact their prescriber if LOTRONEX does not adequately control IBS symptoms after 4 weeks of taking 1 mg twice-a-day.

## Patient Responsibilities

Patients should be instructed to (cont'd):

- resume LOTRONEX<sup>®</sup> only if their constipation has resolved and after discussion with and the agreement of their treating prescriber.
- stop taking LOTRONEX and contact their prescriber if LOTRONEX 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<sup>®</sup>

- Prometheus sponsors a patient survey to monitor the process of prescribing LOTRONEX in clinical practice.
- The survey is important for monitoring the Prescribing Program for LOTRONEX<sup>™</sup>.



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## Encourage Your Patients to Enroll in the Voluntary Follow-Up Survey for LOTRONEX<sup>®</sup>

- Prometheus sponsors a patient survey to monitor the process of prescribing LOTRONEX in clinical practice.
- The survey is important for monitoring the Prescribing Program for LOTRONEX<sup>™</sup> (PPL).

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LOTRONEX safely and effectively. See full prescribing information for LOTRONEX.

### LOTRONEX (alosetron hydrochloride) Tablets

Initial U.S. Approval: 2000

#### WARNING: SERIOUS GASTROINTESTINAL ADVERSE REACTIONS

See full prescribing information for complete boxed warning.

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.

- Only prescribers who have enrolled in the Prometheus Prescribing Program for LOTRONEX should prescribe LOTRONEX. (5.3)
- LOTRONEX is indicated only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have not responded adequately to conventional therapy. (1)
- Discontinue LOTRONEX immediately in patients who develop constipation or symptoms of ischemic colitis. Do not resume LOTRONEX in patients who develop ischemic colitis. (2.1, 5.1, 5.2)

#### RECENT MAJOR CHANGES

Contraindications, Lack of Understanding of Patient Acknowledgement Form (4.3)	09/2010
Warnings and Precautions, Prescribing Program for LOTRONEX (5.3)	09/2010
Patient Counseling Information (17)	09/2010

#### INDICATIONS AND USAGE

LOTRONEX is a selective serotonin 5-HT<sub>3</sub> 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. (1)

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. (1)

#### DOSAGE AND ADMINISTRATION

- Starting dose is 0.5 mg twice a day (2.1)
- May increase dose to 1 mg twice a day after 4 weeks if starting dosage is well tolerated but does not adequately control IBS symptoms (2.1)
- Discontinue LOTRONEX in patients who have not had adequate control of IBS symptoms after 4 weeks of treatment with 1 mg twice a day. (2.1)

#### DOSAGE FORMS AND STRENGTHS

Tablets: 0.5 and 1 mg (3)

#### CONTRAINDICATIONS

- Do not initiate in patients with constipation (4.1)
- 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 (4.2)
- Inability to understand or comply with the Patient Acknowledgement Form (4.3)
- Concomitant use of fluvoxamine (4.4)

#### WARNINGS AND PRECAUTIONS

- Serious Complications of Constipation: May occur in some patients without warning. Include obstruction, ileus, impaction, toxic megacolon, and secondary bowel ischemia and in rare cases perforation and death have been reported. Risk is increased in patients who are elderly, debilitated, or taking medications that decrease bowel motility. (5.1)
- Discontinue LOTRONEX immediately if constipation occurs. (5.1)
- Ischemic colitis: May occur in some patients without warning. Promptly evaluate patients with signs of ischemic colitis (e.g., rectal bleeding, bloody diarrhea, new or worsening abdominal pain). (5.2)
- Discontinue LOTRONEX immediately if signs of ischemic colitis occur, such as rectal bleeding, bloody diarrhea, or new or worsening abdominal pain. (5.2)
- To prescribe LOTRONEX, prescriber must be enrolled in the Prescribing Program for LOTRONEX and adhere to all components of the Program. (5.3)

#### ADVERSE REACTIONS

Most common adverse reactions (incidence >2% and >placebo) in clinical studies were constipation, abdominal discomfort and pain, nausea, and gastrointestinal discomfort and pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Prometheus at 1-888-423-5227 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

- CYP1A2 inhibitors: Avoid concomitant uses because of increased exposure and half-life of alosetron. Use with fluvoxamine is contraindicated. (4.3, 7.1)
- CYP3A4 inhibitors: Use with caution in combination due to increased exposure of alosetron. (7.2)

#### USE IN SPECIFIC POPULATIONS

- Hepatic impairment: Contraindicated in severe hepatic impairment. Use with caution in patients with mild or moderate hepatic impairment. (4.2, 8.6)
- Geriatric use: Elderly patients may be at greater risk for complications of constipation. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2010

**FULL PRESCRIBING INFORMATION: CONTENTS\***  
**WARNING: SERIOUS GASTROINTESTINAL ADVERSE REACTIONS**

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## FULL PRESCRIBING INFORMATION

### 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 [see *Warnings and Precautions (5.3)*].
- LOTRONEX is indicated only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have not responded adequately to conventional therapy [see *Indications and Usage (1)*]. Before receiving the initial prescription for LOTRONEX, the patient must read and sign the Patient Acknowledgement Form for LOTRONEX [see *Patient Counseling Information (17)*].
- 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 [see *Dosage and Administration (2.1)*, *Warnings and Precautions (5.1)*, *(5.2)*].

## 1 INDICATIONS AND USAGE

LOTRONEX is 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.

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 gastrointestinal 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.

## **2 DOSAGE AND ADMINISTRATION**

For safety reasons, only prescribers who enroll in the Prometheus Prescribing Program for LOTRONEX should prescribe LOTRONEX [*see Warnings and Precautions (5.3)*].

### **2.1 Adult Patients**

To lower the risk of constipation, LOTRONEX should be started at a dosage of 0.5 mg twice a day. Patients who become constipated at this dosage should stop taking LOTRONEX until the constipation resolves. They may be restarted at 0.5 mg once a day. If constipation recurs at the lower dose, LOTRONEX should be discontinued immediately.

Patients well controlled on 0.5 mg once or twice a day may be maintained on this regimen. If after 4 weeks the dosage is well tolerated but does not adequately control IBS symptoms, then the dosage can be increased to 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 can be taken with or without food [*see Clinical Pharmacology (12.3)*].

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.

Clinical trial and postmarketing experience suggest that debilitated patients or patients taking additional medications that decrease gastrointestinal 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.

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 [*see Warnings and Precautions (5.1)*].

### **2.2 Patients With Hepatic Impairment**

LOTRONEX is extensively metabolized by the liver, and increased exposure to LOTRONEX is likely to occur in patients with hepatic impairment. Increased drug exposure may increase the risk of serious adverse reactions. LOTRONEX should be used

with caution in patients with mild or moderate hepatic impairment and is contraindicated in patients with severe hepatic impairment [*see Contraindications (4), Use in Specific Populations (8.6)*].

### **2.3 Information for Pharmacists**

LOTRONEX may be dispensed only on presentation of a prescription for LOTRONEX with a sticker for the Prescribing Program for LOTRONEX attached. A Medication Guide for LOTRONEX must be given to the patient each time LOTRONEX is dispensed as required by law. No telephone, facsimile, or computerized prescriptions are permitted with this program. Refills are permitted to be written on prescriptions.

## **3 DOSAGE FORMS AND STRENGTHS**

0.5 mg and 1 mg tablets

LOTRONEX Tablets, 0.5 mg (0.562 mg alosetron HCl equivalent to 0.5 mg alosetron), are white, oval, film-coated tablets debossed with GX EX1 on one face.

LOTRONEX Tablets, 1 mg (1.124 mg alosetron HCl equivalent to 1 mg alosetron), are blue, oval, film-coated tablets debossed with GX CT1 on one face.

## **4 CONTRAINDICATIONS**

### **4.1 Constipation**

LOTRONEX **should not be initiated** in patients with constipation [*see Warnings and Precautions (5.1)*].

### **4.2 History of Severe Bowel or Hepatic Disorders**

LOTRONEX is contraindicated in patients with a history of the following:

- 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

### **4.3 Lack of Understanding of Patient Acknowledgement Form**

LOTRONEX should not be used by patients who are unable to understand or comply with the Patient Acknowledgement Form for LOTRONEX [*see Patient Counseling Information (17)*].

### **4.4 Concomitant Use of Fluvoxamine**

Concomitant administration of LOTRONEX with fluvoxamine is contraindicated. Fluvoxamine, a known strong inhibitor of CYP1A2, has been shown to increase mean alosetron plasma concentrations (AUC) approximately 6-fold and prolong the half-life by approximately 3-fold [*see Drug Interactions (7.1)*].



## 5 WARNINGS AND PRECAUTIONS

### 5.1 Serious Complications of Constipation

**Some patients have experienced serious complications of constipation without warning.**

Serious complications of constipation, including obstruction, ileus, impaction, toxic megacolon, and secondary bowel ischemia, have been reported with use of LOTRONEX during clinical trials. Complications of constipation have been reported with use of 1 mg twice daily and with lower doses. A dose response relationship has not been established for serious complications of constipation. **The incidence of serious complications of constipation was approximately 0.1% (1 per 1,000 patients) in women receiving either LOTRONEX or placebo.** In addition, rare cases of perforation and death have been reported from postmarketing clinical practice. In some cases, complications of constipation required intestinal surgery, including colectomy. Patients who are elderly, debilitated, or taking additional medications that decrease gastrointestinal motility may be at greater risk for complications of constipation.

LOTRONEX should be discontinued immediately in patients who develop constipation [*see Boxed Warning*].

### 5.2 Ischemic Colitis

**Some patients have experienced 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, the cumulative incidence of ischemic colitis in women receiving LOTRONEX was 0.2% (2 per 1,000 patients, 95% confidence interval 1 to 3) through 3 months and was 0.3% (3 per 1,000 patients, 95% confidence interval 1 to 4) through 6 months.** Ischemic colitis has been reported with use of 1 mg twice daily and with lower doses. A dose-response relationship has not been established. Ischemic colitis was reported in one patient receiving placebo. The patient experience in controlled clinical trials is insufficient to estimate the incidence of ischemic colitis in patients taking LOTRONEX for longer than 6 months.

LOTRONEX should be discontinued immediately in patients with signs of ischemic colitis such as 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.

### 5.3 Prescribing Program for LOTRONEX

To prescribe LOTRONEX, the prescriber must be enrolled in the Prescribing Program for LOTRONEX. To enroll, prescribers must understand the benefits and risks of treatment with LOTRONEX for severe diarrhea-predominant IBS, including the

information in the Prescribing Information, Medication Guide, and Patient Acknowledgement Form for LOTRONEX.

To enroll in the Prescribing Program for LOTRONEX, call 1-888-423-5227 or visit [www.lotronexpl.com](http://www.lotronexpl.com) to complete the Prescriber Enrollment Form.

## 6 ADVERSE REACTIONS

The following adverse reactions are described in more detail in other sections of the label:

- Complications of constipation [see *Boxed Warning, Warnings and Precautions (5.1)*]
- Ischemic colitis [see *Boxed Warning, Warnings and Precautions (5.2)*]

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Patients With Irritable Bowel Syndrome: Table 1 summarizes adverse reactions from 22 repeat-dose studies in patients with IBS who were treated with 1 mg of LOTRONEX twice daily for 8 to 24 weeks. The adverse reactions in Table 1 were reported in 1% or more of patients who received LOTRONEX and occurred more frequently on LOTRONEX than on placebo. A statistically significant difference was observed for constipation in patients treated with LOTRONEX compared to placebo ( $p < 0.0001$ ).

**Table 1. Adverse Reactions Reported in  $\geq 1\%$  of Patients With Irritable Bowel Syndrome and More Frequently on LOTRONEX 1 mg Twice Daily Than Placebo**

Body System Adverse Reaction	Placebo (n = 2,363)	LOTRONEX 1 mg twice daily (n = 8,328)
Gastrointestinal		
Constipation	6%	29%
Abdominal discomfort and pain	4%	7%
Nausea	5%	6%
Gastrointestinal discomfort and pain	3%	5%
Abdominal distention	1%	2%
Regurgitation and reflux	2%	2%
Hemorrhoids	1%	2%

**Gastrointestinal:** Constipation is a frequent and dose-related side effect of treatment with LOTRONEX [see *Warnings and Precautions (5.1)*]. In clinical studies constipation was reported in approximately 29% of patients with IBS treated with LOTRONEX 1 mg twice daily (n = 9,316). This effect was statistically significant compared to placebo (p<0.0001). Eleven percent (11%) of patients treated with LOTRONEX 1 mg twice daily withdrew from the studies due to constipation. Although the number of patients with IBS treated with LOTRONEX 0.5 mg twice daily is relatively small (n = 243), only 11% of those patients reported constipation and 4% withdrew from clinical studies due to constipation. Among the patients treated with LOTRONEX 1 mg twice daily who reported constipation, 75% reported a single episode and most reports of constipation (70%) occurred during the first month of treatment, with the median time to first report of constipation onset of 8 days. Occurrences of constipation in clinical trials were generally mild to moderate in intensity, transient in nature, and resolved either spontaneously with continued treatment or with an interruption of treatment. However, serious complications of constipation have been reported in clinical studies and in postmarketing experience [see *Boxed Warning and Warnings and Precautions (5.1)*]. In Studies 1 and 2, 9% of patients treated with LOTRONEX reported constipation and 4 consecutive days with no bowel movement [see *Clinical Studies (14.2)*]. Following interruption of treatment, 78% of the affected patients resumed bowel movements within a 2-day period and were able to re-initiate treatment with LOTRONEX.

**Hepatic:** A similar incidence in elevation of ALT (>2-fold) was seen in patients receiving LOTRONEX or placebo (1.0% vs. 1.2%). A single case of hepatitis (elevated ALT, AST, alkaline phosphatase, and bilirubin) without jaundice in a patient receiving LOTRONEX was reported in a 12-week study. A causal association with LOTRONEX has not been established.

**Long-Term Safety:** Patient experience in controlled clinical trials is insufficient to estimate the incidence of ischemic colitis in patients taking LOTRONEX for longer than 6 months.

**Women With Severe Diarrhea-Predominant Irritable Bowel Syndrome:** Table 2 summarizes the gastrointestinal adverse reactions from 1 repeat-dose study in female patients with severe diarrhea-predominant IBS who were treated for 12 weeks. The adverse reactions in Table 2 were reported in 3% or more of patients who received LOTRONEX and occurred more frequently with LOTRONEX than with placebo. Other events reported in 3% or more of patients who received LOTRONEX and occurring more frequently with LOTRONEX than with placebo included upper respiratory tract infection, viral gastroenteritis, muscle spasms, headaches, and fatigue.

