

FDA Background Package

For Meeting of Drug Safety and Risk Management Advisory Committee (DSaRM)

Lotronex (alosetron HCl)

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**Center for Drug Evaluation and Research
Food and Drug Administration**

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1 Division Director Memorandum



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
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M E M O R A N D U M**

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From: Claudia Manzo, PharmD
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To: Chair, Members and Invited Guests
Drug Safety and Risk Management Advisory Committee
(DSaRM)

Subject: Overview of the July 10, 2013 DSaRM meeting

The Food and Drug Administration Amendments Act of 2007 requires FDA to bring, at least annually, one or more drugs with Risk Evaluation and Mitigation Strategies (REMS) with elements to assure safe use (ETASU) before its Drug Safety and Risk Management Advisory Committee (DSaRM). On July 10, 2013, the DSaRM will meet to discuss the risk management of Lotronex (alosetron hydrochloride) tablets, Prometheus Laboratories Inc., which is approved for the treatment of women with severe diarrhea predominant irritable bowel syndrome (IBS-D).

On July 10, 2013, the Agency will seek the DSaRM's comments as to whether or not the REMS with ETASU for Lotronex assures safe use, is unduly burdensome to patient access to Lotronex, and to the extent practicable, minimizes the burden to the healthcare delivery system.

The current Lotronex REMS includes a Medication Guide, ETASUs (prescriber certification, documentation of safe use, and pharmacy documentation of safe use), and an Implementation System. The Agency is seeking input from the Committee on issues related to Lotronex REMS.

The following points to consider will be discussed by the committee members:

1. Discuss the current success and challenges of the Lotronex REMS. What aspects of the current REMS are working well and what aspects are not working well?

2. Considering the information provided today regarding the current Lotronex REMS, discuss:
 - a. Whether the REMS assures safe use,
 - b. If the REMS is unduly burdensome to patient access to the drug, and
 - c. To the extent practicable, minimizes the burden to the healthcare delivery system (prescribers and pharmacists).

3. Discuss whether any modifications should be made to the REMS, specifically:
 - a. Discuss whether the following elements to assure safe use are still needed:
 - i. Healthcare providers will be specially certified (training and enrollment)
 - ii. Each patient prescribed Lotronex must have signed a Patient Acknowledgement Form for documentation of safe-use conditions
 - iii. Pharmacists will only dispense Lotronex with documentation of safe use conditions (sticker affixed to prescription)
 - b. If you believe an element to assure safe use is still needed, do you recommend any modifications?
 - c. Do you recommend any other modifications?
 - d. If any changes are recommended, discuss how you would assess the impact of the changes on the safe use of Lotronex.

2 Background

Product Description

Lotronex (alosetron hydrochloride) is a selective 5-HT₃ receptor antagonist. 5-HT₃ 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-HT₃ receptor antagonists such as alosetron inhibit activation of non-selective cation channels, which results in the modulation of the enteric nervous system.

Lotronex is indicated only for women with severe diarrhea-predominant irritable bowel syndrome (IBS).

Other IBS Treatment Options

For patients who have failed conventional therapy, Lotronex is the only approved drug to treat IBS-diarrhea predominant type.

Irritable Bowel Syndrome

Irritable Bowel Syndrome (IBS) “involves a broad range of physiological and psychological alternations that may affect brain-gut regulation, gut function, visceral perception, and mucosal integrity and function. Despite advances in our understanding of basic neuroenteric mechanisms and the role of effectors and transmitters in the brain-gut axis, a reliable biologic marker of IBS has yet to be identified. IBS diagnosis and status depend entirely on an assessment of IBS signs and symptoms. This has made the development of optimal endpoints and study design for evaluation of efficacy of IBS drugs a challenge.”¹

The cause of IBS is unknown. Colonic transit is accelerated in around 45% of patients with diarrhea-predominant IBS (IBS-D) and retarded in approximately 20% of constipation predominant IBS (IBS-C) patients.² The symptoms commonly associated with the syndrome include cramping, abdominal pain, bloating, gas, diarrhea and/or constipation. The symptoms, as they present, can be waxing and waning over time and some patients may experience both constipation and diarrhea. IBS is most commonly seen in female patients.

Disease Severity

IBS-D is not a life threatening disease, but for some patients it significantly interferes with their quality of life and is significantly disabling. While there is not a specific definition of severe IBS-

¹ Trentacosti AM, He R, Burke LB, Griebel D, Kennedy DL. Evolution of Clinical Trials for Irritable Bowel Syndrome: issues in endpoints and study design. *Am J Gastroenterol* 2010; 105:730-734.

² Camilleri M. Irritable bowel syndrome: how useful is the term and the ‘diagnosis’? *Therap Adv Gastroenterol* 2012 November; 5(6):381-386

D, there is an attempt to define it in the current Lotronex label. This wording was added to the labeling, Medication Guide and educational materials at the time of reintroduction of Lotronex to the market in 2002. (see Regulatory History below)

The labeled definition is as follows³:

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.

Regulatory History

Lotronex was approved on February 9, 2000 following a Gastrointestinal Drugs Advisory Committee (GIDAC) meeting held on November 16, 1999 to discuss the efficacy and safety observed with alosetron. The Committee recommended approval of Lotronex by the Agency.

During the first two quarters of 2000, FDA received reports of serious adverse events (SAE) including Ischemic Colitis (IC) and severe complications of constipation (CoC) associated with use of Lotronex. The Agency convened a second GIDAC meeting on June 27, 2000 to discuss the SAE postmarketing cases including IC and severe CoC, hospitalizations, blood transfusions, and death.

On November 28, 2000, GlaxoSmithKline (GSK) voluntarily withdrew Lotronex from the U.S. market due to postmarketing serious gastrointestinal adverse events including IC and severe CoC, some cases leading to hospitalization with surgery, blood transfusions, and death. GSK submitted new safety data to the Agency on December 7, 2001. The Agency convened a third GIDAC meeting on April 23, 2002 to discuss the reported postmarketing safety of serious

³ Lotronex (alosetron) professional labeling, approved 09/2/2010.

gastrointestinal events and to consider the risks and benefits of re-introducing Lotronex to the U.S. market.

On June 7, 2002⁴ Lotronex was approved for re-introduction to the U.S. market under 21 CFR 314.500 Subpart H approval requiring a Risk Minimization Action Plan (RiskMAP) designed to mitigate serious outcomes of the adverse reactions of special interest, i.e., IC, and CoC. At that time the professional labeling for Lotronex was revised to include a BOX WARNING, a narrowed indicated patient population (i.e., severe IBS-D), a lower starting dose to reduce constipation, and a Medication Guide.

The RiskMAP included prescriber enrollment in the Prescribing Program for Lotronex (PPL) which included agreement by the prescriber that they are able and willing to:

- diagnose and manage IBS, IC and COC or refer patients to specialists as needed
- educate patients on the benefits and risks of treatment with Lotronex and provide them with the Medication Guide.
- obtain the patient's signature on the Patient Acknowledgement form (PAF)
- affix program stickers to all prescriptions for Lotronex
- report all serious adverse events with Lotronex
- encourage the patient to enroll in a voluntary patient survey

The PPL also included an educational component for physicians and patients to reinforce labeling revisions and to ensure enhanced patient monitoring especially during the first month of therapy and early recognition and appropriate management of constipation, IC, and CoC. While pharmacies were not certified in the RiskMAP, pharmacists were asked to look for stickers affixed to the prescription before dispensing the drug. The program sticker signified that the conditions of safe use were being followed by the prescriber.

On May 5, 2004 an Advisory Committee meeting of the Drug Safety and Risk Management Advisory Committee was held. The RiskMAP was discussed at that time. In general, the Committee agreed that the program was working.

