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 physicians 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 ----------

Dosage and Administration, Adult Patients (2.1) 4/2008

---------- INDICATIONS AND USAGE ----------

LOTRONEX is a selective serotonin 5-HT_3 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-Physician Agreement (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, physicians 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: Apr 2008

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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 physicians 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-Physician Agreement for LOTRONEX *[see Patient Counseling Information (17.3)]*.**
- **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 physician. LOTRONEX should not be resumed in patients who develop ischemic colitis. Patients who have constipation should immediately contact their physician if the constipation does not resolve after LOTRONEX is discontinued. Patients with resolved constipation should resume LOTRONEX only on the advice of their treating physician.**

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 physicians 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-Physician Agreement

LOTRONEX should not be used by patients who are unable to understand or comply with the Patient-Physician Agreement for LOTRONEX *[see Patient Counseling Information (17.3)]*.

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 physician must be enrolled in the Prescribing Program for LOTRONEX. To enroll, physicians 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-Physician Agreement for LOTRONEX. Physicians

need to be able to:

- diagnose and manage IBS, ischemic colitis, constipation, and complications of constipation or refer patients to specialists as needed.
- educate patients on the benefits and risks of treatment with LOTRONEX, provide them with the Medication Guide, instruct them to read it, and encourage them to ask questions when first considering LOTRONEX. Patients may be educated by the enrolled physician or a healthcare provider under a physician's direction.
- obtain the patient's signature on the Patient-Physician Agreement form, sign it, place the original signed form in the patient's medical record, and give a copy to the patient prior to the initial prescription of LOTRONEX.
- affix program stickers to written prescriptions for LOTRONEX (i.e., the original and all subsequent prescriptions). Stickers will be provided as part of the Prometheus Prescribing Program for LOTRONEX. No telephone, facsimile, or computerized prescriptions are permitted with this program. Refills are permitted to be written on prescriptions.
- report all serious adverse reactions with LOTRONEX to Prometheus at 1-888-423-5227 or to the Food and Drug Administration's MedWatch Program at 1-800-FDA-1088.

To enroll in the Prescribing Program for LOTRONEX, call 1-888-423-5227 or visit www.lotronex.com to complete the Physician 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 ≥1% of Patients With Irritable Bowel Syndrome and More Frequently on LOTRONEX 1 mg Twice Daily Than Placebo

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

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

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

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

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

Table 2. Gastrointestinal Adverse Reactions Reported in ≥3% of Women With Severe Diarrhea-Predominant Irritable Bowel Syndrome and More Frequently on LOTRONEX Than Placebo.

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

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

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

treatment and persisted for 4 to 5 days.

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

In the listing that follows, reported adverse reactions were classified using a standardized coding dictionary. Only those events that an investigator believed were possibly related to LOTRONEX, occurred in at least 2 patients, and occurred at a greater frequency during treatment with LOTRONEX than during placebo administration are presented. Serious adverse reactions occurring in at least 1 patient for whom an investigator believed there was reasonable possibility that the event was related to treatment with LOTRONEX and occurring at a greater frequency in patients treated with LOTRONEX than placebo-treated patients are also presented.

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

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

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

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

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

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

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

Eye: Rare: Light sensitivity of eyes.

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

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

Lower Respiratory: Infrequent: Breathing disorders.

Musculoskeletal: Rare: Muscle pain; muscle stiffness, tightness and rigidity; and

bone and skeletal pain.

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

Non-Site Specific: Infrequent: Malaise and fatigue, cramps, pain, temperature regulation disturbances. *Rare:* Burning sensations, hot and cold sensations, cold sensations, and fungal infections.

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

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

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

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

6.2 Postmarketing Experience

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

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

Neurological: Headache.

Skin: Rash.

7 DRUG INTERACTIONS

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

7.1 CYP1A2 Inhibitors

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

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

7.2 CYP3A4 Inhibitors

Ketoconazole is a known strong inhibitor of CYP3A4. In a pharmacokinetic study, 38 healthy female subjects received ketoconazole 200 mg twice daily for 7 days, with coadministration of alosetron 1 mg on the last day. Ketoconazole increased mean alosetron plasma concentrations (AUC) by 29%. Caution should be used when alosetron and ketoconazole are administered concomitantly. Coadministration of alosetron and strong CYP3A4 inhibitors such as clarithromycin, telithromycin, protease inhibitors, voriconazole, and itraconazole has not been evaluated but should be undertaken with caution because of similar potential drug interactions. The effect of induction or inhibition of other pathways on exposure to alosetron and its metabolites is not known.