**Table 2. Gastrointestinal Adverse Reactions Reported in ≥3% of Women With**

**Severe Diarrhea-Predominant Irritable Bowel Syndrome and More Frequently on LOTRONEX Than Placebo.**

Adverse Reaction	Placebo (n = 176)	LOTRONEX 0.5 mg once daily (n = 175)	LOTRONEX 1 mg once daily (n = 172)	LOTRONEX 1 mg twice daily (n = 176)
Constipation	5%	9%	16%	19%
Abdominal pain	3%	5%	6%	7%
Diarrhea	2%	3%	2%	2%
Hemorrhoidal hemorrhage	2%	3%	2%	2%
Flatulence	2%	2%	1%	3%
Hemorrhoids	2%	1%	1%	3%
Abdominal pain upper	1%	3%	1%	1%

Adverse reactions reported in another study of 701 women with severe diarrhea-predominant IBS were similar to those shown in Table 2. Gastrointestinal adverse reactions reported in 3% or more of patients who received LOTRONEX and occurring more frequently with LOTRONEX than with placebo included constipation (14% and 10% of patients taking LOTRONEX 1 mg twice daily or 0.5 mg as needed, respectively, compared with 2% taking placebo), abdominal pain, nausea, vomiting, and flatulence. Other events reported in 3% or more of patients who received LOTRONEX and occurring more frequently with LOTRONEX than with placebo included nasopharyngitis, sinusitis, upper respiratory tract infection, urinary tract infection, viral gastroenteritis, and cough.

**Constipation:** Constipation was the most frequent adverse reaction among women with severe diarrhea-predominant IBS represented in Table 2. There was a dose response in the groups treated with LOTRONEX in the number of patients withdrawn due to constipation (2% on placebo, 5% on 0.5 mg once daily, 8% on 1 mg once daily, and 11% on 1 mg twice daily). Among these patients with severe diarrhea-predominant IBS treated with LOTRONEX who reported constipation most (75%) reported one episode which occurred within the first 15 days of treatment and persisted for 4 to 5 days.

**Other Events Observed During Clinical Evaluation of LOTRONEX:** During its assessment in clinical trials, multiple and single doses of LOTRONEX were administered, resulting in 11,874 subject exposures in 86 completed clinical studies. The conditions, dosages, and duration of exposure to LOTRONEX varied between trials, and the studies included healthy male and female volunteers as well as male and female patients with IBS and other indications.

In the listing that follows, reported adverse reactions were classified using a standardized coding dictionary. Only those events that an investigator believed were

possibly related to LOTRONEX, occurred in at least 2 patients, and occurred at a greater frequency during treatment with LOTRONEX than during placebo administration are presented. Serious adverse reactions occurring in at least 1 patient for whom an investigator believed there was reasonable possibility that the event was related to treatment with LOTRONEX and occurring at a greater frequency in patients treated with LOTRONEX than placebo-treated patients are also presented.

In the following listing, events are categorized by body system. Within each body system, events are presented in descending order of frequency. The following definitions are used: *infrequent* adverse reactions are those occurring on one or more occasion in 1/100 to 1/1,000 patients; *rare* adverse reactions are those occurring on one or more occasion in fewer than 1/1,000 patients.

Although the events reported occurred during treatment with LOTRONEX, they were not necessarily caused by it.

**Blood and Lymphatic:** *Rare:* Quantitative red cell or hemoglobin defects, and hemorrhage.

**Cardiovascular:** *Infrequent:* Tachyarrhythmias. *Rare:* Arrhythmias, increased blood pressure, and extrasystoles.

**Drug Interaction, Overdose, and Trauma:** *Rare:* Contusions and hematomas.

**Ear, Nose, and Throat:** *Rare:* Ear, nose, and throat infections; viral ear, nose, and throat infections; and laryngitis.

**Endocrine and Metabolic:** *Rare:* Disorders of calcium and phosphate metabolism, hyperglycemia, hypothalamus/pituitary hypofunction, hypoglycemia, and fluid disturbances.

**Eye:** *Rare:* Light sensitivity of eyes.

**Gastrointestinal:** *Infrequent:* Hyposalivation, dyspeptic symptoms, gastrointestinal spasms, ischemic colitis [*see Warnings and Precautions (5.2)*], and gastrointestinal lesions. *Rare:* Abnormal tenderness, colitis, gastrointestinal signs and symptoms, proctitis, diverticulitis, positive fecal occult blood, hyperacidity, decreased gastrointestinal motility and ileus, gastrointestinal obstructions, oral symptoms, gastrointestinal intussusception, gastritis, gastroduodenitis, gastroenteritis, and ulcerative colitis.

**Hepatobiliary Tract and Pancreas:** *Rare:* Abnormal bilirubin levels and cholecystitis.

**Lower Respiratory:** *Infrequent:* Breathing disorders.

**Musculoskeletal:** *Rare:* Muscle pain; muscle stiffness, tightness and rigidity; and bone and skeletal pain.

**Neurological:** *Infrequent:* Hypnagogic effects. *Rare:* Memory effects, tremors, dreams, cognitive function disorders, disturbances of sense of taste, disorders of equilibrium, confusion, sedation, and hypoesthesia.

**Non-Site Specific:** *Infrequent:* Malaise and fatigue, cramps, pain, temperature

regulation disturbances. *Rare*: Burning sensations, hot and cold sensations, cold sensations, and fungal infections.

*Psychiatry: Infrequent*: Anxiety. *Rare*: Depressive moods.

*Reproduction: Rare*: Sexual function disorders, female reproductive tract bleeding and hemorrhage, reproductive infections, and fungal reproductive infections.

*Skin: Infrequent*: Sweating and urticaria. *Rare*: Hair loss and alopecia; acne and folliculitis; disorders of sweat and sebum; allergic skin reaction; eczema; skin infections; dermatitis and dermatosis; and nail disorders.

*Urology: Infrequent*: Urinary frequency. *Rare*: Bladder inflammation; polyuria and diuresis; and urinary tract hemorrhage.

## **6.2 Postmarketing Experience**

In addition to events reported in clinical trials, the following events have been identified during use of LOTRONEX in clinical practice. Because they were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to LOTRONEX.

Gastrointestinal: Impaction, perforation, ulceration, small bowel mesenteric ischemia.

Neurological: Headache.

Skin: Rash.

## **7 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.

### **7.1 CYP1A2 Inhibitors**

Fluvoxamine is a known strong inhibitor of CYP1A2 and also inhibits CYP3A4, CYP2C9, and CYP2C19. In a pharmacokinetic study, 40 healthy female subjects received fluvoxamine in escalating doses from 50 to 200 mg/ day for 16 days, with coadministration of alosetron 1 mg on the last day. Fluvoxamine increased mean alosetron plasma concentrations (AUC) approximately 6-fold and prolonged the half-life by approximately 3-fold. Concomitant administration of alosetron and fluvoxamine is contraindicated [*see Contraindications (4.3)*].

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.

### **7.2 CYP3A4 Inhibitors**

Ketoconazole is a known strong inhibitor of CYP3A4. In a pharmacokinetic study, 38 healthy female subjects received ketoconazole 200 mg twice daily for 7 days, with coadministration of alosetron 1 mg on the last day. Ketoconazole increased mean

alosetron plasma concentrations (AUC) by 29%. 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.

### **7.3 Other CYP Enzymes**

*In vitro* human liver microsome studies and an *in vivo* metabolic probe study demonstrated that alosetron did not inhibit CYP enzymes 3A4, 2C9, or 2C19. *In vitro* at total drug concentrations 27-fold higher than peak plasma concentrations observed with the 1 mg dose, alosetron inhibited CYP enzymes 1A2 (60%) and 2E1 (50%). In an *in vivo* metabolic probe study, alosetron did not inhibit CYP2E1 but did produce 30% inhibition of both CYP1A2 and N-acetyltransferase. Although not studied with alosetron, inhibition of N-acetyltransferase may have clinically relevant consequences for drugs such as isoniazid, procainamide, and hydralazine. The effect on CYP1A2 was explored further in a clinical interaction study with theophylline and no effect on metabolism was observed. Another study showed that alosetron had no clinically significant effect on plasma concentrations of the oral contraceptive agents ethinyl estradiol and levonorgestrel (CYP3A4 substrates). A clinical interaction study was also conducted with alosetron and the CYP3A4 substrate cisapride. No significant effects on cisapride metabolism or QT interval were noted. The effects of alosetron on monoamine oxidases and on intestinal first pass secondary to high intraluminal concentrations have not been examined. Based on the above data from *in vitro* and *in vivo* studies, it is unlikely that alosetron will inhibit the hepatic metabolic clearance of drugs metabolized by the CYP enzymes 2C9, 2C19, or 2E1.

Alosetron does not appear to induce the major cytochrome P450 drug-metabolizing enzyme 3A. Alosetron also does not appear to induce CYP enzymes 2E1 or 2C19. It is not known whether alosetron might induce other enzymes.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

Teratogenic Effects: Pregnancy Category B. Reproduction studies have been performed in rats at doses up to 40 mg/kg/day (about 160 times the recommended human dose based on body surface area) and rabbits at oral doses up to 30 mg/kg/day (about 240 times the recommended daily human dose based on body surface area). These studies have revealed no evidence of impaired fertility or harm to the fetus due to alosetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, LOTRONEX should be used during pregnancy only if clearly needed.

### **8.3 Nursing Mothers**

Alosetron and/or metabolites of alosetron are excreted in the breast milk of lactating rats. It is not known whether alosetron is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when LOTRONEX is administered to a nursing woman.

#### **8.4 Pediatric Use**

Safety and effectiveness in pediatric patients have not been established. Use of LOTRONEX is not recommended in the pediatric population, based upon the risk of serious complications of constipation and ischemic colitis in adults.

#### **8.5 Geriatric Use**

In some studies in healthy men or women, plasma concentrations were elevated by approximately 40% in individuals 65 years and older compared to young adults [*see Warnings and Precautions (5.1)*]. However, this effect was not consistently observed in men.

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 [*see Warnings and Precautions (5.1)*].

#### **8.6 Hepatic Impairment**

Due to the extensive hepatic metabolism of alosetron, 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.

A single 1 mg oral dose of alosetron was administered to 1 female and 5 male patients with moderate hepatic impairment (Child-Pugh score of 7 to 9) and to 1 female and 2 male patients with severe hepatic impairment (Child-Pugh score of >9). In comparison with historical data from healthy subjects, patients with severe hepatic impairment displayed higher systemic exposure to alosetron. The female with severe hepatic impairment displayed approximately 14-fold higher exposure, while the female with moderate hepatic impairment displayed approximately 1.6-fold higher exposure, than healthy females. Due to the small number of subjects and high intersubject variability in the pharmacokinetic findings, no definitive quantitative conclusions can be made. However, due to the greater exposure to alosetron in the female with severe hepatic impairment, alosetron should not be used in females with severe hepatic impairment [*see Dosage and Administration (2.2), Contraindications (4)*].

#### **8.7 Renal Impairment**

Renal impairment (creatinine clearance 4 to 56 mL/min) has no effect on the renal elimination of alosetron due to the minor contribution of this pathway to elimination. The effect of renal impairment on metabolite pharmacokinetics and the effect of end-stage renal disease have not been assessed.

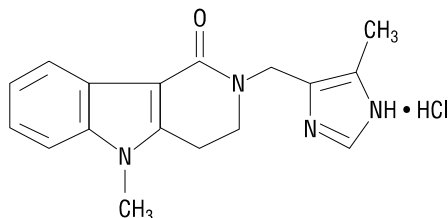


## 10 OVERDOSAGE

There is no specific antidote for overdose of LOTRONEX. Patients should be managed with appropriate supportive therapy. Individual oral doses as large as 16 mg have been administered in clinical studies without significant adverse reactions. This dose is 8 times higher than the recommended total daily dose. Inhibition of the metabolic elimination and reduced first pass of other drugs might occur with overdoses of LOTRONEX [see *Drug Interactions (7)*].

## 11 DESCRIPTION

The active ingredient in LOTRONEX Tablets is alosetron hydrochloride (HCl), a potent and selective antagonist of the serotonin 5-HT<sub>3</sub> receptor type. Chemically, alosetron is designated as 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one, monohydrochloride. Alosetron is achiral and has the empirical formula C<sub>17</sub>H<sub>18</sub>N<sub>4</sub>O•HCl, representing a molecular weight of 330.8. Alosetron is a white to beige solid that has a solubility of 61 mg/mL in water, 42 mg/mL in 0.1M hydrochloric acid, 0.3 mg/mL in pH 6 phosphate buffer, and <0.1 mg/mL in pH 8 phosphate buffer. The chemical structure of alosetron is:



LOTROXEX Tablets are supplied for oral administration as 0.5 mg (white) and 1 mg (blue) tablets. The 0.5 mg tablet contains 0.562 mg alosetron HCl equivalent to 0.5 mg alosetron, and the 1 mg tablet contains 1.124 mg alosetron HCl equivalent to 1 mg of alosetron. Each tablet also contains the inactive ingredients lactose (anhydrous), magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The white film coat for the 0.5 mg tablet contains hypromellose, titanium dioxide, and triacetin. The blue film coat for the 1 mg tablet contains hypromellose, titanium dioxide, triacetin, and indigo carmine.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Alosetron is a potent and selective 5-HT<sub>3</sub> receptor antagonist. 5-HT<sub>3</sub> receptors are ligand-gated cation channels that are extensively distributed on enteric neurons in the human gastrointestinal tract, as well as other peripheral and central locations. Activation of these channels and the resulting neuronal depolarization affect the regulation of

visceral pain, colonic transit, and gastrointestinal secretions, processes that relate to the pathophysiology of IBS. 5-HT<sub>3</sub> receptor antagonists such as alosetron inhibit activation of non-selective cation channels, which results in the modulation of the enteric nervous system.

The cause of IBS is unknown. IBS is characterized by visceral hypersensitivity and hyperactivity of the gastrointestinal tract, which lead to abnormal sensations of pain and motor activity. Following distention of the rectum, patients with IBS exhibit pain and discomfort at lower volumes than healthy volunteers. Following such distention, alosetron reduced pain and exaggerated motor responses, possibly due to blockade of 5-HT<sub>3</sub> receptors.

## **12.2 Pharmacodynamics**

In healthy volunteers and patients with IBS, alosetron (2 mg orally, twice daily for 8 days) increased colonic transit time without affecting orocecal transit time. In healthy volunteers, alosetron also increased basal jejunal water and sodium absorption after a single 4 mg dose. In patients with IBS, multiple oral dosages of alosetron (4 mg twice daily for 6.5 days) significantly increased colonic compliance.

Single oral doses of alosetron administered to healthy men produced a dose-dependent reduction in the flare response seen after intradermal injection of serotonin. Urinary 6- $\beta$ -hydroxycortisol excretion decreased by 52% in elderly subjects after 27.5 days of alosetron 2 mg administered orally twice daily. This decrease was not statistically significant. In another study utilizing alosetron 1 mg administered orally twice daily for 4 days, there was a significant decrease in urinary 6- $\beta$ -hydroxycortisol excretion. However, there was no change in the ratio of 6- $\beta$ -hydroxycortisol to cortisol, indicating a possible decrease in cortisol production. The clinical significance of these findings is unknown.