Lotronex Risk-Benefit Characterization⁵

Risks

Serious Complications of Constipation

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

⁴ Lotronex was re-authorized on June 7, 2002 and re-marketed on November 20, 2002.

⁵ Risks and Benefits appear as described in the currently approved Lotronex professional labeling (approved 09/02/2010)

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.”

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.”

It is important to note that not all cases of ischemic colitis are life-threatening, and as will be discussed below, it appears that with early identification of ischemic colitis, prompt professional attention, the serious sequelae of surgery, transfusion, and death have been reduced⁶. This will be discussed further in the Division of Pharmacovigilance section below.

Benefits

Retrospective analyses were conducted prior to reintroduction of Lotronex to the U.S. market since it was anticipated that Lotronex would be limited to patients (only women with severe IBS-D) who would potentially receive the most benefit. It should be noted that these analyses were challenging because there was no standard for determining severe IBS patients and so

⁶ Chang I, Tong K, Ameen V. Ischemic colitis and complications of constipation associated with the use of alosetron under a risk management plan: clinical characteristics, outcomes, and incidences. *Am J Gastroenterol* 2010; 105:866-875.

symptoms related to severity such as abdominal pain and discomfort and urgency were evaluated. The following are the efficacy results as stated in the label.

- “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.”

Lotronex Product Labeling

With the reintroduction of Lotronex to the market in 2002 the information contained in the professional label, Medication Guide, and RiskMAP limited use to patients with severe IBS, enhanced the safety message regarding IC and SoC, revised the dosing and administration recommendations, including instructions to stop taking the medication if it was not working. These changes were directed to reducing the risk of exposure to Lotronex. During the FDA review of safety data and considering discussions at the 2002 GIDAC, it was apparent that there were no laboratory assessments or clinical characteristics of the patients who experienced IC which could be used to further limit the population of patients taking Lotronex. The new labeling information along with educational programs has enhanced the safe of the use of Lotronex. The current Lotronex professional product labeling and Medication Guide can be found in **Appendix A and B**.

3 Risk Evaluation and Mitigation Strategy

Section 505-1 of the Food, Drug, and Cosmetic Act (FDCA), as amended by the Food and Drug Administration Amendments Act of 2007 (FDAAA), authorizes the FDA to require pharmaceutical sponsors to develop and comply with a Risk Evaluation and Mitigation Strategy (REMS) for a drug if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. A REMS is a required risk management plan that uses risk minimization strategies beyond the professional labeling. The elements of a REMS can include: a Medication Guide or patient package insert (PPI), a communication plan to healthcare providers, elements to assure safe use, and an implementation system. All REMS approved for drugs or biologics under New Drug Applications (NDA) and Biologics License Applications (BLA) must have a timetable for submission of assessments of the REMS. These assessments are prepared by the Sponsor and reviewed by FDA.

A Medication Guide provides FDA approved patient-focused labeling and can be required as part of the approved labeling if FDA determines one or more of the following apply:

- Patient labeling could help prevent serious adverse events.
- The product has serious risks that could affect a patient’s decision to use or continue to use the drug.
- Patient adherence to directions is crucial to product effectiveness.

A communication plan consists of FDA approved materials used to aid a sponsor’s implementation of the REMS and/or inform healthcare providers about serious risk(s) of an approved product. This can include, for example, “Dear Healthcare Professional” letters, collaboration with professional societies, and education pieces (such as letters, drug fact sheets) to inform prescribers of the risks and the safe use practices for the drug.

Elements to assure safe use (ETASU) can include one or more of the following requirements:

- Healthcare providers who prescribe the drug have particular training or experience or special certifications
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
- The drug may be dispensed only in certain healthcare settings
- The drug may be dispensed to patients with evidence of safe-use conditions
- Each patient must be subject to monitoring
- Patients must be enrolled in a registry

Because ETASU can impose significant burdens on the healthcare system and reduce patient access to treatment, ETASU are required only if FDA determines that the product could be approved only if, or would be withdrawn unless, ETASU are required to mitigate a specific serious risk listed in the labeling. Accordingly, section 505-1(f)(2) of the FDCA specifies that ETASU:

- Must be commensurate with specific serious risk(s) listed in the labeling.
- Cannot be unduly burdensome on patient access to the drug.
- To minimize the burden on the healthcare delivery system, must, to the extent practicable, conform with REMS elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs.

A REMS may also include an implementation system to enable the Sponsor to monitor, evaluate, and improve the implementation of the elements.

Lotronex REMS

Lotronex was identified as a drug deemed to have in effect an approved REMS because the product had a RiskMAP with elements to assure safe use in effect on the March 25, 2008.⁷ The Sponsor submitted a proposed REMS and the REMS was approved on September 2, 2010.

The goals of the Lotronex REMS 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 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.

The Lotronex REMS includes a Medication Guide and the following Elements to Assure Safe Use with the following elements:

- Healthcare providers who prescribe Lotronex will be specially certified (will affix stickers to prescriptions for patients who meet conditions of safe use).
- Each patient prescribed Lotronex must have signed a Patient Acknowledgement Form for documentation of safe-use conditions.
- Pharmacists will only dispense Lotronex to patients with documentation of safe-use conditions (i.e. sticker affixed to the prescription).
 - Prescriptions will not be transmitted by facsimile, telephone, or computer

The Lotronex REMS also includes an implementation system to monitor compliance with the program requirements and a timetable for submission of assessments. Since the approval of the Lotronex REMS program the Sponsor (Prometheus) was required to submit REMS Assessments to the FDA every 6 months for the first year from the date of initial approval of the REMS and then annually thereafter.

See **Appendix C** for the Lotronex REMS document

4 REMS Assessment

Lotronex REMS Assessment Plan

The major components of the Lotronex REMS assessment plan, put into place to evaluate whether or not the REMS is achieving its goals, include the following:

1. Process measures:
 - The number of certified prescribers enrolled in the program

⁷ The effective date of Title IX, subtitle A of FDAAA.

- The number of prescriptions written for Lotronex by non-certified prescribers
 - The number of prescriptions dispensed for Lotronex that are written by non-certified prescribers
 - The number of prescribers who are removed from the program due to non-compliance
 - Corrective and preventive actions to address non-compliance with distribution and dispensing requirements
 - An assessment of the distribution and dispensing of the Medication Guide and corrective actions taken to address non-compliance
2. Drug Utilization measures:
- Drug use patterns to include the reasons for Lotronex use, patient demographics, and the prescribing medical specialties
3. Outcomes measures:
- An assessment (including number and summaries) of spontaneously reported adverse events of interest such as ischemic colitis (IC), serious complications of constipation (CoC), as well as death from all causes
4. Knowledge measures:
- Patient, prescriber, and pharmacist surveys administered to assess knowledge of the risks and how to safely use the drug

Most Recent Lotronex REMS Assessment Report Findings

On August 30, 2012, the Sponsor submitted their most recent Lotronex REMS assessment report which covered the period from July 1, 2011 to June 30, 2012. The Sponsor's Advisory Committee meeting backgrounder provides details and results from this most recent report. Of note, the findings that will be shared have not changed significantly from the prior assessments. Below is FDA's interpretation of whether the REMS is meeting its goals based upon the findings from the most recent REMS assessment report.

Assessment of the First REMS Goal

Although the REMS program does not allow for a direct assessment of the first REMS goal - 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 for whom benefits exceed the risks - there are a number of indirect data measures that suggest this goal is being met. Ideally, an assessment of whether or not Lotronex is being used in an appropriate population would include not only Lotronex drug use pattern data, such as reasons for use and patient demographics, but also other key indicators of appropriate use such as:

- 6 months or longer duration of patients' IBS-D symptomatology
- inadequate response to conventional treatment(s) prior to initiation of Lotronex

- whether anatomic or biochemical abnormalities of the gastrointestinal tract have been excluded prior to initiation of Lotronex; and
- Severe IBS-D conditions, such as disability or restriction of daily activities

To obtain these types of data would, at a minimum, require use of a much more in-depth patient-level database than a typical drug utilization database.