7.3 Other CYP Enzymes

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

only if clearly needed.

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

Postmarketing experience suggests that elderly patients may be at greater risk for complications of constipation therefore, appropriate caution and follow-up should be exercised if LOTRONEX is prescribed for these patients *[see Warnings and Precautions (5.1)]*.

8.6 Hepatic Impairment

Due to the extensive hepatic metabolism of alosetron, increased exposure to alosetron and/or its metabolites is likely to occur in patients with hepatic impairment. Alosetron should not be used in patients with severe hepatic impairment and should be used with caution in patients with mild or moderate hepatic impairment.

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

8.7 Renal Impairment

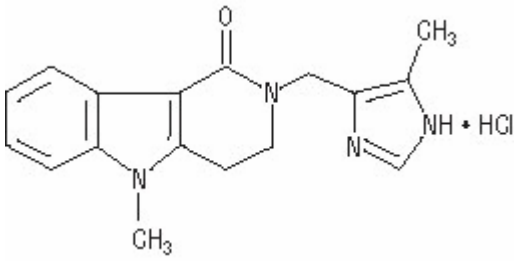
Renal impairment (creatinine clearance 4 to 56 mL/min) has no effect on the renal elimination of alosetron due to the minor contribution of this pathway to elimination. The effect of renal impairment on metabolite pharmacokinetics and the effect of end-stage renal disease have not been assessed.

10 OVERDOSAGE

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

11 DESCRIPTION

The active ingredient in LOTRONEX Tablets is alosetron hydrochloride (HCl), a potent and selective antagonist of the serotonin 5-HT_3 receptor type. Chemically, alosetron is designated as 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one, monohydrochloride. Alosetron is achiral and has the empirical formula $C_{17}H_{18}N_4O$•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-HT_3 receptor antagonist. 5-HT_3 receptors are ligand-gated cation channels that are extensively distributed on enteric neurons in the human gastrointestinal tract, as well as other peripheral and central locations. Activation of these channels and the resulting neuronal depolarization affect the regulation of visceral pain, colonic transit, and gastrointestinal secretions, processes that relate to the pathophysiology of IBS. 5-HT_3 receptor antagonists such as alosetron inhibit activation of non-selective cation channels, which results in the modulation of the enteric nervous system.

The cause of IBS is unknown. IBS is characterized by visceral hypersensitivity and

hyperactivity of the gastrointestinal tract, which lead to abnormal sensations of pain and motor activity. Following distention of the rectum, patients with IBS exhibit pain and discomfort at lower volumes than healthy volunteers. Following such distention, alosetron reduced pain and exaggerated motor responses, possibly due to blockade of 5-HT_3 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 ^{14}C-labeled alosetron in Caucasian males (n = 3) and females (n = 3) and an Asian male (n = 1) showed similar serum metabolite profiles. Unchanged alosetron was the major component in serum, with other metabolites being present at low concentrations, none amounting to more than 15% of the unmetabolized alosetron concentration. The circulating metabolites were identified as 6-hydroxy glucuronide, 6-hydroxy sulphate, 7-hydroxy sulphate, hydroxymethyl imidazole, and mono- and bis-oxygenated imidazole derivatives of alosetron. The metabolites are unlikely to contribute to the biological activity of alosetron. Of the circulating Phase I metabolites, only the hydroxymethyl imidazole has weak pharmacological activity, around 10-fold less potent than alosetron. Total recovery of radioactivity in the excreta was 85 ± 6%. The majority of the radiolabeled dose is excreted in the urine (74 ± 5%). The major urinary metabolites were the 6-hydroxy glucuronide and the mono- and bis-oxygenated imidazole derivatives of alosetron. 11 ± 4% of the radiolabeled dose was excreted in the feces with less than 1% of the dose being excreted as the unchanged alosetron.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In 2-year oral studies, alosetron was not carcinogenic in mice at doses up to 30 mg/kg/day or in rats at doses up to 40 mg/kg/day. These doses are about 60 to 160 times, respectively, the recommended human dose of alosetron of 2 mg/day (1 mg twice daily) based on body surface area. Alosetron was not genotoxic in the Ames tests, the mouse lymphoma cell (L5178Y/TK$^{\pm}$) 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 ≥50% of days)	(515)	1 mg twice daily (778)
5	Women with severe diarrhea-predominant IBS (defined as average pain ≥moderate, urgency ≥50% of days, and/or restriction of daily activities ≥25% of days)	(176)	0.5 mg once daily (177)
			1 mg once daily (175)
			1 mg twice daily (177)