## **12.3 Pharmacokinetics**

The pharmacokinetics of alosetron have been studied after single oral doses ranging from 0.05 to 16 mg in healthy men. The pharmacokinetics of alosetron have also been evaluated in healthy women and men and in patients with IBS after repeated oral dosages ranging from 1 mg twice daily to 8 mg twice daily.

**Absorption:** Alosetron was rapidly absorbed after oral administration with a mean absolute bioavailability of approximately 50% to 60% (approximate range, 30% to >90%). After administration of radiolabeled alosetron, only 1% of the dose was recovered in the feces as unchanged drug. Following oral administration of a 1 mg alosetron dose to young men, a peak plasma concentration of approximately 5 ng/mL occurred at 1 hour. In young women, the mean peak plasma concentration was approximately 9 ng/mL, with a similar time to peak.

Plasma concentrations were 30% to 50% lower and less variable in men compared to women given the same oral dose. Population pharmacokinetic analysis in IBS patients confirmed that alosetron concentrations were influenced by gender (27% lower in men).

**Food Effects:** Alosetron absorption is decreased by approximately 25% by co-administration with food, with a mean delay in time to peak concentration of 15 minutes [*see Dosage and Administration (2.1)*].

**Distribution:** Alosetron demonstrates a volume of distribution of approximately 65 to 95 L. Plasma protein binding is 82% over a concentration range of 20 to 4,000 ng/mL.

**Metabolism and Elimination:** Plasma concentrations of alosetron increase proportionately with increasing single oral doses up to 8 mg and more than proportionately at a single oral dose of 16 mg. Twice-daily oral dosing of alosetron does not result in accumulation. The terminal elimination half-life of alosetron is approximately 1.5 hours (plasma clearance is approximately 600 mL/min). Population pharmacokinetic analysis in patients with IBS confirmed that alosetron clearance is minimally influenced by doses up to 8 mg.

Renal elimination of unchanged alosetron accounts for only 13% of the dose. Renal clearance is approximately 112 mL/min.

A study with <sup>14</sup>C-labeled alosetron in Caucasian males (n = 3) and females (n = 3) and an Asian male (n = 1) showed similar serum metabolite profiles. Unchanged alosetron was the major component in serum, with other metabolites being present at low concentrations, none amounting to more than 15% of the unmetabolized alosetron concentration. The circulating metabolites were identified as 6-hydroxy glucuronide, 6-hydroxy sulphate, 7-hydroxy sulphate, hydroxymethyl imidazole, and mono- and bis-oxygenated imidazole derivatives of alosetron. The metabolites are unlikely to contribute to the biological activity of alosetron. Of the circulating Phase I metabolites, only the hydroxymethyl imidazole has weak pharmacological activity, around 10-fold less potent than alosetron. Total recovery of radioactivity in the excreta was 85 ± 6%. The majority of the radiolabeled dose is excreted in the urine (74 ± 5%). The major urinary metabolites were the 6-hydroxy glucuronide and the mono- and bis-oxygenated imidazole derivatives of alosetron. 11 ± 4% of the radiolabeled dose was excreted in the feces with less than 1% of the dose being excreted as the unchanged alosetron.

Alosetron is metabolized by human microsomal cytochrome P450 (CYP), shown *in vitro* to involve enzymes 2C9 (30%), 3A4 (18%), and 1A2 (10%). Non-CYP-mediated Phase I metabolic conversion also contributes to an extent of about 11%. However, *in vivo* data suggest that CYP1A2 plays a more prominent role in alosetron metabolism (62 to 97% of alosetron clearance) based on correlation of alosetron clearance with *in vivo* CYP1A2 activity measured by probe substrate, increased clearance induced by smoking, and inhibition of clearance by fluvoxamine [*see Contraindications (4), Drug Interactions (7)*].

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

In 2-year oral studies, alosetron was not carcinogenic in mice at doses up to 30 mg/kg/day or in rats at doses up to 40 mg/kg/day. These doses are about 60 to 160 times, respectively, the recommended human dose of alosetron of 2 mg/day (1 mg twice daily) based on body surface area. Alosetron was not genotoxic in the Ames tests, the mouse lymphoma cell (L5178Y/TK<sup>±</sup>) forward gene mutation test, the human lymphocyte chromosome aberration test, the ex vivo rat hepatocyte unscheduled DNA synthesis (UDS) test, or the *in vivo* rat micronucleus test for mutagenicity. Alosetron at oral doses up to 40 mg/kg/day (about 160 times the recommended daily human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male or female rats.

## **14 CLINICAL STUDIES**

### **14.1 Dose-Ranging Study**

Data from a dose-ranging study of women (n = 85) who received LOTRONEX 0.5 mg twice daily indicated that the incidence of constipation (14%) was lower than that experienced by women receiving 1 mg twice daily (29%). Therefore, to lower the risk of constipation, LOTRONEX should be started at a dosage of 0.5 mg twice a day. The efficacy of the 0.5 mg twice-daily dosage in treating severe diarrhea-predominant IBS has not been adequately evaluated in clinical trials. [*See Dosage and Administration (2.1)*]

## 14.2 Efficacy Studies

LOTRONEX has been studied in women with IBS in five 12-week US multicenter, randomized, double-blind, placebo-controlled clinical studies.

**Table 3. Efficacy Studies Conducted in Women With Irritable Bowel Syndrome (IBS)**

Study	Patient Population	Placebo (n)	LOTRONEX Dose (n)
1 and 2	Non-constipated women with IBS	(640)	1 mg twice daily (633)
3 and 4	Women with severe diarrhea-predominant IBS (defined as bowel urgency $\geq 50\%$ of days)	(515)	1 mg twice daily (778)
5	Women with severe diarrhea-predominant IBS (defined as average pain $\geq$ moderate, urgency $\geq 50\%$ of days, and/or restriction of daily activities $\geq 25\%$ of days)	(176)	0.5 mg once daily (177)
			1 mg once daily (175)
			1 mg twice daily (177)

**Studies in Non-Constipated Women with Irritable Bowel Syndrome:** Studies 1 and 2 were conducted in non-constipated women with IBS meeting the Rome Criteria<sup>1</sup> for at least 6 months. Women with severe pain or a history of severe constipation were excluded. A 2-week run-in period established baseline IBS symptoms.

About two thirds of the women had diarrhea-predominant IBS. Compared with placebo, 10% to 19% more women with diarrhea-predominant IBS who received LOTRONEX had adequate relief of IBS abdominal pain and discomfort during each month of the study.

**Studies in Women With Severe Diarrhea-Predominant Irritable Bowel Syndrome:** LOTRONEX is indicated only for women with severe diarrhea-predominant IBS [see *Indications and Usage (1)*]. The efficacy of LOTRONEX in this subset of the women studied in clinical trials is supported by prospective and retrospective analyses.

**Prospective Analyses:** Studies 3 and 4 were conducted in women with diarrhea-predominant IBS and bowel urgency on at least 50% of days at entry. Women receiving LOTRONEX had significant increases over placebo (13% to 16%) in the median percentage of days with urgency control.

The lower gastrointestinal functions of stool consistency, stool frequency, and sense of incomplete evacuation were also evaluated by patients' daily reports. Stool consistency was evaluated on a scale of 1 to 5 (1 = very hard, 2 = hard, 3 = formed,

4 = loose, and 5 = watery). At baseline, average stool consistency was approximately 4 (loose) for both treatment groups. During the 12 weeks of treatment, the average stool consistency decreased to approximately 3.0 (formed) for patients who received LOTRONEX and 3.5 for the patients who received placebo in the 2 studies.

At baseline, average stool frequency was approximately 3.2 per day for both treatment groups. During the 12 weeks of treatment, the average daily stool frequency decreased to approximately 2.1 and 2.2 for patients receiving LOTRONEX and 2.7 and 2.8 for patients receiving placebo in the 2 studies.

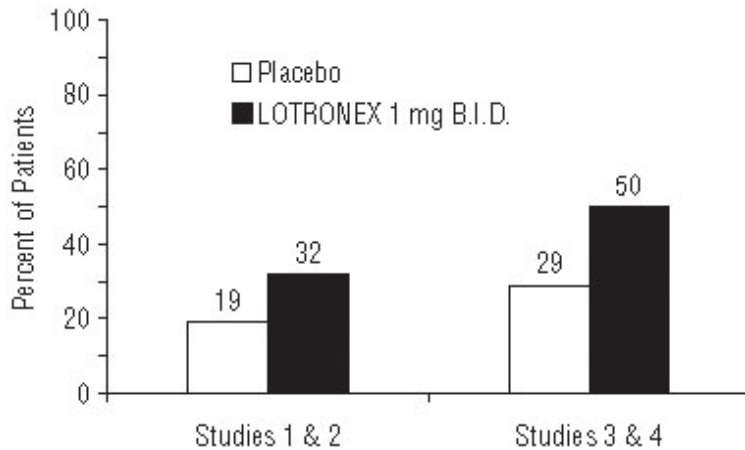
There was no consistent effect upon the sense of incomplete evacuation during the 12 weeks of treatment for patients receiving LOTRONEX as compared to patients receiving placebo in either study.

Study 5 was conducted in women with severe diarrhea-predominant IBS and 1 or more of the following: frequent and severe abdominal pain or discomfort, frequent bowel urgency or fecal incontinence, disability or restriction of daily activities due to IBS. To evaluate the proportion of patients who responded to treatment, patients were asked every 4 weeks to compare their IBS symptoms during the previous month of treatment with how they usually felt during the 3 months prior to the study using an ordered 7-point scale (substantially worse to substantially improved). A responder was defined as a subject who reported moderate or substantial improvement on this global improvement scale (GIS). At Week 12, all three groups receiving LOTRONEX had significantly greater percentages of GIS responders compared to the placebo group (43% to 51% vs. 31%) using a Last Observation Carried Forward (LOCF) analysis. It should be noted that approximately 4% of subjects in each LOTRONEX dose group who were classified as responders using this approach were observed only through week 4. At each of the 4 week intervals of the treatment phase, all three dosages of LOTRONEX provided improvement in the average adequate relief rate of IBS pain and discomfort, stool consistency, stool frequency, and sense of urgency compared with placebo.

*Retrospective Analyses:* In analyses of patients from Studies 1 and 2 who had diarrhea-predominant IBS and indicated their baseline run-in IBS symptoms were severe at the start of the trial, LOTRONEX provided greater adequate relief of IBS pain and discomfort than placebo. In further analyses of Studies 1 and 2, 57% of patients had urgency at baseline on 5 or more days per week. In this subset, 32% of patients on LOTRONEX had urgency no more than 1 day in the last week of the trial, compared with 19% of patients on placebo.

In Studies 3 and 4, 66% of patients had urgency at baseline on 5 or more days per week. In this subset, 50% of patients on LOTRONEX had urgency no more than 1 day in the last week of the trial, compared with 29% of patients on placebo. Moreover, in the same subset, 12% on LOTRONEX had urgency no more than 2 days per week in any of the 12 weeks on treatment compared with 1% of placebo patients.

**Figure 1. Percent of Patients With Urgency on >5 Days/Week at Baseline Who Improved to No More Than 1 Day in the Final Week**



In Studies 1 and 2, patient-reported subjective outcomes related to IBS were assessed by questionnaires obtained at baseline and week 12. Patients in the more severe subset who received LOTRONEX reported less difficulty sleeping, less tiredness, fewer eating problems, and less interference with social activities and work/main activities due to IBS symptoms or problems compared to those who received placebo. Change in the impact of IBS symptoms and problems on emotional and mental distress and on physical and sexual activity in women who received LOTRONEX were not statistically different from those reported by women who received placebo.

### **14.3 Long-Term Use**

In a 48-week multinational, double-blind, placebo-controlled study, LOTRONEX 1 mg twice daily was evaluated in 714 women with non-constipated IBS. A retrospective analysis of the subset of women with severe diarrhea-predominant IBS (urgency on at least 10 days during the 2-week baseline period) was performed. Of the 417 patients with severe diarrhea-predominant IBS, 62% completed the trial.

LOTRONEX (n = 198) provided a greater average rate of adequate relief of IBS pain and discomfort (52% vs. 41%) and a greater average rate of satisfactory control of bowel urgency (60% vs. 48%) compared with placebo (n = 219). Significant improvement of these symptoms occurred for most of the 48-week treatment period with no evidence of tachyphylaxis.

## 15 REFERENCES

1. Thompson WG, Creed F, Drossman DA, et al. Functional bowel disease and functional abdominal pain. *Gastroenterol Int.* 1992;5:75-91.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

LOTROXEX Tablets, 0.5 mg (0.562 mg alosetron HCl equivalent to 0.5 mg alosetron) are white, oval, film-coated tablets debossed with GX EX1 on one face.

Bottles of 30 (NDC 65483-894-03) with child-resistant closures.

LOTROXEX Tablets, 1 mg (1.124 mg alosetron HCl equivalent to 1 mg alosetron), are blue, oval, film-coated tablets debossed with GX CT1 on one face.

Bottles of 30 (NDC 65483-895-03) with child-resistant closures.

**Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from light and moisture.**

## 17 PATIENT COUNSELING INFORMATION

*See Medication Guide*

### **Prescriber and Patient Responsibilities**

Patients should be fully counseled on and understand the risks and benefits of LOTROXEX before an initial prescription is written. The patient may be educated by the enrolled prescriber or a healthcare provider under a prescriber's direction.

Prescribers must:

- counsel patients for whom LOTROXEX is appropriate about the benefits and risks of LOTROXEX and discuss the impact of IBS symptoms on the patient's life.
- give the patient a copy of the Medication Guide, which outlines the benefits and risks of LOTROXEX, and instruct the patient to read it carefully. Answer all questions the patient may have about LOTROXEX. The complete text of the Medication Guide is printed at the end of this document.
- review the Patient Acknowledgement Form for LOTROXEX with the patient, answer all questions, and give a copy of the signed Patient Acknowledgement Form to the patient.
- provide each patient with appropriate instructions for taking LOTROXEX.

Copies of the Patient Acknowledgement Form for LOTROXEX and additional copies of the Medication Guide are available by contacting Prometheus at 1-888-423-5227 or visiting [www.lotronexppl.com](http://www.lotronexppl.com).

Patients who are prescribed LOTROXEX should be instructed to:

- read the Medication Guide before starting LOTROXEX and each time they refill their prescription.
- not start taking LOTROXEX if they are constipated.



- immediately discontinue LOTRONEX 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. Contact their prescriber again if their constipation does not resolve after discontinuation of LOTRONEX. Resume LOTRONEX only if their constipation has resolved and after discussion with and the agreement of their treating prescriber.
- stop taking LOTRONEX and contact their prescriber if LOTRONEX does not adequately control IBS symptoms after 4 weeks of taking 1 mg twice a day.