In lieu of the aforementioned approach, both the prescriber and patient surveys serve as proxy measures to determine whether Lotronex is being used appropriately. Knowledge, Attitude, and Behavior (KAB) surveys are used as part of most REMS assessments. The methodologies for the Lotronex REMS KAB surveys were submitted to the Agency for review. The methodology was deemed to be appropriate to effectively assess prescribers', pharmacists', and patients' knowledge of the risks associated with and safe use of Lotronex. The surveys conducted by the Sponsor included questions to assess the goals of the REMS and were determined to be acceptable by the Agency reviewers, although all surveys are limited since they are generally convenience samples that may not represent the population of prescribers and patients.

The prescriber survey indicates that overall, prescribers do recognize the individual patient factors that need to be considered before deciding whether or not to initiate Lotronex in a particular patient. Although it can be debated whether or not prescriber knowledge predicts appropriate prescriber actions, the demographics of the 628 patients who completed the survey are reassuring. Specifically, patients taking the Lotronex survey were predominantly females, mostly being treated for IBS-D, and most of whom had been suffering with the disease for more than 6 months, had tried and failed conventional treatments, and who had suffered significant quality of life issues due to their disease.

In addition to ensuring Lotronex use in severely affected patients, the first goal also reflects the intention of the REMS to mitigate the risk of IC and serious CoC. To definitively assess whether the REMS has been successful in mitigating these serious risks would require the determination of a precise event rate of each adverse event prior to and after the implementation of the REMS program. These types of data can be difficult to generate due to a myriad of factors, not the least of which includes assuring an accurate diagnosis of IC as there can be many other causes of abdominal pain and rectal bleeding. An aspirational goal could be that there would be no IC or serious CoC cases at all; however, even in the most appropriately selected patients, it is unlikely that either risk can be completely prevented. At best, the hope is that awareness of IC and serious CoC would be raised to such a degree that cases are identified early and then appropriately managed.

During this reporting period, there were eight reports of IC and one report of serious CoC. Of these eight IC cases:

- all were female
- only two cases specified the indication for which Lotronex was prescribed, and in both cases it was for IBS-D

- diagnosis of IC was made by colonoscopy or sigmoidoscopy in seven of eight cases.
- three cases were treated as outpatients;
- three cases were hospitalized, and no cases required surgery
- no cases of colon necrosis were reported

In the one report of serious CoC, the patient presented to the emergency department, was treated with a laxative, and the event resolved. There were no deaths identified during this reporting period.

Reported cases of IC and serious CoC during the most recent REMS assessment period appear to have been identified early, appropriately diagnosed and treated. In addition, with regards to IC, none of the cases involved colon necrosis or required surgical intervention.

Based on these findings from the most recent assessment report, FDA concludes that the first goal of the Lotronex REMS is being met.

Assessment of the Second REMS Goal

Assessing the second Lotronex REMS goal - the communication of the risk of IC and serious CoC to patients, pharmacists, and prescribers - involves use of “Knowledge, Attitude and Behavior” (KAB) surveys.

Results of the patient survey administered during this period showed that 80% of patients knew that severe CoC is a potential complication with Lotronex treatment and that 67% knew that IC is a potential complication. While the knowledge rate for IC is lower than for severe CoC, it is encouraging that in response to a question describing specific symptoms of IC and asking what steps patients would take in response to such symptoms, 93% knew that they needed to stop taking Lotronex and to call their doctor right away.

For the physician survey, greater than 90% of physicians responded correctly to key questions testing knowledge of symptoms of IC and serious CoC, as well as the appropriate steps to take if the patient reports such symptoms.

Among pharmacists, in response to questions dealing with indication, disease severity criteria, as well as duration of IBS-D symptoms, pharmacist knowledge rates ranged between 80% to 90%. Eighty-seven percent of pharmacists knew to make sure that a program sticker appears on prescription prior to dispensation; while 63% of pharmacists knew not to accept telephone, FAX, or computerized prescriptions for Lotronex.

Based on these findings from the most recent assessment report, FDA concludes that the second goal of the Lotronex REMS is being met. As noted, the KAB surveys have recognized limitations, including potentially small sample sizes, as well as the fact that since these are convenience samples, and hence results may not be generally representative. Although the survey data may have limitations, the FDA interprets these survey data as indicating that the

REMS is effective in meeting its educational goal of informing stakeholders of the risks of IC serious CoC.

The most recent REMS assessment findings suggest that the Lotronex REMS goals are being met, but the review of the assessment report as will be summarized by the Sponsor, suggests that some of the REMS processes that are in place to assure an effective program may need refinement to improve compliance and/or potentially decrease burden. The Sponsor's presentation of prescription data will demonstrate that over the most recent 12 month period for which there are data, 10% of prescriptions dispensed were written by non-enrolled prescribers. Additionally, the pharmacist survey analysis found that only 63% of pharmacists knew not to accept telephone, FAX, or computerized prescriptions for Lotronex. The Committee should discuss potential modifications to the REMS program to address these findings.

5 Pharmacist Verification of Presence of an Affixed Sticker

The means by which safe use conditions are verified, one component of the Lotronex REMS, varies significantly across REMS programs. In most REMS, the pharmacies or other settings that dispense or administer the drug verify safe use conditions. Safe use conditions might include verification that prescribers are certified, that patients have signed a PAF, or that a laboratory test has been conducted. In the Lotronex REMS, certified prescribers are asked to place a sticker on all Lotronex prescriptions, and pharmacists are asked to look for these stickers before dispensing the drug. While pharmacies are not certified in the REMS, pharmacists are asked to look for these stickers before dispensing the drug. The program sticker signifies to the pharmacist that the conditions of safe use are being followed by the prescriber. The requirement for the sticker precludes electronic prescribing or even faxed prescriptions for Lotronex. The Lotronex REMS is currently the only program with such a sticker requirement. In contrast, in the iPLEDGE program for isotretinoin, pharmacists must go to the iPLEDGE website and obtain a special "Risk Management Authorization" number, which confirms that the prescriber is certified and that the patient has answered contraception questions and received a negative pregnancy test.

In recent years, pharmacists have expressed concern that existing methods for pharmacist verification of safe use conditions do not fit within their routine workflow, are difficult to integrate into their systems, and are unnecessarily burdensome. In addition, there has been concern that many of the existing methods for verifying safe use conditions lack "hard stops" to prevent unauthorized dispensing. When a pharmacist that is unaware of the existence of a REMS or does not follow REMS procedures, they may dispense a drug without verifying that safe use conditions are in place.

To address these concerns, pharmacists and other stakeholders, including FDA, have worked with the National Council on Prescription Drug Programs (NCPDP) to develop standards for the electronic communication of REMS information via existing pharmacy systems. Using NCPDP's Telecommunications Standard, which is the standard used to handle third-party billing in retail

pharmacies, it is possible for retail pharmacies to automatically verify that safe use conditions are in place when they submit pharmacy claims (accommodations have been made to ensure that safe use conditions are verified for patients who pay out-of-pocket as well). Furthermore, in the event that certain REMS safe use conditions are not in place (e.g., a required lab test hasn't been completed), the pharmacy practice management system is able to issue a "hard stop" to prevent dispensing.

The first REMS programs to use this electronic system for the verification of safe use conditions were those for Transmucosal Immediate-Release Fentanyl (TIRF) products. While such a system is not currently used for Lotronex, it may present a viable electronic alternative option to stickers for preventing dispensing of prescriptions of Lotronex written by non-enrolled prescribers.