## Medication Guide

### MEDICATION GUIDE LOTRONEX<sup>®</sup> (LOW-trah-nex) Tablets (alosetron hydrochloride)

**Before using LOTRONEX for the first time, you should:**

- Understand that LOTRONEX has serious risks for some people.
- Read and follow the directions in this Medication Guide.
- Sign a Patient Acknowledgement Form.

Read this Medication Guide carefully before you sign the Patient Acknowledgement Form. You must sign the Patient Acknowledgement Form before you start LOTRONEX. Read the Medication Guide you get with each refill for LOTRONEX. There may be new information. This Medication Guide does not take the place of talking with your doctor.

#### **1. What is the most important information I should know about LOTRONEX?**

**A. LOTRONEX is a medicine only for some women with severe chronic irritable bowel syndrome (IBS) whose:**

- main problem is diarrhea and
- IBS symptoms have not been helped enough by other treatments.

**B. Some patients have developed serious bowel side effects while taking LOTRONEX. Serious bowel (intestine) side effects can happen suddenly, including the following.**

- 1. Serious complications of constipation:** About 1 out of every 1,000 women who take LOTRONEX may get serious complications of constipation. These complications **may lead to a hospital stay and, in rare cases, blood transfusions, surgery, and death.** People who are older, who are weak from illness, or who take other constipating medicines may be more likely to have serious complications of constipation with LOTRONEX.

**To lower your chances of getting serious complications of constipation, do the following:**

- **If you are constipated,** do not start taking LOTRONEX.
  - **If you get constipated while taking LOTRONEX,** stop taking it right away and call your doctor.
  - **If your constipation does not get better after stopping LOTRONEX,** call your doctor again.
  - **If you stopped taking LOTRONEX, do not start taking LOTRONEX again** unless your doctor tells you to do so.
- 2. Ischemic colitis (reduced blood flow to the bowel):** About 3 out of every 1,000 women who take LOTRONEX over a 6-month period may get a serious

problem where blood flow to parts of the large bowel is reduced. This is called ischemic colitis. The chance of getting ischemic colitis when you take LOTRONEX for more than 6 months is not known. **Ischemic colitis may lead to a hospital stay and, in rare cases, blood transfusions, surgery, and death.**

**To lower your chances of getting serious complications of ischemic colitis, stop taking LOTRONEX and call your doctor right away if you get:**

- new or worse pain in your stomach area (abdomen) or
- blood in your bowel movements.

### **C. Is LOTRONEX right for you?**

**LOTRONEX may be right for you if all of these things are true about you:**

- Your doctor has told you that your symptoms are due to IBS.
- Your IBS bowel problem is diarrhea.
- Your IBS has lasted for 6 months or longer.
- You tried other IBS treatments and they did not give you the relief you need.
- Your IBS is severe.

You can tell if your IBS is severe if **at least 1** of the following is true for you:

- You have lots of painful stomach cramps or bloating.
- You often cannot control the need to have a bowel movement, or you have “accidents” where your underwear gets dirty from diarrhea or bowel movements.
- You cannot lead a normal home or work life because you need to be near a bathroom.

Enough testing has not been done to confirm if LOTRONEX works in men or children under age 18.

### **D. There is a special prescribing program for LOTRONEX.**

Only doctors who have signed up with the company that makes LOTRONEX should write prescriptions for LOTRONEX. As part of signing up, these doctors have said that they understand about IBS and the possible side effects of LOTRONEX. They have agreed to use a special sticker on **written** prescriptions for LOTRONEX, so the pharmacist will know that the doctors have signed up with the company. No telephone, facsimile, or computerized prescriptions are permitted with this program. Refills may be written on prescriptions.

You may be taught about LOTRONEX by your doctor or healthcare provider under a doctor’s direction. Your doctor will ask you to sign a Patient Acknowledgement Form after you read this Medication Guide for the first time. Signing the Patient Acknowledgement Form means that you understand the benefits and risks of

LOTRONEX and that you have read and understand this Medication Guide.

## **2. What is LOTRONEX?**

LOTRONEX is a medicine only for some women with severe chronic IBS whose:

- main problem is diarrhea and
- IBS symptoms have not been helped enough by other treatments.

LOTRONEX does not cure IBS, and it may not help every person who takes it. For those who are helped, LOTRONEX reduces lower stomach area (abdominal) pain and discomfort, the sudden need to have a bowel movement (bowel urgency), and diarrhea from IBS. If you stop taking LOTRONEX, your IBS symptoms may return within 1 or 2 weeks to what they were before you started taking LOTRONEX.

LOTRONEX is not recommended for children.

## **3. Who should not take LOTRONEX?**

LOTRONEX is not right for everyone. **Do not take LOTRONEX if any of the following apply to you:**

- Your main IBS problem is constipation or you are constipated most of the time.
- You have had a serious problem from constipation. **If you are constipated now, do not start taking LOTRONEX.**
- You have had serious bowel blockages.
- You have had blood flow problems to your bowels, such as ischemic colitis.
- You have had blood clots.
- You have had Crohn's disease, ulcerative colitis, diverticulitis, or severe liver disease.
- You do not understand this Medication Guide or the Patient Acknowledgement Form, or you are not willing to follow them.
- You are taking fluvoxamine (LUVOX<sup>®</sup>).

## **4. What should I talk about with my doctor before taking LOTRONEX?**

Talk with your doctor:

- about the possible benefits and risks of LOTRONEX.
- about how much of a problem IBS is in your life and what treatments you have tried.
- about any other illnesses you have and medicines you take or plan to take. These include prescription and non-prescription medicines, supplements, and herbal remedies. Certain illnesses and medicines can increase your chance of getting serious side effects while taking LOTRONEX. Other medicines may interact with how the body handles LOTRONEX.
- about any allergies that you have. See the end of the Medication Guide for a complete list of ingredients in LOTRONEX.
- if you are pregnant, planning to get pregnant, or breastfeeding.

## **5. How should I take LOTRONEX?**

- Take LOTRONEX exactly as your doctor prescribes it. You can take LOTRONEX with or without food.
- Begin with 0.5 mg two times a day for 4 weeks to see how LOTRONEX affects you. You and your doctor may decide that you should keep taking this dose if you are doing well.
- Check with your doctor 4 weeks after starting LOTRONEX:
  - If you try 0.5 mg two times a day for 4 weeks, it may not control your symptoms. If you do not get constipation or other side effects from LOTRONEX, your doctor may increase your dose up to 1 mg two times a day.
  - If 1 mg two times a day does not work after 4 weeks, LOTRONEX is not likely to help you. You should stop taking it and call your doctor.
- **If you miss a dose of LOTRONEX**, just skip that dose. Do **not** take 2 doses the next time. Wait until the next time you are supposed to take it and then take your normal dose.
- **Follow the important instructions in the section “What is the most important information I should know about LOTRONEX?”** about when you must stop taking the medicine and when you should call your doctor.
- **If you see other doctors** about your IBS or side effects from LOTRONEX, tell the doctor who prescribed LOTRONEX.

## **6. What are the possible side effects of LOTRONEX?**

Constipation is the most common side effect among women with IBS who take LOTRONEX. **Some patients have developed serious bowel side effects while taking LOTRONEX.** Read the section “**What is the most important information I should know about LOTRONEX?**” at the beginning of this Medication Guide for information about the serious side effects you may get with LOTRONEX.

This Medication Guide does not tell you about all the possible side effects of LOTRONEX. Your doctor or pharmacist can give you a more complete list.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

## **7. How should I store LOTRONEX?**

- Store LOTRONEX between 59°F to 86°F (15°C to 30°C).
- Protect LOTRONEX from light and getting wet (moisture).

**Keep LOTRONEX and all medicines out of the reach of children.**

## **8. General information about the safe and effective use of LOTRONEX**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you have any questions or concerns about LOTRONEX, ask your doctor. Do not use LOTRONEX for a condition for which it was not prescribed. Do not share your

medicine with other people. It may harm them.

Your doctor or pharmacist can give you more information about LOTRONEX that was written for healthcare professionals. You can also contact the company that makes LOTRONEX (toll free) at 1-888-423-5227 or at [www.lotronexppl.com](http://www.lotronexppl.com).

### **9. What are the ingredients of LOTRONEX?**

**Active Ingredient:** alosetron hydrochloride.

**Inactive Ingredients:** lactose (anhydrous), magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The white film-coat for the 0.5 mg tablet contains hypromellose, titanium dioxide, and triacetin. The blue film-coat for the 1 mg tablet contains hypromellose, titanium dioxide, triacetin, and indigo carmine.

Manufactured for:

Prometheus Laboratories Inc.

9410 Carroll Park Drive

San Diego, CA 92121

*This Medication Guide has been approved by the U.S. Food and Drug Administration.*

Revised September 2010

LX002D



**PROMETHEUS**<sup>®</sup>  
Therapeutics & Diagnostics

*For the person in every patient*

Prometheus Laboratories Inc.

San Diego, CA 92121

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September 2010

LX001D

## Welcome to the Prescribing Program for LOTRONEX (PPL)

The Prescribing Program for LOTRONEX connects you with support, education and access to information about the safety of LOTRONEX. The Prescribing Program for LOTRONEX facilitates healthcare provider and patient education on the safety of LOTRONEX. Healthcare providers who are appropriately licensed to prescribe may enroll in the Prescribing Program for LOTRONEX. Only those enrolled can prescribe LOTRONEX.

**INDICATION:** LOTRONEX is indicated only for women with severe diarrhea-predominant irritable bowel syndrome who have: chronic irritable bowel syndrome symptoms (generally lasting 6 months or longer), had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and not responded adequately to conventional therapy. Diarrhea-predominant irritable bowel syndrome 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 irritable bowel syndrome. Because of infrequent but serious gastrointestinal adverse events 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 consult the [Complete Prescribing Information](#).

[Home](#) | [Complete Prescribing Information](#) | [PROMETHEUS Website](#)  
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## Lotronex PPL landing Page

**LOTROXEX**  
(alosetron HCl) 0.5 & 1 MG  
TABLETS



FOR PATIENTS

FOR PRESCRIBERS

FOR PHARMACISTS

Click through to relevant Web pages here

### Welcome to the Prescribing Program for LOTRONEX™ (PPL)

The Prescribing Program for LOTRONEX connects you with support, education and access to information about the safety of LOTRONEX®. The Prescribing Program for LOTRONEX facilitates healthcare provider and patient education on the safety of LOTRONEX. Healthcare providers who are appropriately licensed to prescribe may enroll in the Prescribing Program for LOTRONEX. Only those enrolled can prescribe LOTRONEX.

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This will click through to the prescribing information for LOTRONEX

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Welcome to the Prescribing Program for LOTRONEX (PPL)

Only prescribers who enroll in the Prescribing Program for LOTRONEX can prescribe LOTRONEX. The link below will help you enroll in the Prescribing Program for LOTRONEX.

- [Prescriber Enrollment](#)

INDICATION: LOTRONEX is indicated only for women with severe diarrhea-predominant irritable bowel syndrome who have: chronic irritable bowel syndrome symptoms (generally lasting 6 months or longer), had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and not responded adequately to conventional therapy. Diarrhea-predominant irritable bowel syndrome 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 irritable bowel syndrome. Because of infrequent but serious gastrointestinal adverse events 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.

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**PRESCRIBING PROGRAM  
FOR LOTROXEX™ (PPL)**

[Prescriber Enrollment](#)

**Welcome to the Prescribing Program for LOTROXEX™ (PPL)**

Only prescribers who enroll in the Prescribing Program for LOTROXEX can prescribe LOTROXEX®. The link below will help you enroll in the Prescribing Program for LOTROXEX.

- [Prescriber Enrollment](#)

Click here to go the "Enrolling in the Prescribing Program for LOTROXEX (PPL)" page – See prescriber Page 2

**INDICATION:** LOTROXEX is indicated only for women with severe diarrhea-predominant irritable bowel syndrome who have: chronic irritable bowel syndrome symptoms (generally lasting 6 months or longer), had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and not responded adequately to conventional therapy. Diarrhea-predominant irritable bowel syndrome 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 irritable bowel syndrome. Because of infrequent but serious gastrointestinal adverse events associated with LOTROXEX, 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 LOTROXEX in men.

Please consult the [Complete Prescribing Information](#).

Click here to link to the prescribing information for LOTROXEX



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## Prescriber Enrollment

The Prescribing Program for LOTRONEX™ (PPL) facilitates patient safety. The program allows both patients and prescribers to understand the appropriate use of LOTRONEX® and its potential risks, as well as adverse events and how to handle them.

### EDUCATION:

Prior to enrolling in the Prescribing Program for LOTRONEX, the prescribers should read the educational section entitled [PPL Prescriber Education Slide Deck](#).

Use the following resources to learn more about the Prescribing Program for LOTRONEX:

- [Prescriber Enrollment Form](#)
- [Medication Guide](#)
- [Patient Acknowledgement Form](#)

The [Prescribing Information for LOTRONEX](#) may be downloaded and saved or may also be obtained by calling 1-888-423-5227.

To order enrollment materials via a secure Internet connection, select [NEXT](#).

To enroll via telephone or fax, please contact: 1-888-423-5227.

To return to the Prescribers Home page, select [RETURN](#).

Please consult the [Complete Prescribing Information](#).

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**PRESCRIBING PROGRAM  
FOR LOTROXEX™ (PPL)**

**Prescriber Enrollment**

**Prescriber Enrollment**

The Prescribing Program for LOTROXEX™ (PPL) facilitates patient safety. The program allows both patients and prescribers to understand the appropriate use of LOTROXEX® and its potential risks, as well as adverse events and how to handle them.

**EDUCATION:**

This clicks through to an education slide deck for prescribers

Prior to enrolling in the Prescribing Program for LOTROXEX, the prescribers should read the educational section entitled [PPL Prescriber Education Slide Deck](#).

This clicks through to a downloadable version of the prescriber enrollment form

Use the following resources to learn more about the Prescribing Program for LOTROXEX:

This click through to a downloadable version of the Medication Guide

- [Prescriber Enrollment Form](#)
- [Medication Guide](#)
- [Patient Acknowledgement Form](#)

This clicks through to a downloadable version of the Patient Acknowledgement Form

This clicks through to the prescribing information for LOTROXEX

The [Prescribing Information for LOTROXEX](#) may be downloaded and saved or may also be obtained by calling 1-888-423-5227.

This clicks through to the next step in ordering enrollment materials (pages 3 a, b)

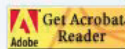
To order enrollment materials via a secure Internet connection, select **NEXT**.

To enroll via telephone or fax, please contact: 1-888-423-5227.

To return to the Prescribers Home page, select **RETURN**.

This will click through to the prescribing information for LOTROXEX

Please consult the [Complete Prescribing Information](#).



To begin the enrollment process, please read the Enrollment information below and click the “I AGREE” at the bottom of the page.

**PRESCRIBING PROGRAM FOR LOTRONEX™ (PPL):**

*Prometheus will ensure that healthcare providers who prescribe LOTRONEX are specially certified in the Prescribing Program for LOTRONEX (PPL). To become certified, each prescriber enrolls into the Prescribing Program for LOTRONEX by submitting a completed Prescriber Enrollment Form and attesting to the following:*

I request to participate in the Prescribing Program for LOTRONEX and acknowledge that I have read and understand the complete Prescribing Information and other enrollment materials for LOTRONEX. I understand the risks associated with its use and will follow the requirements of the Prescribing Program for LOTRONEX described below. I understand the importance of reporting all cases of ischemic colitis and serious complications of constipation to Prometheus at 1-888-423-5227.

I understand that LOTRONEX is approved only for women with severe, diarrhea-predominant irritable bowel syndrome 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.

Diarrhea-predominant irritable bowel syndrome 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 irritable bowel syndrome.

I understand that if I prescribe LOTRONEX for my patient(s), I must be able to perform the following:

- diagnose and manage irritable bowel syndrome, ischemic colitis, constipation, and complications of constipation, or refer patients to a specialist as needed.
- ensure that all patients under my care are educated by me or healthcare provider in my practice about the benefits and risks of the drug.

I agree to:





## Prescriber PPL webpage 3a

Search  ?

### FOR PRESCRIBERS

#### PRESCRIBING PROGRAM FOR LOTRONEX™ (PPL) Prescriber Enrollment

To begin the enrollment process, please read the Enrollment information below and click the "I AGREE" at the bottom of the page.

#### PRESCRIBING PROGRAM FOR LOTRONEX™ (PPL):

Prometheus will ensure that healthcare providers who prescribe LOTRONEX are specially certified in the Prescribing Program for LOTRONEX (PPL). To become certified, each prescriber enrolls into the Prescribing Program for LOTRONEX by submitting a completed Prescriber Enrollment Form and attesting to the following:

I request to participate in the Prescribing Program for LOTRONEX and acknowledge that I have read and understand the complete Prescribing Information and other enrollment materials for LOTRONEX. I understand the risks associated with its use and will follow the requirements of the Prescribing Program for LOTRONEX described below. I understand the importance of reporting all cases of ischemic colitis and serious complications of constipation to Prometheus at 1-888-423-5227.

I understand that LOTRONEX is approved only for women with severe, diarrhea-predominant irritable bowel syndrome who have:

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- frequent and severe abdominal pain/discomfort,
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- diagnose and manage irritable bowel syndrome, ischemic colitis, constipation, and complications of constipation, or refer patients to a specialist as needed.
- ensure that all patients under my care are educated by me or a healthcare provider in my practice about the benefits and risks of the drug.

I agree to:

This webpage scrolls down (continues on page 3b)



provide each of my patients with a copy of the LOTRONEX Medication Guide at initiation of LOTRONEX treatment.

- review the content of the Medication Guide and encourage the patient to read it and ask questions.
- have each patient sign the Patient Acknowledgement Form. The original signed form must be placed in the patient's medical record, and a copy given to the patient.
- inform my patients about the Patient Follow-Up Survey, encourage them to participate and provide them with a Patient Follow-Up Survey Pre-Enrollment Form
- affix Prescribing Program for LOTRONEX program stickers to written prescriptions for LOTRONEX (i.e., the original and all subsequent prescriptions). Stickers will be provided as part of the Prescribing Program for LOTRONEX. Refills are permitted to be written on prescriptions.
- ensure that all prescriptions for LOTRONEX are written and not transmitted by telephone, facsimile, or computer.

To order enrollment materials, select **LAGREE**.

To return to the Prescriber Home page, select RETURN.

Please consult the Complete Prescribing Information.

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## Prescriber PPL webpage 3b

This webpage is a continuation of prescriber PPL webpage 3a

This will click through to the page where prescribers fill in personal information to order enrollment materials

This will click through to the prescribing information for LOTRONEX

- provide each of my patients with a copy of the LOTRONEX Medication Guide at initiation of LOTRONEX treatment.
- review the content of the Medication Guide and encourage the patient to read it and ask questions.
- have each patient sign the Patient Acknowledgement Form. The original signed form must be placed in the patient's medical record, and a copy given to the patient.
- inform my patient about the Patient Follow-Up Survey, encourage them to participate and provide them with a Patient Follow-Up Survey Pre-Enrollment Form
- affix Prescribing Program for LOTRONEX program stickers to written prescriptions for LOTRONEX (i.e., the original and all subsequent refills). Stickers will be provided as part of the Prescribing Program for LOTRONEX. Refills are permitted to be written on prescriptions.
- ensure that all prescriptions for LOTRONEX are written and not transmitted by telephone, facsimile, or computer.

To order enrollment materials, select **AGREE**.  
To return to the Prescriber Home page, select **RETURN**.

[▲ Back to top](#)

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Please fill in the following information and press the “submit” button, to order the materials for enrollment in the Prescribing Program for LOTRONEX™ (PPL).

- Required fields

Enrolling Prescriber:

\*First Name:

Middle Name:

\*Last Name:

Name Suffix: (Sr. Jr III...)

\*DEA Number:

Prescriber’s Office Address:

\*Address 1:

Address 2:

\*City:

\*State:

\*Phone #:

Fax #:

\*E-mail:

Please consult the [Complete Prescribing Information](#).

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# Prescriber PPL webpage 4

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## FOR PRESCRIBERS

### PRESCRIBING PROGRAM FOR LOTIRONEX™ (PPL) Prescriber Enrollment

Please fill in the following information and press the "submit" button, to order materials for enrollment in the Prescribing Program for LOTIRONEX™ (PPL).

\* Required fields

Enrolling Prescriber:

\*First Name:

Middle Name:

\*Last Name:

Name Suffix:  (Sr. Jr. III...)

\*DEA Number:

Prescriber's Office Address:

\*Address 1:

Address 2:

\*City:

\*State:

\*ZIP Code:

\*Phone #:

Fax #:

\*E-mail:

Submit

Prescriber to fill in this information and "submit" To order enrollment materials

This will click through to the prescribing information for LOTIRONEX

Please consult the [Complete Prescribing Information](#).



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The Prescribing Program for LOTRONEX™



IMPORTANT INFORMATION ENCLOSED

## The Prescribing Program for LOTRONEX™

---



  
**LOTRONEX**  
(alose tron HCl) <sup>0.5 & 1 MG</sup> TABLETS

**IMPORTANT INFORMATION ENCLOSED**

## **Important Information for Patients**

### **The Prescribing Program for LOTRONEX™**

Provides clear guidelines to help your doctor determine whether LOTRONEX® (alosetron HCl) therapy is right for you.

Provides you with a clear understanding of the risks and benefits of LOTRONEX therapy.

Makes sure you provide informed consent before beginning LOTRONEX therapy.

#### **You will follow these 3 simple steps:**

**1 Review the Medication Guide** with your doctor and keep a copy.

**2 Read and sign the Patient Acknowledgement Form.**

This form is intended to confirm that both you and your doctor have read and understand the risks and benefits. It also confirms that you are ready to start LOTRONEX therapy. And it reviews the important instructions your doctor will give you for taking LOTRONEX and asks you to agree to these instructions.

**3 Receive a written prescription** with the Prescribing Program for LOTRONEX sticker attached and take that prescription to the pharmacy.

**Please see the accompanying complete prescribing information, including Boxed Warning, for LOTRONEX.**



## Important Information for Patients

### The Prescribing Program for LOTRONEX™

Provides clear guidelines to help your doctor determine whether LOTRONEX® (alosetron HCl) therapy is right for you.

Provides you with a clear understanding of the risks and benefits of LOTRONEX therapy.

Makes sure you provide informed consent before beginning LOTRONEX therapy.

### You will follow these 3 simple steps:

**1**

**Review the Medication Guide** with your doctor and keep a copy.

**2**

**Read and sign the Patient Acknowledgement Form.**

This form is intended to confirm that both you and your doctor have read and understand the risks and benefits. It also confirms that you are ready to start LOTRONEX therapy. And it reviews the important instructions your doctor will give you for taking LOTRONEX and asks you to agree to these instructions.

**3**

**Receive a written prescription** with the Prescribing Program for LOTRONEX sticker attached and take that prescription to the pharmacy.

Please see the accompanying complete prescribing information, including Boxed Warning, for LOTRONEX.

## Instructions for using the Prescribing Program for LOTRONEX™ Stickers

- Tear off this panel before handing the booklet to the patient.
- Keep the extra stickers in the patient's medical record.
- Do not share stickers with other prescribers.
- Attach a self-adhesive Prescribing Program sticker on EVERY prescription for LOTRONEX® (alosetron HCl) to signify that the prescription is in compliance with the Prescribing Program for LOTRONEX. Stickers are not required for refills.

Please see accompanying complete prescribing information, including Boxed Warning, for LOTRONEX.

**LOTRONEX® (alosetron HCl) tablets**

The sticker indicates that this prescription  
is in compliance with the  
Prescribing Program for LOTRONEX™  
**REFILL PERMITTED**

## Instructions for using the Prescribing Program for LOTRONEX™ Stickers

- Tear off this panel before handing the booklet to the patient.
- Keep the extra stickers in the patient's medical record.
- Do not share stickers with other prescribers.
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Please see accompanying complete prescribing information, including Boxed Warning, for LOTRONEX.

### **LOTRONEX® (alosecron HCl) tablets**

The sticker indicates that this prescription is in compliance with the Prescribing Program for LOTRONEX.™

**REFILL PERMITTED**

### **LOTRONEX® (alosecron HCl) tablets**

The sticker indicates that this prescription is in compliance with the Prescribing Program for LOTRONEX.™

**REFILL PERMITTED**

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**REFILL PERMITTED**

### **LOTRONEX® (alosecron HCl) tablets**

The sticker indicates that this prescription is in compliance with the Prescribing Program for LOTRONEX.™

**REFILL PERMITTED**





9410 Carroll Park Drive  
San Diego, CA 92121  
888-423-5227  
888-824-0896 fax  
[www.prometheuslabs.com](http://www.prometheuslabs.com)

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**LOTRONEX**<sup>®</sup>  
(alose tron HCl) 0.5 & 1 MG  
TABLETS



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[www.prometheuslabs.com](http://www.prometheuslabs.com)

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**LOTROXEN**  
(alose tron HCl) 0.5 & 1 MG  
TABLETS

XX Month 20XX

Dear Prescriber:

Thank you for contacting Prometheus regarding the **Prescribing Program for LOTRONEX™ (PPL)**.

We have received your Prescriber Enrollment Form and have enclosed your Prescribing Program for LOTRONEX materials.

Each Prescribing Program for LOTRONEX kit contains:

- LOTRONEX Medication Guide
- (2) Patient Acknowledgement Forms
- (4) LOTRONEX Prescribing Program for LOTRONEX Stickers
- LOTRONEX Patient Follow-Up Survey Pre-Enrollment Form - Please encourage your patients to enroll in the voluntary Patient Follow-Up Survey Program.
- LOTRONEX Prescribing Information

If you need additional Prescribing Program for LOTRONEX kits or have questions about the materials received, please contact Prometheus Client Services at 1-888-423-5227.

Regards,

Client Services  
Prometheus Laboratories Inc.



### ***Patient Acknowledgement Form***

*LOTRONEX<sup>®</sup> (alosetron hydrochloride) is 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. LOTRONEX has not been shown to help men with irritable bowel syndrome (IBS) or patients under age 18. My doctor, or a healthcare provider under a doctor's direction, answered my questions about treatment with LOTRONEX. I have read and I understand the Medication Guide for LOTRONEX including the section "Who should not take LOTRONEX?" and,*

- I understand that about 1 out of every 1,000 women who take LOTRONEX may get serious complications of constipation. I understand that about 3 out of every 1,000 women who take LOTRONEX over a 6-month period may get a serious problem where blood flow to parts of the large bowel is reduced (ischemic colitis). I understand that the serious condition of ischemic colitis, and other serious complications of constipation, can happen suddenly. These serious complications may lead to a hospital stay, and in rare cases, blood transfusions, surgery, and death. I also understand that certain patients may be more likely to develop a serious bowel condition while taking LOTRONEX. These include older patients, those who have other health problems and those who take other medicines that may cause constipation.
- I understand that certain people may be more likely to develop a serious bowel condition while taking LOTRONEX including people who:
  - are older,
  - have other health problems, and
  - take other medications that may cause constipation.
- I understand LOTRONEX is a medication that should only be used for some women with severe chronic irritable bowel syndrome (IBS), whose main problem is diarrhea, and whose IBS symptoms have not been helped enough by other treatments.
- I will follow instructions in the Medication Guide about:
  - **telling my doctor**, before taking LOTRONEX, about any illnesses I have, or other medicines I am taking or planning to take.
  - **taking LOTRONEX** exactly as my doctor prescribes it.
  - **stopping LOTRONEX** and calling my doctor right away if I get constipated, if I have new or worse pain in my stomach area (abdomen), or if I see blood in my bowel movements.
  - **calling my doctor again** if the constipation I called about before has not gotten better.
  - **not starting LOTRONEX again** unless my doctor tells me to do so, if I stopped taking it because I got constipated.
  - **talking with my doctor 4 weeks after starting LOTRONEX** to recheck my IBS symptoms.

— **stopping LOTRONEX and calling my doctor** if my IBS symptoms have not improved after 4 weeks of taking 1 mg of LOTRONEX 2 times a day.

- If I see other doctors about my IBS or possible side effects from LOTRONEX, I will tell the doctor who prescribed LOTRONEX.

*My signature below indicates that I have read, understood, and agree with all the statements made above and that I have asked any questions that I have about LOTRONEX therapy. I would like to begin treatment with LOTRONEX.*

---

Name of Patient (print)

---

Signature

---

Date

*After the patient signs this Patient Acknowledgement Form, the patient should receive a copy and the original signed form should be kept in the patient's medical record.*

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[www.prometheuslabs.com](http://www.prometheuslabs.com)

## Patient Acknowledgement Form



LOTROXEX® (alosetron hydrochloride) is 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. LOTROXEX has not been shown to help men with irritable bowel syndrome (IBS) or patients under age 18.