6 Pharmacovigilance Review

This review evaluates post-market reports of serious⁸ cases of ischemic colitis (IC) and complications of constipation (CoC) with a focus on cases of blood transfusions, surgery, or death reported for Lotronex from the FDA Adverse Event Reporting System (FAERS). This review includes reports received following re-introduction of Lotronex under the RiskMAP and REMS.

Methods and Materials

Case Definition

FAERS database was searched by diagnosis (IC or CoC) and clinical outcome (death, surgery, or transfusion)

Diagnosis: Ischemic Colitis or Complications of Constipation

1. Table 1 describes the criteria for cases of IC or CoC as either probable or possible.⁹
2. Cases were excluded if the date of event occurred prior to November 20, 2002, date when Lotronex was re-marketed.

⁸ Serious outcome per 21CFR 600.80, 2013

⁹ Chang, L., Tong, K., Ameen, V. Ischemic colitis and the complications of constipation associated with the use of alosetron under a risk management plan: clinical characteristics, outcomes, and incidences. *Am J Gastroenterol* 2010;105:866-75

	Ischemic colitis	Complications of Constipation
Probable	Diagnosis supported by clinical evidence PLUS endoscopic and/or biopsy findings. In some cases with good documentation of biopsy and/or endoscopy findings, but poor documentation of clinical evidence, the clinical evidence was assumed	N/A
Possible	Diagnosis supported primarily by clinical evidence. Some cases include radiographic and/or endoscopic findings that were compatible with, but not diagnostic of, ischemic colitis.	Medical history, diagnoses reported, and supportive tests confirmed by health care personnel that were consistent with one of the diagnoses listed for CoC.*
Insufficient evidence to support diagnosis	Not enough evidence to make a possible or probable diagnosis.	Medical history, diagnoses reported, and supportive tests not consistent with any of the diagnoses listed for CoC

*obstruction, perforation, intestinal ulceration, toxic megacolon, ileus, fecal impaction

Clinical Outcome: Death, Surgery or Transfusion

1. Explicitly reported that there was a death, surgery or blood transfusion attributable to IC or CoC (defined in Table 1) with Lotronex use.
2. Cases were excluded if the date of event occurred prior to November 20, 2002, date when Lotronex was re-marketed.

FAERS Search Strategy

Diagnosis: Ischemic Colitis or Complications of Constipation

The FDA Adverse Event Reporting System (FAERS) was searched with the strategy described in Table 2.

Date of Search	May 30, 2013	
Date Range	November 20, 2002 to December 31, 2012	
Product Terms	Product active ingredient: alosetron, alosetron hydrochloride Product name: alosetron, alosetron hydrochloride, Lotronex	
Seriousness	Death, Hospitalization, Life Threatening, Congenital Anomaly, Other	
Search terms (MedDRA 16.0)	<u>Ischemic Colitis:</u> Colitis ischaemic, Intestinal ischaemia, Colitis, Abdominal pain, Abdominal discomfort, Gastrointestinal pain, Haematochezia, Diarrhoea haemorrhagic	<u>Complications of Constipation:</u> Colonic Stenosis, gastrointestinal pain, ileal perforation, ileus, ileus paralytic, intestinal obstruction, Intestinal perforation, impaired gastric emptying, Large intestine perforation, Lower gastrointestinal haemorrhage, small intestinal obstruction, bowel obstruction, Megacolon, Faecaloma

Clinical Outcome: Death, Surgery or Transfusion

An additional FAERS search was conducted to identify all cases of death, surgery or transfusion reported with Lotronex use regardless of event terms. The cases were then reviewed to determine if the outcome may be related to IC or CoC.

Results

The FAERS searches identified 54 cases of IC (n=45) and CoC (n=9) probably or possibly related to Lotronex use since market re-introduction based on our case definition in Table 1. A safety evaluator and a medical officer independently reviewed the reports and agreed with the selected cases.

Summary of FAERS Cases

Diagnosis: Ischemic Colitis or Complications of Constipation (n = 54)

Ischemic Colitis (n = 45)	Complication of Constipation (n = 9)
<ul style="list-style-type: none"> ○ Diagnostic Certainty of IC Cases (mutually exclusive Categories) (n = 45) <ul style="list-style-type: none"> ○ Both histologic and endoscopic evidence: 20 (45%) ○ Endoscopic evidence only: 13 (29%) ○ Histologic evidence only: 1 (2%) ○ Radiologic evidence only: 5 (11%) ○ Diagnosis provided by physician without documentation: 6 (13%) ○ Gender: Male 0, Female 45, Unk 0 ○ Age (years): 52 mean <ul style="list-style-type: none"> ○ 21-30: 6 (13%) ○ 31-40: 4 (9%) ○ 41-50: 4 (9%) ○ 51-60: 12 (27%) ○ 61-70: 11 (24%) ○ 71-80: 2 (4%) ○ > 80: 1(2%) ○ Not Reported: 5 (11%) ○ Indications for use as stated in the report <ul style="list-style-type: none"> ○ IBS-Diarrhea predominant: 25 (56%) ○ IBS: 13 (29%) ○ IBS-Alternating: 0 (0%) ○ Diarrhea: 1 (2%) ○ Post-infectious diarrhea: 1 (2%) ○ Not Reported: 5 (11%) ○ Time to onset (days): 533 mean, 189 median, 2 to 3141 range (n = 42) ○ Contraindications as stated in the report (n = 1): <ul style="list-style-type: none"> ○ Ischemic colitis, or history of: 1 ○ Outcomes (Categories mutually exclusive) (n = 45) <ul style="list-style-type: none"> ○ Only Lotronex discontinuation: 26 (58%) 	<ul style="list-style-type: none"> ○ Complication of Constipation Reported (n = 9) <ul style="list-style-type: none"> ○ bowel obstruction: 4 (44%) ○ fecal impaction: 4 (44%) ○ bowel perforation: 1 (11%) ○ Gender: Male 2, Female 7, Unk 0 ○ Age (years): 57 mean <ul style="list-style-type: none"> ○ 21-30: 1 (11%) ○ 31-40: 0 (0%) ○ 41-50: 3 (33%) ○ 51-60: 2 (22%) ○ 61-70: 1 (11%) ○ 71-80: 1 (11%) ○ > 80: 1 (11%) ○ Not Reported: 0 (0%) ○ Indications for use as stated in the report <ul style="list-style-type: none"> ○ IBS-Diarrhea predominant: 5 (56%) ○ IBS: 3 (33%) ○ IBS-Alternating: 0 (0%) ○ Diarrhea: 1 (11%) ○ Not Reported: 0 (0%) ○ Time to onset (days): 104 mean, 25 median, 5 to 465 range (n = 7) ○ Contraindications as stated in the report (n = 2): <ul style="list-style-type: none"> ○ Male patient: 2 ○ Outcomes (Categories mutually exclusive) (n = 9) <ul style="list-style-type: none"> ○ Required hospitalization: 6 (67%) ○ Required surgery for an obstructed, necrotic, ruptured bowel: 1 (11%) ○ Only Lotronex discontinuation: 1 (11%) ○ Required transfusions: 0 (0%) ○ Death: 1 (11%) ○ Outcomes (Regulatory Definition) (Categories