My doctor, or a healthcare provider under a doctor's direction, answered my questions about treatment with LOTROXEX. I have read and I understand the Medication Guide for LOTROXEX including the section "Who should not take LOTROXEX?" and,

- I understand that about 1 out of every 1,000 women who take LOTROXEX may get serious complications of constipation. I understand that about 3 out of every 1,000 women who take LOTROXEX over a 6-month period may get a serious problem where blood flow to parts of the large bowel is reduced (ischemic colitis). I understand that the serious condition of ischemic colitis, and other serious complications of constipation, can happen suddenly. These serious complications may lead to a hospital stay, and in rare cases, blood transfusions, surgery, and death. I also understand that certain patients may be more likely to develop a serious bowel condition while taking LOTROXEX. These include older patients, those who have other health problems and those who take other medicines that may cause constipation.
- I understand that certain people may be more likely to develop a serious bowel condition while taking LOTROXEX including people who:
  - are older,
  - have other health problems, and
  - take other medications that may cause constipation.
- I understand LOTROXEX is a medication that should only be used for some women with severe chronic irritable bowel syndrome (IBS), whose main problem is diarrhea, and whose IBS symptoms have not been helped enough by other treatments.
- I will follow instructions in the Medication Guide about:
  - **telling my doctor**, before taking LOTROXEX, about any illnesses I have, or other medicines I am taking or planning to take.
  - **taking LOTROXEX** exactly as my doctor prescribes it.
  - **stopping LOTROXEX** and calling my doctor right away if I get constipated, if I have new or worse pain in my stomach area (abdomen), or if I see blood in my bowel movements.
  - **calling my doctor** again if the constipation I called about before has not gotten better.
  - **not starting LOTROXEX again** unless my doctor tells me to do so, if I stopped taking it because I got constipated.
  - **talking with my doctor 4 weeks after starting LOTROXEX** to recheck my IBS symptoms.
  - **stopping LOTROXEX and calling my doctor** if my IBS symptoms have not improved after 4 weeks of taking 1 mg of LOTROXEX 2 times a day.
- If I see other doctors about my IBS or possible side effects from LOTROXEX, I will tell the doctor who prescribed LOTROXEX.

My signature below indicates that I have read, understood, and agree with all the statements made above and that I have asked any questions that I have about LOTROXEX therapy. I would like to begin treatment with LOTROXEX.

Name of Patient (print)

Signature

After the patient signs this Patient Acknowledgement Form, the patient should receive a copy and the original signed form should be kept in the patient's medical record.

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Date



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Therapeutics & Diagnostics  
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9410 Carroll Park Drive  
San Diego, CA 92121  
888-423-5227  
888-824-0896 fax

[www.prometheuslabs.com](http://www.prometheuslabs.com)

## MEDICATION GUIDE

### LOTRONEX® (LOW-trah-nex) Tablets (alosecron hydrochloride)

#### Before using LOTRONEX for the first time, you should:

- Understand that LOTRONEX has serious risks for some people.
- Read and follow the directions in this Medication Guide.
- Sign a Patient Acknowledgement Form.

Read this Medication Guide carefully before you sign the Patient Acknowledgement Form. You must sign the Patient Acknowledgement Form before you start LOTRONEX. Read the Medication Guide you get with each refill for LOTRONEX. There may be new information. This Medication Guide does not take the place of talking with your doctor.

#### 1. What is the most important information I should know about LOTRONEX?

##### A LOTRONEX is a medicine only for some women with severe chronic irritable bowel syndrome (IBS) whose:

- main problem is diarrhea and
- IBS symptoms have not been helped enough by other treatments.

##### B Some patients have developed serious bowel side effects while taking LOTRONEX.

Serious bowel (intestine) side effects can happen suddenly, including the following.

1. **Serious complications of constipation:** About 1 out of every 1,000 women who take LOTRONEX may get serious complications of constipation. These complications may lead to a hospital stay and, in rare cases, blood transfusions, surgery, and death. People who are older, who are weak from illness, or who take other constipating medicines may be more likely to have serious complications of constipation with LOTRONEX.

To lower your chances of getting serious complications of constipation, do the following:

- If you are constipated, do not start taking LOTRONEX.
- If you get constipated while taking LOTRONEX, stop taking it right away and call your doctor.
- If your constipation does not get better after stopping LOTRONEX, call your doctor again.
- If you stopped taking LOTRONEX, do not start taking LOTRONEX again unless your doctor tells you to do so.

2. **Ischemic colitis (reduced blood flow to the bowel):** About 3 out of every 1,000 women who take LOTRONEX over a 6-month period may get a serious problem where blood flow to parts of the large bowel is reduced. This is called ischemic colitis. The chance of getting ischemic colitis when you take LOTRONEX for more than 6 months is not known. Ischemic colitis may lead to a hospital stay and, in rare cases, blood transfusions, surgery, and death.

To lower your chances of getting serious complications of ischemic colitis, stop taking LOTRONEX and call your doctor right away if you get:

- new or worse pain in your stomach area (abdomen) or
- blood in your bowel movements.

##### C Is LOTRONEX right for you?

LOTRONEX may be right for you if all of these things are true about you:

- Your doctor has told you that your symptoms are due to IBS.
- Your IBS bowel problem is diarrhea.
- Your IBS has lasted for 6 months or longer.
- You tried other IBS treatments and they did not give you the relief you need.
- Your IBS is severe.

You can tell if your IBS is severe if at least 1 of the following is true for you:

- You have lots of painful stomach cramps or bloating.
- You often cannot control the need to have a bowel movement, or you have “accidents” where your underwear gets dirty from diarrhea or bowel movements.
- You cannot lead a normal home or work life because you need to be near a bathroom.

Enough testing has not been done to confirm if LOTRONEX works in men or children under age 18.

##### D There is a special prescribing program for LOTRONEX.

Only doctors who have signed up with the company that makes LOTRONEX should write prescriptions for LOTRONEX. As part of signing up, these doctors have said that they understand about IBS and the possible side effects of LOTRONEX. They have agreed to use a special sticker on written prescriptions for LOTRONEX, so the pharmacist will know that the doctors have signed up with the company. No telephone, facsimile, or computerized prescriptions are permitted with this program. Refills may be written on prescriptions. You may be taught about LOTRONEX by your doctor or healthcare provider under a doctor's direction. Your doctor will ask you to sign a Patient Acknowledgement Form after you read this Medication Guide for the first time. Signing the Patient Acknowledgement Form means that you understand the benefits and risks of LOTRONEX and that you have read and understand this Medication Guide.

#### 2. What is LOTRONEX?

LOTRONEX is a medicine only for some women with severe chronic IBS whose:

- main problem is diarrhea and
- IBS symptoms have not been helped enough by other treatments.

LOTRONEX does not cure IBS, and it may not help every person who takes it. For those who are helped, LOTRONEX reduces lower stomach area (abdominal) pain and discomfort, the sudden need to have a bowel movement (bowel urgency), and diarrhea from IBS. If you stop taking LOTRONEX, your IBS symptoms may return within 1 or 2 weeks to what they were before you started taking LOTRONEX.

LOTRONEX is not recommended for children.

*Please see additional important information on reverse side.*



## LOTROX<sup>®</sup> (LOW-trah-nex) Tablets (alosetron hydrochloride)

### 3. Who should not take LOTROX?

LOTROX is not right for everyone. Do not take LOTROX if any of the following apply to you:

- Your main IBS problem is constipation or you are constipated most of the time.
- You have had a serious problem from constipation. If you are constipated now, do not start taking LOTROX.
- You have had serious bowel blockages.
- You have had blood flow problems to your bowels, such as ischemic colitis.
- You have had blood clots.
- You have had Crohn's disease, ulcerative colitis, diverticulitis, or severe liver disease.
- You do not understand this Medication Guide or the Patient Acknowledgement Form, or you are not willing to follow them.
- You are taking fluvoxamine (LUVOX<sup>®</sup>)

### 4. What should I talk about with my doctor before taking LOTROX?

Talk with your doctor:

- about the possible benefits and risks of LOTROX.
- about how much of a problem IBS is in your life and what treatments you have tried.
- about any other illnesses you have and medicines you take or plan to take. These include prescription and non-prescription medicines, supplements, and herbal remedies. Certain illnesses and medicines can increase your chance of getting serious side effects while taking LOTROX. Other medicines may interact with how the body handles LOTROX.
- about any allergies that you have. See the end of the Medication Guide for a complete list of ingredients in LOTROX.
- if you are pregnant, planning to get pregnant, or breastfeeding.

### 5. How should I take LOTROX?

- Take LOTROX exactly as your doctor prescribes it. You can take LOTROX with or without food.
- Begin with 0.5 mg two times a day for 4 weeks to see how LOTROX affects you. You and your doctor may decide that you should keep taking this dose if you are doing well.
- Check with your doctor 4 weeks after starting LOTROX:
  - If you try 0.5 mg two times a day for 4 weeks, it may not control your symptoms. If you do not get constipation or other side effects from LOTROX, your doctor may increase your dose up to 1 mg two times a day.
  - If 1 mg two times a day does not work after 4 weeks, LOTROX is not likely to help you. You should stop taking it and call your doctor.
- If you miss a dose of LOTROX, just skip that dose. Do not take 2 doses the next time. Wait until the next time you are supposed to take it and then take your normal dose.
- Follow the important instructions in the section "What is the most important information I should know about LOTROX?" about when you must stop taking the medicine and when you should call your doctor.
- If you see other doctors about your IBS or side effects from LOTROX, tell the doctor who prescribed LOTROX.

### 6. What are the possible side effects of LOTROX?

Constipation is the most common side effect among women with IBS who take LOTROX. Some patients have developed serious bowel side effects while taking LOTROX. Read the section "What is the most important information I should know about LOTROX?" at the beginning of this Medication Guide for information about the serious side effects you may get with LOTROX.

The Medication Guide does not tell you about all the possible side effects of LOTROX. Your doctor or pharmacist can give you a more complete list.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

### 7. How should I store LOTROX?

- Store LOTROX between 59°F to 86°F (15°C to 30°C).
  - Protect LOTROX from light and getting wet (moisture).
- Keep LOTROX and all medicines out of the reach of children.

### 8. General information about the safe and effective use of LOTROX

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you have any questions or concerns about LOTROX, ask your doctor. Do not use LOTROX for a condition for which it was not prescribed. Do not share your medicine with other people. It may harm them.

Your doctor or pharmacist can give you more information about LOTROX that was written for healthcare professionals. You can also contact the company that makes LOTROX (toll free) at 1-888-423-5227 or at [www.lotroxexpl.com](http://www.lotroxexpl.com).

### 9. What are the ingredients of LOTROX?

Active Ingredient: alosetron hydrochloride.

Inactive Ingredients: lactose (anhydrous), magnesium stearate, microcrystalline cellulose, and pregelatinized starch.

The white film-coat for the 0.5 mg tablet contains hypromellose, titanium dioxide, and triacetin. The blue film-coat for the 1 mg tablet contains hypromellose, titanium dioxide, triacetin, and indigo carmine.

Manufactured for: Prometheus Laboratories Inc., 9410 Carroll Park Drive, San Diego, CA 92121

This Medication Guide has been approved by the US Food and Drug Administration.

Revised XXX.2010 LX002D



Please see additional important information on reverse side.



***Patient Follow-Up Survey for LOTRONEX<sup>®</sup> Tablets  
Pre-Enrollment Form***



***What is the purpose of the Survey?***

The Follow-Up Survey for Lotronex will help us learn more about Lotronex. Everyone who takes Lotronex is invited to voluntarily sign up. If you sign up you will get questions in the mail about how you are doing on Lotronex. You do not have to sign up if you do not wish to, but signing up will help us learn more about Lotronex. The Survey is being done by Prometheus Laboratories Inc., the makers of Lotronex, located in San Diego, California. The Survey results will be shared with the US Food and Drug Administration (FDA) to help all patients; however, your identity and individual responses will be kept confidential.

***How will the Survey work?***

By sending in this Pre-Enrollment Form, you agree to participate in the Survey and be contacted by mail and phone. Detailed information about the Survey, including the consent form and initial Survey questions, will be sent to you after you agree to sign up. You will receive a small payment for your time.

***Will my information be confidential?***

The information that you provide on this Pre-Enrollment Form will be kept confidential by Prometheus.

***How do I enroll in the Follow-Up Survey for Lotronex?***

Please complete the Pre-Enrollment Form now, seal it, and mail it in the postage paid envelope today. **You need to send in the Pre-Enrollment Form only once.** Once received by the Lotronex Survey Center, a Coordinating Center Associate will mail you the program materials. If you get more Pre-Enrollment Forms with your new prescriptions and have already enrolled, please discard them.

***What if I still have more questions?***

If you have any questions about enrolling in the Survey, please call the Lotronex Survey Center toll free at 1-800-349-7419.

***Pre-Enrollment Contact Information***

**I agree to be contacted by mail and phone about participating in the Patient Follow-Up Survey for LOTRONEX.**

(Please print)

Name \_\_\_\_\_  
First Middle Initial Last

Address \_\_\_\_\_  
City State Zip Telephone Number (with area code)

Date of Birth \_\_\_\_\_ Female/Male  
Month/Day/Year (Circle One)

Your Signature \_\_\_\_\_ Date \_\_\_\_\_

Are you currently under 18 years of age? Yes No  
(If yes, your parent or guardian must sign this form below.)

Parent/Guardian Signature \_\_\_\_\_ Date \_\_\_\_\_

# Patient Follow-Up Survey for LOTRONEX® Tablets Pre-Enrollment Form



### What is the purpose of the Survey?

The Follow-Up Survey for LOTRONEX will help us learn more about LOTRONEX. Everyone who takes LOTRONEX is invited to voluntarily sign up. If you sign up you will get questions in the mail about how you are doing on LOTRONEX. You do not have to sign up if you do not wish to, but signing up will help us learn more about LOTRONEX. The Survey is being done by Prometheus Laboratories Inc., the makers of LOTRONEX, located in San Diego, California. The Survey results will be shared with the US Food and Drug Administration (FDA) to help all patients; however, your identity and individual responses will be kept confidential.

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### What if I still have more questions?

If you have any questions about enrolling in the Survey, please call the LOTRONEX Survey Center toll-free at 1-800-349-7419.

Please fold into thirds, seal, and mail in envelope provided.

## Pre-Enrollment Contact Information

**I agree to be contacted by mail and phone about participating in the Patient Follow-Up Survey for LOTRONEX.**

(Please print)

Name \_\_\_\_\_  
First Middle initial Last

Address \_\_\_\_\_

\_\_\_\_\_  
City State Zip Telephone Number (with area code)

Date of Birth \_\_\_\_\_ Female / Male  
MonthlyDay/Year Circle One

Your Signature \_\_\_\_\_ Date \_\_\_\_\_

Are you currently under 18 years of age? Yes  No  (If yes, your parent or guardian must sign this form below.)

Parent/Guardian Signature \_\_\_\_\_ Date \_\_\_\_\_

## Instructions for using the Prescribing Program for LOTRONEX™ (PPL) stickers

Please follow these 3 simple steps:

### With *new* LOTRONEX® patients:

- 1 **Review the Medication Guide** with the patient and give the patient a copy.
- 2 **Have your patient read and sign the Patient Acknowledgement Form**—put the original in the patient’s file and give a copy to the patient.

### With *all* LOTRONEX patients:

- 3 **Give the patient a written prescription with Prescribing Program for LOTRONEX sticker attached**—stickers are required on the initial prescription and subsequent written prescription renewals.