<ul style="list-style-type: none"> ○ Required hospitalization: 18 (40%) ○ Required surgery for an obstructed, necrotic, ruptured bowel: 1 (2%) ○ Required transfusions: 0 (0%) ○ Death: 0 (0%) ○ Outcomes (Regulatory Definition) (Categories mutually exclusive) (n = 45) <ul style="list-style-type: none"> ○ Hospitalization: 20 (44%) ○ Other: 25 (56%) ○ Event Year (n = 45) <ul style="list-style-type: none"> ○ 2003: 9 (20%) ○ 2004: 6 (13%) ○ 2005: 2 (4%) ○ 2006: 2 (4%) ○ 2007: 4 (9%) ○ 2008: 1 (2%) ○ 2009: 4 (9%) ○ 2010: 4 (9%) ○ 2011: 3 (7%) ○ 2012: 10 (22%) ○ Report Type <ul style="list-style-type: none"> ○ Expedited: 43 (96%) ○ Direct: 2 (4%) 	<ul style="list-style-type: none"> ○ Death: 1 (11%) ○ Hospitalization: 7 (78%) ○ Life Threatening: 1 (11%) ○ Event Year (n = 10) <ul style="list-style-type: none"> ○ 2003: 3 (33%) ○ 2004: 2 (22%) ○ 2005: 0 (0%) ○ 2006: 1 (11%) ○ 2007: 0 (0%) ○ 2008: 0 (0%) ○ 2009: 1 (11%) ○ 2010: 1 (11%) ○ 2011: 1 (11%) ○ 2012: 0 (0%) ○ Report Type <ul style="list-style-type: none"> ○ Expedited: 9 (100%) ○ Direct: 0 (0%)
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Narrative Summaries of Cases with Outcomes of Interest

Case of Death (n = 1)

Case 7351436 (CoC, 2010, Domestic, MCN 2010PL000034): A 60-year-old female with a history of irritable bowel syndrome, Crohn’s disease, diabetes, hypertension and hypothyroidism developed a small bowel perforation in 2009 while on Lotronex. The patient underwent surgery for the perforated bowel, but subsequently developed sepsis and died. The patient was taking Lotronex 1 mg once daily for irritable bowel syndrome for over 1 year prior to the small bowel perforation. Concomitant medications were omeprazole, insulin, atenolol, atorvastatin, folic acid, warfarin, levothyroxine, candesartan, solifenacin, metformin, mesalamine, atropine/diphenoxylate, prednisone and 6-mercaptopurine. The treating gastroenterologist reported the small bowel perforation was possibly due to Lotronex.

Cases of Surgery (n = 2)

Case 6812842 (IC, 2008, Domestic, MCN 2008PL000161): A 60 year-old female was on Lotronex 0.5 mg every third day for the treatment of irritable bowel syndrome with diarrhea starting September 11, 2008 was admitted to the hospital on [REDACTED] (b) (6) for irregular bowel habits with intermittent diarrhea and constipation, severe abdominal pain starting October 16, 2008. The patient was seen in the hospital emergency department and was subsequently admitted to the hospital. The patient experienced increasing signs of sepsis and circulatory compromise and was taken to the operating room for an exploratory laparotomy on [REDACTED] (b) (6). The left colon was mobilized and the entire colon was evaluated. The colon was not particularly abnormal but was boggy in the area of the distal sigmoid just above the

rectum where an area of thickening was noted. A partial colectomy was conducted after decompression of the colon. The pathologic diagnosis was ischemic colitis of the resected distal colon. The patient was discharged from the hospital on [REDACTED] (b) (6). The patient's medical history included irritable bowel syndrome, atherosclerotic vascular disease, hyperlipidemia, fatty liver, hypertension, hemorrhoidal disease, hepatocellular disease, arthritis, mild diabetes mellitus, rosacea, chronic venous insufficiency, and hepatomegaly. Concomitant medications used at the time of the event were simvastatin, triamterene/hydrochlorothiazide, Relafen (nabumetone), MetroGel (metronidazole), NuLev, and Darvocet (propoxyphene).

Case 6148242 (CoC, 2006, Domestic, MCN US-GLAXOSMITHKLINE-A0623243A): A physician, who is the patient's husband, reported the occurrence of small bowel obstruction in a 41-year-old female patient who received Lotronex once daily for IBS over a 2-year period. Past medical history included myotonic dystrophy and multiple unspecified surgeries. Concomitant medications included Desogen (desogestrel and ethinyl estradiol) and Provigil (modafinil). In September 2006, the patient experienced constipation and reduced the dose to once every other day. Later in September 2006, the patient discontinued Lotronex. On [REDACTED] (b) (6), the patient was admitted to the hospital with a small bowel obstruction and was scheduled for surgery.

Pharmacovigilance Review Discussion

There are 54 cases in the final case series for IC (n = 45) and CoC (n = 9) that were considered probably or possibly related to Lotronex use following marketing reintroduction under the RiskMAP or REMS. Of the 54 cases, the review only identified 3 cases with the outcomes of interest; 2 surgeries and 1 death.

The 1 case of death subsequent to CoC was due to a bowel perforation (Case 7351436). The cause of the bowel perforation in the death case was confounded by the patient's history of Crohn's disease and other medications. Small bowel perforations can occur in patients with Crohn's disease, particularly when there is any degree of obstruction present or if there is fistulizing disease.

The findings in this review indicate that there have been a small number of cases with the outcomes of interest. Findings from this review, however, should be interpreted in the context of the known limitations of the nature of the FAERS database, specifically; it is a spontaneous reporting system. Because reporting is voluntary, the FAERS database is subject to underreporting as well as reporting bias. For any adverse event reviewed, the actual number of events and the number of patients exposed to the drug is not known. Incidence or estimated drug risk cannot be calculated. Also, the quality of reports and level of detail is highly variable.

7 Drug Utilization Review

In preparation for the Drug Safety and Risk Management (DSaRM) Advisory Committee meeting on July 10, 2013, to discuss the Risk Evaluation and Mitigation Strategy (REMS) program for Lotronex, this review examines the recent annual drug utilization patterns for Lotronex for the

time period 2008 through 2012. Because the majority of Lotronex products were sold to U.S. outpatient retail pharmacies, this review focuses on the outpatient retail pharmacy drug utilization patterns.

Utilization Data Summary, Years 2008 through 2012

- The number of dispensed prescriptions increased by 32% from approximately 31,000 prescriptions dispensed during year 2008 to approximately 41,000 prescriptions dispensed during year 2012.
- During year 2012, approximately 41,000 prescriptions were dispensed and approximately 10,300 patients received a dispensed prescription for Lotronex from U.S. outpatient retail pharmacies.
- The majority of prescriptions dispensed and patients receiving dispensed prescriptions were female during each year examined with between 11% -12% use in males.
- For the cumulative time period, Gastroenterology specialists were the top prescribing specialty accounting for approximately 71% (129,000 prescriptions) of total prescriptions dispensed followed by Internal Medicine specialists with approximately 10% (17,500 prescriptions) of total prescriptions.
- For the cumulative time period examined, “Irritable Colon” (ICD-9 code 564.1) was the most common diagnosis associated with the use of Lotronex in females with approximately 71% of drug use mentions. The top desired actions were predominantly antidiarrheal-related.

Methods and Material

Determining Settings of Care

The IMS Health, IMS National Sales Perspectives™ (see **Appendix D** for full database description) was used to determine the various retail and non-retail channels of distribution for Lotronex. During year 2012, approximately 77% of Lotronex were distributed to outpatient retail pharmacy settings, 18% to mail-order/specialty pharmacies, and 5% were to non-retail pharmacies.¹⁰ Based on the distribution patterns of Lotronex, outpatient retail pharmacy utilization data were examined. Neither non-retail nor mail-order/specialty settings were included in this analysis.

Data Sources Used

Proprietary drug use databases were used to conduct this analysis (see **Appendix D** for full database descriptions).

U.S. outpatient retail pharmacy drug utilization for Lotronex was obtained from the IMS Health, Vector One® : National (VONA) and Total Patient Tracker (TPT) databases. From these two

¹⁰ IMS Health, IMS National Sales Perspectives™. Extracted May 2013. File: NSP 2013-341_Lotronex_AC_5.2013.xlsx

sources, nationally projected estimates of the number of prescriptions dispensed and unique patients who received a dispensed prescription, stratified by patient sex, were obtained for years 2008 through year 2012, annually.

Additionally, the top specialties prescribing Lotronex were also obtained from IMS Health, Vector One[®]: National (VONA). Diagnoses associated with the use of Lotronex and corresponding desired action was obtained from the Encuity Research, LLC., Treatment Answers[™] for years 2008-2012, cumulative.

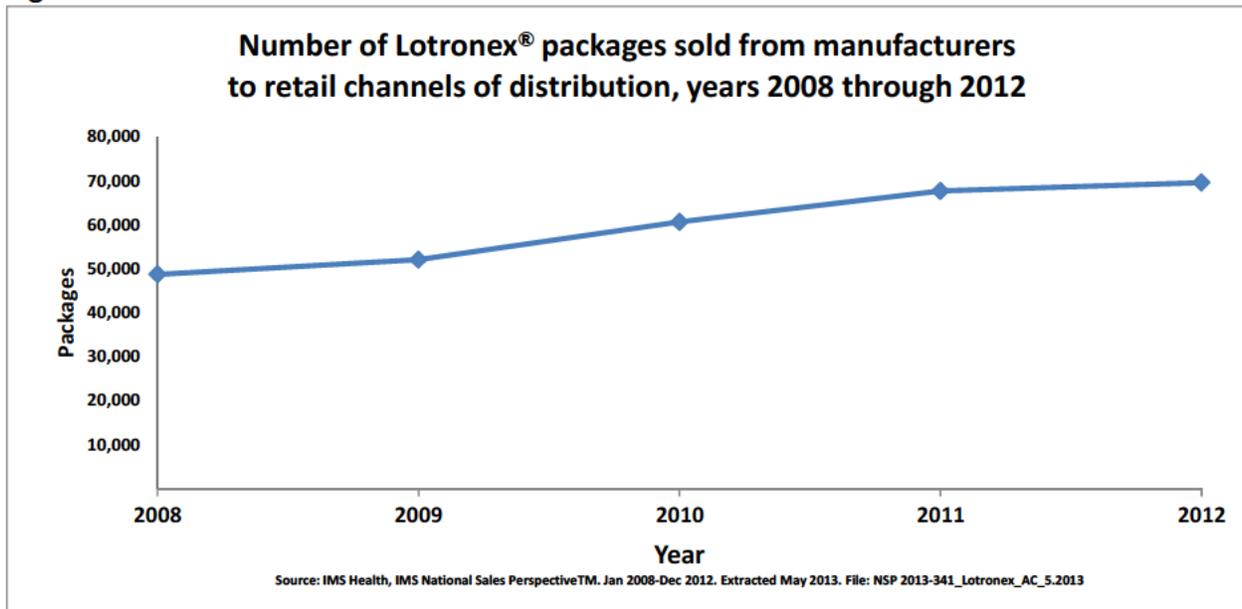
Symphony Health Solutions' PHAST Prescription[™] Monthly was used to obtain the estimated number of healthcare providers who prescribed Lotronex through outpatient retail pharmacies for years 2008 through 2012.

Results

Outpatient dispensed Prescriptions for Lotronex

Figure 1 below displays the nationally estimated number of dispensed prescriptions for Lotronex from U.S. outpatient retail pharmacies for years 2008 through 2012. The number of dispensed prescriptions gradually increased from approximately 31,000 prescriptions dispensed during year 2008 to approximately 41,000 prescriptions dispensed during year 2012 accounting for a 32% increase overall.

Figure 1.



Outpatient dispensed prescriptions for Lotronex by Patient Sex

Table 4 below provides the nationally estimated number of prescriptions dispensed for Lotronex, stratified by patient sex, from U.S. outpatient pharmacies for years 2008 through 2012. During each year examined. The majority of Lotronex prescriptions were dispensed to females accounting for 88%-89% of the total during each year examined. During year 2012, approximately 36,000 prescriptions (88% of total) were dispensed to females while about 5,000 prescriptions (12% of total) were dispensed to males.

Table 4.

Nationally estimated number of prescriptions for Lotronex®, stratified by patient sex, dispensed from U.S. retail pharmacies, years 2008 through 2012										
	Year 2008		Year 2009		Year 2010		Year 2011		Year 2012	
	Total Rx		Total Rx		Total Rx		Total Rx		Total Rx	
	(N)	% Share	(N)	% Share						
Alosetron total	31,311	100.0%	33,122	100.0%	35,741	100.0%	40,424	100.0%	41,349	100%
female	27,817	88.8%	29,482	89.0%	31,581	88.4%	35,410	87.6%	36,324	87.8%
male	3,481	11.1%	3,635	11.0%	4,160	11.6%	4,995	12.4%	5,005	12.1%
unspecified	13	<0.1%	5	<0.1%	--	--	19	<0.1%	21	<0.1%

Source: IMS Health Vector One® VONA, Years 2008 - 2012. Extracted May 2013. File: VONA_2013-341_Lotronex_TRx & gender_Jan 2008 to Dec 2012

Number of patients receiving dispensed prescriptions for Lotronex

Table 5 below provides the nationally estimated number of unique patients, stratified by patient sex, who received a dispensed prescription for Lotronex from U.S. outpatient retail pharmacies for years 2008 through 2012. The patient count data were similar to the dispensed prescription data. The total number of patients receiving dispensed prescriptions for Lotronex increased by approximately 33% from 7,800 patients during year 2008 to 10,300 patients during year 2012. During each year examined, the majority of patients receiving Lotronex prescriptions were female accounting for 88%-89% of total patients. During year 2012, approximately 9,000 patients (88% of total) receiving dispensed Lotronex prescriptions were female while about 1,000 patients (12% of total) were male.

Table 5.

Nationally estimated number of patients, stratified by patient sex, who received a dispensed prescription for Lotronex® from outpatient U.S. retail pharmacies, years 2008 through 2012										
	Year 2008		Year 2009		Year 2010		Year 2011		Year 2012	
	Patients		Patients		Patients		Patients		Patients	
	(N)	% Share	(N)	% Share	(N)	% Share	(N)	% Share	(N)	% Share
Alosetron total	7,789	100%	8,455	100%	9,724	100%	10,622	100%	10,332	100%
female	6,876	88.3%	7,479	88.5%	8,613	88.6%	9,360	88.1%	9,130	88.4%
male	905	11.6%	969	11.5%	1,112	11.4%	1,255	11.8%	1,197	11.6%
unspecified	9	0.1%	5	0.1%			7	0.1%	5	<0.1%

Source: IMS Health Vector One® Total Patient Tracker (TPT), 2008 - 2012. Extracted May 2013. Files: TPT_2013-341_Lotronex_patients_ & gender_Jan_2008_to_Dec_2012.xls; TPT_2013-341_Lotronex_Jan_2008_to_Dec_2012.xls

Top Prescribing Specialty Groups for Lotronex

Table 6 below provides the nationally estimated number of prescriptions dispensed for Lotronex by the top 10 prescribing specialties. Over the cumulative time period from year 2008 through 2012, Gastroenterology specialists were the top prescribing specialty accounting for approximately 71% (129,000 prescriptions) of total prescriptions dispensed. Internal Medicine specialists followed accounting for approximately 10% (17,500 prescriptions) of total prescriptions. General Practice/Internal Medicine/Doctor of Osteopathy specialists accounted for approximately 8% (14,000 prescriptions) of total prescriptions.

Table 6.