- Keep the extra stickers in the patient’s medical record.
- Do not share stickers with other prescribers.
- Attach a self-adhesive Prescribing Program for LOTRONEX sticker on EVERY prescription for LOTRONEX to signify that the prescription is in compliance with the Prescribing Program for LOTRONEX.
- Refills are permitted to be written on prescription.

**Only prescribers enrolled in the Prescribing Program for LOTRONEX may prescribe LOTRONEX.**

**No telephone, facsimile, or computerized prescriptions are permitted with this program.**



**To order additional stickers or for questions, call 1-888-423-5227 or visit [www.lotronexppl.com](http://www.lotronexppl.com)**

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#### **LOTRONEX® (alosetron HCl) tablets**

The sticker indicates that this prescription  
is in compliance with the  
Prescribing Program for LOTRONEX™

**REFILL PERMITTED**

Please see the accompanying complete Prescribing Information, including Boxed Warning, for LOTRONEX.



PROMETHEUS®  
Therapeutics & Diagnostics

*For the person in every patient*

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San Diego, CA 92121  
888-423-5227  
888-824-0896 fax  
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## Instructions for using the Prescribing Program for LOTRONEX<sup>®</sup> (PPL) stickers

Please follow these 3 simple steps:

With *new* LOTRONEX<sup>®</sup> patients:

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<p><b>LOTRONEX<sup>®</sup> (alosetron HCl) tablets</b> The sticker indicates that this prescription is in compliance with the Prescribing Program for LOTRONEX<sup>®</sup></p> <p><b>REFILL PERMITTED</b></p>
<p><b>LOTRONEX<sup>®</sup> (alosetron HCl) tablets</b> The sticker indicates that this prescription is in compliance with the Prescribing Program for LOTRONEX<sup>®</sup></p> <p><b>REFILL PERMITTED</b></p>
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Please see the accompanying complete Prescribing Information, including Boxed Warning, for LOTRONEX.

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**PATIENT FOLLOW-UP SURVEY FOR  
 LOTRONEX® (alosetron hydrochloride) TABLETS  
 PRE-ENROLLMENT FORM**

***What is the purpose of the Survey?***

The Follow-Up Survey for Lotronex will help us learn more about Lotronex. Everyone who takes Lotronex is invited to voluntarily sign up. If you sign up you will get questions in the mail about how you are doing on Lotronex. You do not have to sign up if you do not wish to, but signing up will help us learn more about Lotronex. The Survey is being done by Prometheus Laboratories Inc., the makers of Lotronex, located in San Diego, California. The survey results will be shared with the US Food and Drug Administration (FDA) to help all patients; however, your identity and individual responses will be kept confidential.

***How will the Survey work?***

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***What if I still have more questions?***

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I agree to be contacted by mail and phone about participating in the Patient Follow-Up Survey for LOTRONEX.

(Please print)

Name \_\_\_\_\_  
                     First                                    Middle Initial                                    Last

Address \_\_\_\_\_

City \_\_\_\_\_ State \_\_\_\_\_ ZIP \_\_\_\_\_

Telephone Number \_\_\_\_\_  
Area code \_\_\_\_\_

Date of Birth \_\_\_\_\_ Female/Male  
Month/Day/Year (Circle One)

Your Signature \_\_\_\_\_ Date \_\_\_\_\_

**Are you currently under 18 years of age? Yes No**

**If yes, your parent or guardian must sign this form below.**

Parent/Guardian Signature \_\_\_\_\_ Date \_\_\_\_\_





LX007C

### PATIENT FOLLOW-UP SURVEY FOR LOTRONEX® (alosetron hydrochloride) TABLETS PRE-ENROLLMENT FORM

#### What is the purpose of the Survey?

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FOLD HERE BEFORE MAILING

PULL HERE TO REMOVE SURVEY CARD

I agree to be contacted by mail and phone about participating in the Patient Follow-Up Survey for LOTRONEX.

(Please print)

Name \_\_\_\_\_  
First Middle Initial Last

Address \_\_\_\_\_

City \_\_\_\_\_ State \_\_\_\_\_ ZIP \_\_\_\_\_

Telephone Number \_\_\_\_\_  
Area code

Date of Birth \_\_\_\_\_ Female/Male  
Month/Day/Year (Circle One)

Your Signature \_\_\_\_\_ Date \_\_\_\_\_

Are you currently under 18 years of age?  Yes  No

If yes, your parent or guardian must sign this form below.

Parent/Guardian Signature \_\_\_\_\_ Date \_\_\_\_\_



BEFORE MAILING FOLD HERE FIRST



NO POSTAGE  
NECESSARY  
IF MAILED  
IN THE  
UNITED STATES

**BUSINESS REPLY MAIL**

FIRST-CLASS MAIL PERMIT NO. 1828 KANSAS CITY, MO

POSTAGE WILL BE PAID BY ADDRESSEE



REMOVE  
TAB  
BEFORE  
MAILING



LOTRONEX SURVEY  
3822 SUMMIT ST.  
KANSAS CITY, MO 64111-9756



BEFORE MAILING FOLD HERE SECOND



### ***Patient Acknowledgement Form***

*LOTRONEX<sup>®</sup> (alosetron hydrochloride) is 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. LOTRONEX has not been shown to help men with irritable bowel syndrome (IBS) or patients under age 18. My doctor, or a healthcare provider under a doctor's direction, answered my questions about treatment with LOTRONEX. I have read and I understand the Medication Guide for LOTRONEX including the section "Who should not take LOTRONEX?" and,*

- I understand that about 1 out of every 1,000 women who take LOTRONEX may get serious complications of constipation. I understand that about 3 out of every 1,000 women who take LOTRONEX over a 6-month period may get a serious problem where blood flow to parts of the large bowel is reduced (ischemic colitis). I understand that the serious condition of ischemic colitis, and other serious complications of constipation, can happen suddenly. These serious complications may lead to a hospital stay, and in rare cases, blood transfusions, surgery, and death. I also understand that certain patients may be more likely to develop a serious bowel condition while taking LOTRONEX. These include older patients, those who have other health problems and those who take other medicines that may cause constipation.
- I understand that certain people may be more likely to develop a serious bowel condition while taking LOTRONEX including people who:
  - are older,
  - have other health problems, and
  - take other medications that may cause constipation.
- I understand LOTRONEX is a medication that should only be used for some women with severe chronic irritable bowel syndrome (IBS), whose main problem is diarrhea, and whose IBS symptoms have not been helped enough by other treatments.
- I will follow instructions in the Medication Guide about:
  - **telling my doctor**, before taking LOTRONEX, about any illnesses I have, or other medicines I am taking or planning to take.
  - **taking LOTRONEX** exactly as my doctor prescribes it.
  - **stopping LOTRONEX** and calling my doctor right away if I get constipated, if I have new or worse pain in my stomach area (abdomen), or if I see blood in my bowel movements.
  - **calling my doctor** again if the constipation I called about before has not gotten better.
  - **not starting LOTRONEX again** unless my doctor tells me to do so, if I stopped taking it because I got constipated.
  - **talking with my doctor 4 weeks after starting LOTRONEX** to recheck my IBS symptoms.

- **stopping LOTRONEX and calling my doctor** if my IBS symptoms have not improved after 4 weeks of taking 1 mg of LOTRONEX 2 times a day.
- If I see other doctors about my IBS or possible side effects from LOTRONEX, I will tell the doctor who prescribed LOTRONEX.

*My signature below indicates that I have read, understood, and agree with all the statements made above and that I have asked any questions that I have about LOTRONEX therapy. I would like to begin treatment with LOTRONEX.*

---

Name of Patient (print)

---

Signature

---

Date

*After the patient signs this Patient Acknowledgement Form, the patient should receive a copy and the original signed form should be kept in the patient's medical record.*

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9410 Carroll Park Drive  
San Diego, CA 92121  
888-423-5227  
888-824-0896 fax  
[www.prometheuslabs.com](http://www.prometheuslabs.com)

## Patient Acknowledgement Form



LOTRONEX® (alosetron hydrochloride) is 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. LOTRONEX has not been shown to help men with irritable bowel syndrome (IBS) or patients under age 18.

My doctor, or a healthcare provider under a doctor's direction, answered my questions about treatment with LOTRONEX. I have read and I understand the Medication Guide for LOTRONEX including the section "Who should not take LOTRONEX?" and,

- I understand that about 1 out of every 1,000 women who take LOTRONEX may get serious complications of constipation. I understand that about 3 out of every 1,000 women who take LOTRONEX over a 6-month period may get a serious problem where blood flow to parts of the large bowel is reduced (ischemic colitis). I understand that the serious condition of ischemic colitis, and other serious complications of constipation, can happen suddenly. These serious complications may lead to a hospital stay, and in rare cases, blood transfusions, surgery, and death. I also understand that certain patients may be more likely to develop a serious bowel condition while taking LOTRONEX. These include older patients, those who have other health problems and those who take other medicines that may cause constipation.
- I understand that certain people may be more likely to develop a serious bowel condition while taking LOTRONEX including people who:
  - are older,
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- I understand LOTRONEX is a medication that should only be used for some women with severe chronic irritable bowel syndrome (IBS), whose main problem is diarrhea, and whose IBS symptoms have not been helped enough by other treatments.
- I will follow instructions in the Medication Guide about:
  - **telling my doctor**, before taking LOTRONEX, about any illnesses I have, or other medicines I am taking or planning to take.
  - **taking LOTRONEX** exactly as my doctor prescribes it.
  - **stopping LOTRONEX** and calling my doctor right away if I get constipated, if I have new or worse pain in my stomach area (abdomen), or if I see blood in my bowel movements.
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  - **stopping LOTRONEX and calling my doctor** if my IBS symptoms have not improved after 4 weeks of taking 1 mg of LOTRONEX 2 times a day.
- If I see other doctors about my IBS or possible side effects from LOTRONEX, I will tell the doctor who prescribed LOTRONEX.

My signature below indicates that I have read, understood, and agree with all the statements made above and that I have asked any questions that I have about LOTRONEX therapy. I would like to begin treatment with LOTRONEX.

Name of Patient (print)

Signature

After the patient signs this Patient Acknowledgement Form, the patient should receive a copy and the original signed form should be kept in the patient's medical record.

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Date



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## Welcome to the Prescribing Program for LOTRONEX (PPL)

This Medication Guide has been approved by the US Food and Drug Administration.  
Please click here for important product information about LOTRONEX: [Medication Guide](#).

[Home](#) | [Complete Prescribing Information](#) | [PROMETHEUS Website](#)  
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FOR PATIENTS

### Welcome to the Prescribing Program for LOTROXEX™ (PPL)

This Medication Guide has been approved by the US Food and Drug Administration.  
Please click here for important product information about LOTROXEX®: [Medication Guide.](#)

Click here for a downloadable version of the medication guide



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XX Month 20XX

Dear Pharmacist:

Important Information for Pharmacists

Prometheus would like to remind you about important aspects of LOTRONEX<sup>®</sup> (alosetron HCl) Tablets and the Prescribing Program for LOTRONEX<sup>™</sup> (PPL).

LOTRONEX is a selective serotonin 5-HT<sub>3</sub> antagonist indicated only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have:

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

Diarrhea-predominant irritable bowel syndrome 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 irritable bowel syndrome.

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. Patients who develop constipation or symptoms of ischemic colitis should discontinue use of LOTRONEX immediately. Patients who develop ischemic colitis should not resume LOTRONEX therapy. Because of the serious gastrointestinal 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.

The Prescribing Program for LOTRONEX was implemented in order to ensure that the benefits of LOTRONEX treatment outweigh the potential risks. You, the pharmacist, play an important role in the Prescribing Program for LOTRONEX. To become familiar with the Prescribing Program for LOTRONEX, please read the attached Prescribing Information and Medication Guide.

**In order to comply with the Prescribing Program for LOTRONEX, pharmacists need to:**

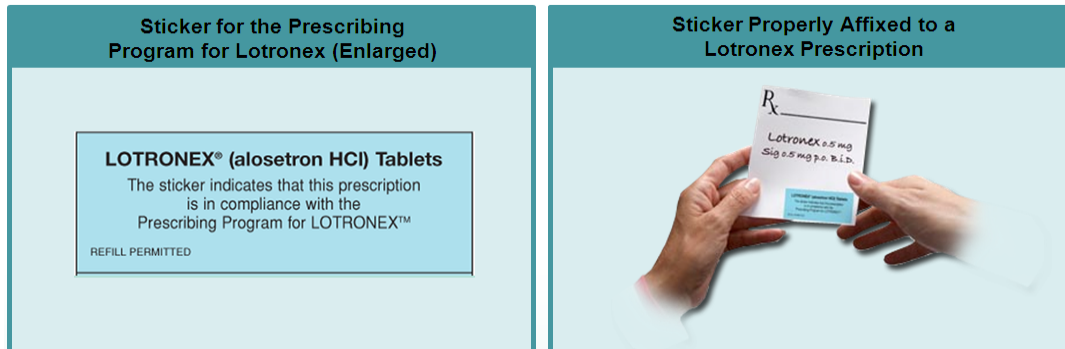




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- **Dispense only prescriptions that have a Prescribing Program for LOTRONEX Sticker - never fill telephone, facsimile, or computer-generated prescriptions; refills are only permitted on written prescriptions (Figure 1)**
- **If a Prescribing Program for LOTRONEX sticker is not present on the prescription, call Prometheus Client Services at 1-888-423-5227 to confirm that the prescriber is enrolled in the PPL.**
- **Dispense a Retail Pack for LOTRONEX, which in addition to the medicine contains the Medication Guide, Prescribing Information, and Patient Follow-Up Survey Pre-Enrollment Form (Figure 2).**



**Figure 1. The PPL Sticker Ensures Appropriate Prescribing and Dispensing of LOTRONEX**



**Figure 2. Full Trade Packs of LOTRONEX**

We have enclosed a copy of the LOTRONEX Medication Guide (MG), which must be provided to patients with every filled prescription. This Medication Guide contains information that can be used to facilitate discussions about the risks of therapy. The Medication Guide explains the dosing regimen for initiating therapy with LOTRONEX.

Only prescribers who have enrolled in the Prescribing Program for LOTRONEX should prescribe LOTRONEX. LOTRONEX is indicated only for women with severe diarrhea-predominant irritable bowel syndrome who have not responded adequately to conventional therapy.

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



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death. Patients who develop constipation or symptoms of ischemic colitis should discontinue use of LOTRONEX immediately. Patients who develop ischemic colitis should not resume LOTRONEX therapy.

Enclosed for your reference are the following educational materials that will provide additional details on LOTRONEX and the Prescribing Program for LOTRONEX:

- The LOTRONEX full Prescribing Information
- The LOTRONEX Medication Guide

For more information on the Prescribing Program for LOTRONEX, including an educational slide deck (PPL Pharmacist Educational Slide Deck) designed to educate pharmacists on their role within the PPL, contact Prometheus at 1-888-423-5227 or visit us online at [www.lotronexpl.com](http://www.lotronexpl.com).

Sincerely,  
Medical Affairs Department  
Prometheus Laboratories Inc.



# **LOTTRONEX<sup>®</sup> (alosetron HCl) Tablets:**

## **Understanding the Benefits and Risks**

### **The Prescribing Program for LOTTRONEX<sup>™</sup> Pharmacist Education Slide Deck**

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Please see complete Prescribing Information for LOTTRONEX.

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# **LOTTRONEX<sup>®</sup> (alosetron HCl) Tablets:**

## **Understanding the Benefits and Risks**

### **The Prescribing Program for LOTTRONEX<sup>™</sup> Pharmacist Education Slide Deck**

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# **Section 1:**

## **Purpose**



# **Section 1:**

## **Purpose**



## Purpose of the Pharmacist Educational Slide Deck for LOTRONEX<sup>®</sup> (alosetron HCl)

- By reviewing the information provided in this presentation, pharmacists who dispense LOTRONEX will better understand the:
  - **Restricted distribution process for this product;**
  - **Risks and benefits of LOTRONEX;**
  - **Etiology of irritable bowel syndrome;**
  - **Prescribing Program for LOTRONEX<sup>™</sup> (PPL).**

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## Purpose of the Pharmacist Educational Slide Deck for LOTRONEX<sup>®</sup> (alosetron HCl)

- By reviewing the information provided in this presentation, pharmacists who dispense LOTRONEX will better understand the:
  - Restricted distribution process for this product;**
  - Risks and benefits of LOTRONEX;**
  - Etiology of irritable bowel syndrome;**
  - Prescribing Program for LOTRONEX<sup>™</sup>(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 to ensure the benefits of the drug outweigh the risks of serious gastrointestinal adverse events. A REMS is a strategy to address the serious risks associated with a drug. The REMS can range from periodic assessment of a product's postmarketing safety profile to strict limitations on the way a drug is prescribed, distributed, or dispensed.

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## 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<sup>®</sup> to ensure the benefits of the drug outweigh the risks of serious gastrointestinal adverse events. A REMS is a strategy to address the serious risks associated with a drug. The REMS can range from periodic assessment of a product's postmarketing safety profile to strict limitations on the way a drug is prescribed, distributed, or dispensed.



## Goal of the Prescribing Program for LOTRONEX™ and Key Elements

The Prescribing Program for LOTRONEX™ (PPL) was implemented to help reduce 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 LOTRONEX (alosetron hydrochloride) by ensuring that LOTRONEX is used in only severely affected patients in whom the benefits exceed the risks.
- To ensure that the risk of IC and serious CoC with use of LOTRONEX are communicated to patients, pharmacists, and prescribers.

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- To ensure that the risk of IC and serious CoC with use of LOTRONEX are communicated to patients, pharmacists, and prescribers.



## Goal 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.
- pharmacists may only dispense LOTRONEX from prescriptions with a sticker and written by prescribers participating in the PPL.

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## Goals of the Prescribing Program for LOTRONEX™ and Key Elements (cont'd)

The Key Elements of the LOTRONEX<sup>®</sup> 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.
- pharmacists may only dispense LOTRONEX from prescriptions with a sticker and written by prescribers participating in the PPL.

## **Section 2:** **Indication and Usage**



## **Section 2:** **Indication and Usage**

**Please see complete Prescribing Information for LOTRONEX for full details.**



## **LOTRONEX<sup>®</sup> (alosetron HCl): Indication and Usage**

**LOTRONEX<sup>®</sup> (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.

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## **LOTRONEX<sup>®</sup> (alosetron HCl): Indication and Usage**

**LOTRONEX<sup>®</sup> (alosetron HCl) is indicated ONLY for women with severe diarrhea-predominant IBS who have:**

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- **not responded adequately to conventional therapy.**

**Please see complete Prescribing Information for LOTRONEX for full details.**





## LOTRONEX<sup>®</sup> (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.

10

## LOTRONEX<sup>®</sup> (alosetron HCl): Indication and Usage (cont'd)

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



## **Section 3:**

# **Important Safety Information**

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<sup>®</sup> (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<sup>™</sup> 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.

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## **LOTRONEX<sup>®</sup> (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.**

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13

## **LOTRONEX<sup>®</sup> (alosetron HCl): Boxed Warning (cont'd)**

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**Please see complete Prescribing Information for LOTRONEX for full details about risks.**

## LOTRONEX<sup>®</sup> (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.

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## LOTRONEX<sup>®</sup> (alosetron HCl): Warnings and Precautions

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**Please see complete Prescribing Information for LOTRONEX for full details about risks.**



## LOTRONEX<sup>®</sup> (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.

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## LOTRONEX<sup>®</sup> (alosetron HCl): Warnings and Precautions (cont'd)

### Serious Complications of Constipation (cont'd)

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- 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.

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## LOTRONEX® (alosetron HCl): Warnings and Precautions (cont'd)

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- **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<sup>®</sup> (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.

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## LOTRONEX<sup>®</sup> (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<sup>®</sup> (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.**

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  - **severe hepatic impairment.**

**Please see complete Prescribing Information for LOTRONEX for full details about risks.**





## **LOTRONEX<sup>®</sup> (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.

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## **LOTRONEX<sup>®</sup> (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.**

### 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.

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## **LOTRONEX<sup>®</sup> (alosecron HCl):**

### **Drug Interactions**

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**Please see complete Prescribing Information for LOTRONEX for full details about risks.**

### 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.

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## LOTRONEX<sup>®</sup> (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<sup>®</sup> (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.

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**Please see complete Prescribing Information for LOTRONEX for full details about risks.**

### 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.

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## LOTRONEX<sup>®</sup> (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<sup>a</sup>

Gastrointestinal Adverse Reactions	LOTROXEX <sup>®</sup> (alosetron HCl) 1 mg BID (n=8,328 <sup>b</sup> )	Placebo (n=2,363)
Constipation <sup>c</sup>	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%

<sup>a</sup> Reported in ≥1% of LOTROXEX patients and occurring more frequently on LOTROXEX 1mg twice-a-day than on placebo.

<sup>b</sup> Data reported from 22 repeat-dose studies in patients with IBS treated for 8 to 24 weeks.

<sup>c</sup> P<0.0001 vs placebo.

Please see complete Prescribing Information for LOTROXEX for full details about risks.

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**b** Data reported from 22 repeat-dose studies in patients with IBS treated for 8 to 24 weeks.

**c**  $P < 0.0001$  vs placebo.

**Please see complete Prescribing Information for LOTRONEX for full details about risks.**



## LOTRONEX® (alosetron HCl): Adverse Reactions

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

- In clinical studies constipation was reported in ~29% of patients with IBS treated with LOTRONEX 1 mg twice-a-day (n=9,316):
  - **The effect was statistically significant compared with placebo ( $P<0.0001$ ).**
  - **11% of patients treated with LOTRONEX 1 mg twice-a-day withdrew from the studies due to constipation.**
- Although the number of IBS patients treated with LOTRONEX 0.5 mg twice-a-day is relatively small (n=243), 11% of patients reported constipation and 4% of patients withdrew from clinical studies due to constipation.

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

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## LOTRONEX<sup>®</sup> (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.

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## LOTRONEX<sup>®</sup> (alosetron HCl): Overdosage

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# **Section 4:**

## **The Prescribing Program for LOTRONEX™**



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## **The Prescribing Program for LOTRONEX™**



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

- Prescribers must read the full PI and understand the benefits and risks of treatment with LOTRONEX® for women with severe diarrhea-predominant IBS.
- Prescribers then complete the Prescriber Enrollment Form at [www.lotronexppl.com](http://www.lotronexppl.com) or call 1-888-423-5227 or ask a Prometheus representative for enrollment materials:
  - **The form must be returned to Prometheus before a prescriber can be considered enrolled in the PPL.**
- Starter PPL kits including Medication Guides and stickers that need to be affixed to every prescription are provided after enrollment.

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## The Prescribing Program for LOTRONEX™

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

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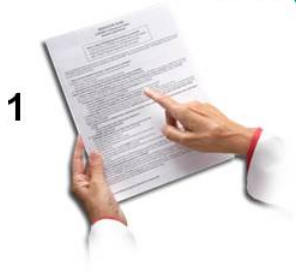
## The Prescribing Program for LOTRONEX™

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## Overview of Prescriber Responsibilities for the Prescribing Program for LOTTRONEX™



**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) 30

## Overview of Prescriber Responsibilities for the Prescribing Program for LOTTRONEX™



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Provide patient with written prescription with affixed PPL sticker (refills are permitted on written prescriptions)

## **Section 5:**

### **Role of the Pharmacist in the Prescribing Program for LOTRONEX™**

## **Section 5:**

### **Role of the Pharmacist in the Prescribing Program for LOTRONEX™**

- Learn about the Prescribing Program for LOTRONEX™ (PPL).
- Understand the benefits and risks of treatment with LOTRONEX® for severe diarrhea-predominant IBS, including the information in the Retail Pack for LOTRONEX, which contains the Prescribing Information, the Medication Guide, and the Patient Follow-Up Survey Pre-Enrollment Form.
- To ensure documentation of safe-use conditions, pharmacists must confirm the validity of every prescription of LOTRONEX by ensuring that the PPL sticker is present on the prescription prior to dispensing LOTRONEX to a patient.

Please see complete Prescribing Information for LOTRONEX for full details.

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## Pharmacist Responsibilities

- Learn about the Prescribing Program for LOTRONEX™ (PPL).
- Understand the benefits and risks of treatment with LOTRONEX® for severe diarrhea-predominant IBS, including the information in the Retail Pack for LOTRONEX, which contains the Prescribing Information, the Medication Guide, and the Patient Follow-Up Survey Pre-Enrollment Form.
- To ensure documentation of safe-use conditions, pharmacists must confirm the validity of every prescription of LOTRONEX by ensuring that the PPL sticker is present on the prescription prior to dispensing LOTRONEX to a patient.

- If a PPL sticker is not present on the prescription, call Prometheus Client Services at 1-888-423-5227 to confirm that the prescriber is enrolled in the Prescribing Program for LOTRONEX.
- Provide each patient with their prescribed treatment of LOTRONEX<sup>®</sup> and the Retail Pack. The Retail Pack includes a copy of the LOTRONEX Medication Guide.

Please see complete Prescribing Information for LOTRONEX for full details.

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## Pharmacist Responsibilities (cont'd)

- If a PPL sticker is not present on the prescription, call Prometheus Client Services at 1-888-423-5227 to confirm that the prescriber is enrolled in the Prescribing Program for LOTRONEX.
- Provide each patient with their prescribed treatment of LOTRONEX<sup>®</sup> and the Retail Pack. The Retail Pack includes a copy of the LOTRONEX Medication Guide.

Please see complete Prescribing Information for LOTRONEX for full details.



## Prescribing Program for LOTRONEX™

- To prescribe LOTRONEX® (alosetron HCl), prescribers (physicians) must be enrolled in the Prescribing Program for LOTRONEX™ (PPL).
- To enroll, prescribers must understand the benefits and risks of treatment with LOTRONEX for women with severe diarrhea-predominant IBS, including the information in the Prescribing Information, Medication Guide, and Patient Acknowledgement Form for LOTRONEX.
- Pharmacists should also learn about and understand the benefits and risks associated with LOTRONEX treatment.

Please see complete Prescribing Information for LOTRONEX for full details.

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## The Prescribing Program for LOTRONEX™

- To prescribe LOTRONEX® (alosetron HCl), prescribers (physicians) must be enrolled in the Prescribing Program for LOTRONEX™ (PPL).
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- Pharmacists should also learn about and understand the benefits and risks associated with LOTRONEX treatment.

**Please see complete Prescribing Information for LOTRONEX for full details.**



## Prescribing Program for LOTRONEX™ (cont'd)

- Upon enrollment in the Prescribing Program for LOTRONEX™ (PPL), stickers for prescriptions are provided to prescribers.
- Stickers affixed to a prescription of LOTRONEX® indicate the following:
  - Certifies participation of a prescriber in the PPL.
  - LOTRONEX 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.



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## The Prescribing Program for LOTRONEX™ (cont'd)

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

**LOTROXEX® (alosetron HCl) Tablets**

The sticker indicates that this prescription is in compliance with the Prescribing Program for LOTROXEX™

REFILL PERMITTED

**Sticker Properly Affixed to a Lotronex Prescription**







# Overview of Pharmacist Responsibilities A Simple 2-Step Process



Verify validity of LOTRONEX prescription by checking for the PPL sticker (refills are permitted on written prescriptions)

2



**Dispense a Retail Pack for LOTRONEX, which includes Medication Guide, Prescribing Information, Medicine, and Patient Follow-Up Survey Pre-Enrollment Form**

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

# Overview of Pharmacist Responsibilities A Simple 2-Step Process



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**Note to Pharmacist:**

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

## **Your Role in The Prescribing Program For LOTRONEX™ (PPL)**

You play an important role in the Prescribing Program for LOTRONEX. Please read the attached complete Prescribing Information, which includes the Medication Guide. To become familiar with the requirements of the PPL, please review the attached PPL Pharmacist Education Slide Deck.

- [PPL Pharmacist Education Slide Deck](#)
- [Medication Guide](#)

Pharmacists need to:

- dispense only prescriptions that have a Prescribing Program Sticker – never fill telephone, facsimile, or computer-generated prescriptions; refills are permitted on written prescriptions.
- dispense a Retail Pack for LOTRONEX, which includes Medication Guide, Prescribing Information, Medicine, and Patient Follow-Up Survey Pre-Enrollment Form.

Please consult the [Complete Prescribing Information](#).

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**FOR PHARMACISTS**

**YOUR ROLE IN THE  
PRESCRIBING PROGRAM  
FOR LOTROXEX™ (PPL)**

- PPL Pharmacist  
Education Slide Deck
- Medication Guide

This click through to a Lotronex for pharmacists downloadable version of the Medication Guide

This will click through to the prescribing information for LOTROXEX

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- [PPL Pharmacist Education Slide Deck](#)
- [Medication Guide](#)

This clicks through to an educational slide deck on Lotronex for pharmacists.

Pharmacists need to:

- dispense only prescriptions that have a Prescribing Program Sticker - never fill telephone, facsimile, or computer-generated prescriptions; refills are permitted on written prescriptions
- dispense a Retail Pack for LOTROXEX®, which includes Medication Guide, Prescribing Information, Medicine, and Patient Follow-Up Survey Pre-Enrollment Form.

Please consult the [Complete Prescribing Information](#).



[Home](#) | [Complete Prescribing Information](#) | [PROMETHEUS Website](#) | [Site Map](#) | [Reference Page](#)



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Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-21107

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SUPPL-14

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PROMETHEUS  
LABORATORIES  
INC

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LOTRONEX

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JOYCE A KORVICK

09/02/2010