Nationally estimated number of prescriptions dispensed for Lotronex® by top prescribing specialties through U.S. outpatient retail pharmacies, years 2008 through 2012 cumulative		
Years 2008 through 2012		
	Total Rx (N)	Share (%)
Total alosetron	181,987	100.0%
Gastroenterology	129,490	71.2%
Internal Medicine	17,517	9.6%
General/Family Practice Osteopathy	14,247	7.8%
Unspecified	5,229	2.9%
Nurse Practitioner	3,848	2.1%
Physician Assistant	3,595	2.0%
General Surgery	1,537	0.8%
All Others Surgery	1,134	0.6%
Pediatric	744	0.4%
Other	550	0.3%
All others	4,100	2.3%

Source: IMS Health Vector One VONA. Years 2008-2012. File: VONA_2013-341_Lotronex_AC_TRx & specialty_years_2008-2012_5 23.13.xls

Prescriber counts for Lotronex

Table 7 below provides the number of unique prescribers of Lotronex during years 2008 through 2012. During year 2008 there was a total of approximately 3,500 prescribers of Lotronex. The number of prescribers of Lotronex increased to approximately 4,100 prescribers during year 2012.

Table 7.

Number of healthcare providers who prescribed Lotronex® in the outpatient retail pharmacy setting, years 2008 through 2012					
	2008	2009	2010	2011	2012
	Writer Rx Count				
Alosetron	3,504	3,767	4,088	4,172	4,101

Source: Symphony Health Solutions' PHAST Prescription. Extracted May 2013. File: SHA PHAST 2013-341 Lotronex_AC_prescriber_count by year_5-24-13.xlsx

Indications for Lotronex Use

Table 8 below provides the top diagnoses associated with Lotronex use, stratified by patient sex and desired action, as reported by U.S. office-based physicians during years 2008 through 2012, cumulative. The number of drug use mentions¹¹ for males from office-based physician visits was below the acceptable count allowable to provide a reliable estimate of national use, however, use was captured in this population as seen in dispensed prescription and patient data. Approximately 90% of drug uses for Lotronex (533,000 uses, 95% CI 424,000 – 643,000) were reported in females by office-based physician practices. Over the cumulative time period examined, “Irritable Colon” (ICD-9 code 564.1) was the most common diagnosis associated with the use of Lotronex in females with approximately 71% of drug use mentions (381,000 uses, 95% CI 288,000-473,000). The top desired actions for Lotronex were for “Antidiarrheal” (36% of drug uses), “Gastrointestinal Antispasmodic” (22% of drug uses), and “Serotonin Antagonist” (11% of drug uses) purposes when used for the diagnosis of “Irritable Colon”. The second most common diagnosis associated with the use of Lotronex in females was “Gastrointestinal System Symptoms NEC” accounting for approximately 25.5% of drug use mentions (136,000 uses, 95% CI 81,000 – 191,000). The top desired actions were for “Antidiarrheal” (53% of drug uses), “Gastrointestinal Antispasmodic” (29% of drug uses), and “Bowel Rest” (11% of drug uses) purposes when used for the diagnosis of “Gastrointestinal System Symptoms NEC”.

¹¹ The term "drug uses" to refer to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

Table 8.

Top diagnoses with desired action, stratified by sex associated with the use of Lotronex® by U.S. Office-Based Physician Surveys, years 2008 through 2012			
Years 2008 - 2012			
	Uses (N)	95% C.I.	Share (%)
Total Market	590,000	475,000 - 705,000	100.0%
FEMALE	533,000	424,000 - 643,000	90.4%
5641 IRRITABLE COLON	381,000	288,000 - 473,000	71.4%
ANTIDIARRHEAL	135,000	80,000 - 191,000	35.6%
GI ANTISPASMODIC	82,000	39,000 - 125,000	21.7%
SEROTONIN ANTAGONIST	43,000	12,000 - 73,000	11.2%
DECREASE SYMPTOMS	28,000	3,000 - 52,000	7.2%
ALL OTHERS	134,000	79,000 - 189,000	35.2%
UNSPECIFIED	22,000	< 500 - 44,000	5.8%
7879 GI SYSTEM SYMPTOMS NEC	136,000	81,000 - 191,000	25.5%
ANTIDIARRHEAL	73,000	32,000 - 113,000	53.4%
GI ANTISPASMODIC	40,000	10,000 - 70,000	29.4%
BOWEL REST	15,000	< 500 - 33,000	10.7%
RELIEVE ABDOMINAL CRAMPS	14,000	< 500 - 32,000	10.5%
PAIN RELIEF	10,000	< 500 - 25,000	7.4%
ALL OTHERS	32,000	5,000 - 58,000	23.4%
5645 FUNCTIONAL DIARRHEA	13,000	< 500 - 30,000	2.4%
ANTIDIARRHEAL	13,000	< 500 - 30,000	100.0%
7890 ABDOMINAL PAIN	4,000	< 500 - 14,000	0.8%
UNSPECIFIED	4,000	< 500 - 14,000	100.0%
MALE	25,000	1,000 - 49,000	4.3%
5641 IRRITABLE COLON	10,000	< 500 - 25,000	40.1%
TX IRRITABLE BOWEL	6,000	< 500 - 18,000	59.8%
UNSPECIFIED	4,000	< 500 - 14,000	40.2%
7879 GI SYSTEM SYMPTOMS NEC	10,000	< 500 - 25,000	39.1%
GI ANTISPASMODIC	5,000	< 500 - 16,000	51.3%
ANTIDIARRHEAL	5,000	< 500 - 15,000	48.7%
V700 ROUTINE MEDICAL EXAM	5,000	< 500 - 16,000	20.8%
TX IRRITABLE BOWEL	5,000	< 500 - 16,000	100.0%
UNSPECIFIED	32,000	5,000 - 58,000	5.4%

Source: Encuity Research, LLC., TreatmentAnswers™. File:Encuity_2013-341_Lotronex_ACdx4_and desired action_Cumulative_2008 to 2012.xls

Drug Utilization Review Discussion

The findings in this review indicate that the total number of prescriptions dispensed and patients receiving dispensed prescriptions have gradually increased during the examined time. The majority of use is in females with between 11% - 12% use in males. During the time examined, gastroenterology specialists were the top prescribing specialty accounting for approximately 71% of the total Lotronex prescriptions dispensed followed by Internal Medicine specialists with 10% of the total. "Irritable Colon" was the top diagnosis associated with use of Lotronex in females with a predominantly "antidiarrheal" desired action. The number of prescribers of Lotronex has increased with approximately 4,100 prescribers during year 2012.

In the August 30, 2012 REMS assessment report submitted by the Sponsor, drug utilization data on prescriber specialty and number of prescribers were included. Although the data represents slightly different time periods as in this analysis, the overall results are similar to the data presented in our analysis.

The number of prescribers or “prescriber count” reported in this review is not nationally projected to the outpatient retail pharmacy level. Instead “prescriber count” represents the number of unique prescribers for those prescriptions that were dispensed at an outpatient retail pharmacy. It is estimated that approximately 82% of all retail prescriptions and approximately 97% of all prescribers are represented in the PHAST database.

Findings from this review should be interpreted in the context of the known limitations of the databases used. Based on the IMS Health, IMS National Sales Perspectives™, sales data for year 2012 showed that approximately 77% of Lotronex packages were distributed to outpatient retail pharmacies, 12% were distributed to mail-order/specialty pharmacies, and 5% to non-retail pharmacies.

Indications for use were obtained using a monthly survey of 3,200 office-based physicians. Although these data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, physician survey data are best used to identify the typical uses for the products in clinical practice, and outpatient prescription data are best used to evaluate utilization trends over time. Results should not be overstated when nationally projected estimates of annual uses or mentions fall below 100,000 as the sample size is very small with correspondingly large confidence intervals.

8 Discussion

The Lotronex REMS was approved to mitigate the risk of ischemic colitis and serious complications of constipation. The REMS includes a Medication Guide, and elements to assure safe use, an implementation system, and a timetable for submission of assessment. The elements to assure safe use include – prescriber certification and documentation of safe use conditions – a signed Patient Acknowledgement Form (PAF), and pharmacy dispensing only in the presence of a sticker on the prescription. As noted earlier, this program is the only REMS program that uses confirmation of placement of a sticker to verify that the prescriber has completed required processes.

The most recent REMS assessment findings suggest that the Lotronex REMS goals are being met, because the survey findings suggest that the patients, prescribers, and pharmacists understand the relevant risks, the appropriate patients appear to be receiving product, and a limited number of cases of IC and serious CoC have been identified.

In addition to determining whether the REMS is meeting its goals, FDAAA requires the Agency to determine if the program is *unduly* burdensome to the healthcare system, given that all REMS with ETASU are potentially burdensome by their nature. The REMS assessment report does not provide direct information to determine the impact of implementing the REMS on prescribers and pharmacists. Although intuitively the requirement that verification of the presence of the sticker on the prescription prior to dispensing Lotronex might seem to add burden to the prescribers and pharmacists, it likely does not fit within many prescribers' and pharmacists' routine workflow, and is difficult to integrate into their systems (pharmacy management and electronic prescribing systems).

FDAAA also requires the Agency to determine if the program impacts drug access to patients. The REMS assessment program does not provide direct information on the impact of the program on drug access to patients. The drug utilization information might be used as a proxy to assess patient access, although there can be many reasons to explain drug utilization patterns besides patient access concerns. The Agency is seeking the Committee's advice about whether there is an issue with patient access.

The Agency is seeking the Committee's advice about whether the program is unduly burdensome on the healthcare system and on patient access. In doing so, the Committee is asked to consider the information provided by the Agency and the Sponsor to determine whether the REMS should be modified. The modification of a REMS is always an option should the Agency and drug Sponsor decide that a change will continue to satisfactorily mitigate the serious risk and minimize the burden on stakeholders. When considering the modification of a REMS, it is important to review the role of each element in helping to meet the goals of the REMS, whether certain elements are interrelated, and how the impact of removal of individual elements may affect the effectiveness of the program.

9 Summary

The Agency has determined that the Lotronex REMS is meeting its goals based upon the REMS assessment conducted by the Sponsor, review of postmarketing cases of interest in FAERS, and review the drug utilization data. Information regarding the impact of the Lotronex REMS on patient access to the drug or on burden to the healthcare system are less understood. Based on general REMS input from various stakeholders, we surmise that the requirement for pharmacists to verify the presence of a sticker on a prescription as a condition of safe use does not fit within their routine workflow and cannot be integrated into their systems, and may therefore be unduly burdensome. As the Committee discusses the Lotronex REMS the members should determine if there are any modifications to the Lotronex REMS that would help to minimize burden to healthcare system and address patient access while continuing to ensure the safe use. If the Committee determines that the REMS should be modified to address any limitations, the members should opine on various options for the recommended change(s) and the pros and cons of that/those change(s). In addition, should the

Committee make any recommendations for changing the REMS, then the methods to assess the impact of those changes on safe use of Lotronex should also be discussed. If the Committee determines that the REMS should not be modified, then the members should provide that rationale, as well.

10 Appendices

Appendix A

Professional Lotronex Label (09/02/2010)

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-HT₃ antagonist indicated only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have:

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

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

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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 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 $\geq 3\%$ 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

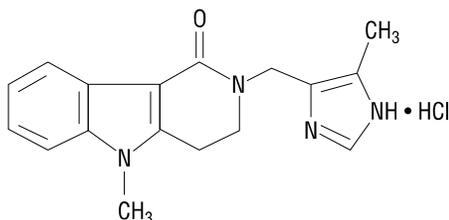
Renal impairment (creatinine clearance 4 to 56 mL/min) has no effect on the renal elimination of alosetron due to the minor contribution of this pathway to elimination. The effect of renal impairment on metabolite pharmacokinetics and the effect of end-stage renal disease have not been assessed.

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-HT₃ 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 C₁₇H₁₈N₄O•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:



LOTRONEX 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-HT₃ receptor antagonist. 5-HT₃ 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-HT₃ 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-HT₃ 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- β -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- β -hydroxycortisol excretion. However, there was no change in the ratio of 6- β -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 ¹⁴C-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⁺) 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 Criteria¹ 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.

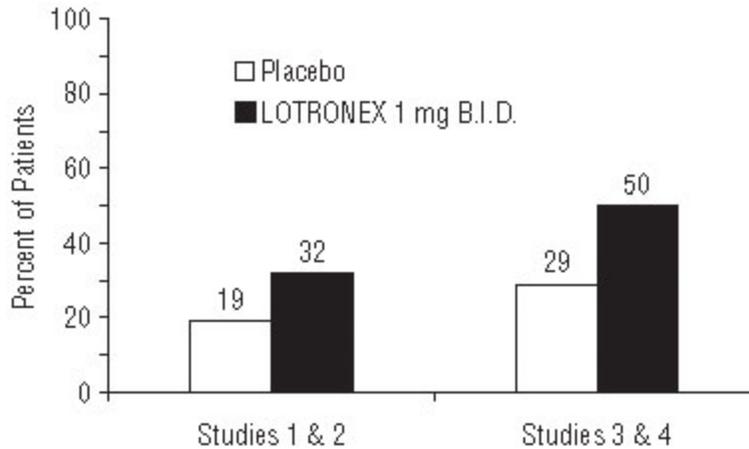
There was no consistent effect upon the sense of incomplete evacuation during the 12 weeks of treatment for patients receiving LOTRONEX as compared to patients receiving placebo in either study.

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.

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.

Appendix B

Lotronex Medication Guide (09/02/2010)

Medication Guide

MEDICATION GUIDE LOTRONEX® (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[®]).

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.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



PROMETHEUS[®]
Therapeutics & Diagnostics

For the person in every patient

Prometheus Laboratories Inc.
San Diego, CA 92121

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September 2010

LX001D

Appendix C

Risk Evaluation and Mitigation Strategy for LOTRONEX (approved on September 2, 2010)

NDA 21-107

LOTRONEX[®] (alose tron hydrochloride) Tablets

Selective 5-HT₃ 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 lotronexpl.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.

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:

-
- 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 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)

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

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.

Appendix D

Drug Utilization Database Descriptions

IMS Health, IMS National Sales Perspectives™: Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS, Vector One®: National (VONA)

The IMS, Vector One®: National (VONA) database measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

Prescriptions are captured from a sample from the universe of approximately 59,000 pharmacies throughout the U.S. There are over 800,000 physicians in the VECTOR One database, which supplies VONA, TPT, & DET. The pharmacies in the database account for most retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. IMS receives all prescriptions from approximately one-third of stores and a significant sample of prescriptions from many of the remaining stores.

IMS Health, Vector One®: Total Patient Tracker (TPT)

The IMS, Vector One®: Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time.

TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

Symphony Health Solutions' PHAST Prescription™

The Symphony Health Solutions' PHAST Prescription Monthly is a syndicated view of U.S. retail and mail order pharmacy prescription activity, updated on a monthly basis. PHAST Prescription Monthly covers over 42,000 retail pharmacies in the sample including mail order and specialty pharmacies. The dispensed prescriptions in the sample represent approximately 82% of all U.S. retail prescriptions (cash, Medicaid, commercial) as well as 60% of all U.S. mail order prescriptions. The retail and mail order prescriptions are projected to the national level.

Encuity Research, LLC., TreatmentAnswers™

Encuity Research, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.