Studies in Non-Constipated Women with Irritable Bowel Syndrome: Studies 1 and 2 were conducted in non-constipated women with IBS meeting the Rome Criteria[1] 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.

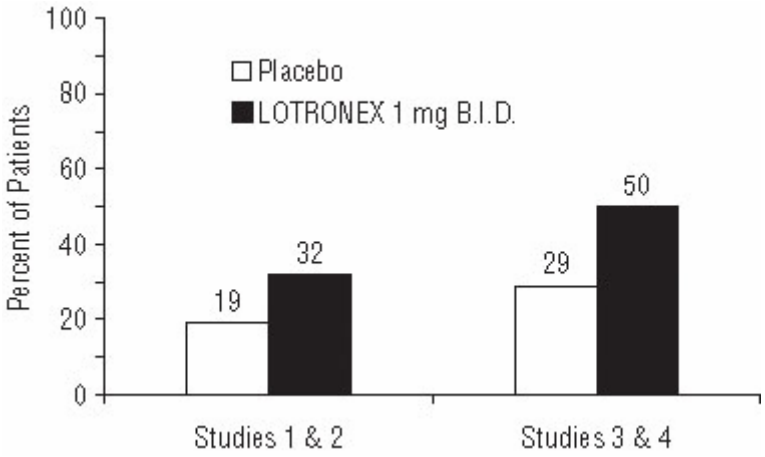
Study 5 was conducted in women with severe diarrhea-predominant IBS and 1 or more of the following: frequent and severe abdominal pain or discomfort, frequent bowel urgency or fecal incontinence, disability or restriction of daily activities due to IBS. To evaluate the proportion of patients who responded 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

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.

Bottles of 30 (NDC 0173-0738-00) with child-resistant closures.

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.

Bottles of 30 (NDC 0173-0690-05) 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 (17.2)

17.1 Physician and Patient Responsibilities

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

Physicians must:

- counsel patients for whom LOTRONEX is appropriate about the benefits and risks of LOTRONEX 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 LOTRONEX, and instruct the patient to read it carefully. Answer all questions the patient may have about LOTRONEX. The complete text of the Medication Guide is printed at the end of this document.
- review the Patient-Physician Agreement for LOTRONEX with the patient, answer all questions, and give a copy of the signed agreement to the patient.
- provide each patient with appropriate instructions for taking LOTRONEX.

Copies of the Patient-Physician Agreement for LOTRONEX and additional copies of the Medication Guide are available by contacting Prometheus at 1-888-423-5227 or visiting www.lotronex.com.

Patients who are prescribed LOTRONEX should be instructed to:

- read the Medication Guide before starting LOTRONEX and each time they refill their prescription.
- not start taking LOTRONEX if they are constipated.
- immediately discontinue LOTRONEX and contact their physician 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 physician 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 physician.
- stop taking LOTRONEX and contact their physician if LOTRONEX does not adequately

control IBS symptoms after 4 weeks of taking 1 mg twice a day.

17.2 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-Physician Agreement with your doctor.

Read this Medication Guide carefully before you sign the Patient-Physician Agreement. You must sign the Patient-Physician Agreement 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. <u>What is the most important information I should know about LOTRONEX?</u>

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 <u>all</u> 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 **<u>at least 1</u>** 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 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 **<u>written</u>** 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-Physician Agreement after you read this Medication Guide for the first time. Signing the Agreement 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-Physician Agreement, 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, let the doctor who prescribed LOTRONEX know.

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 59ºF to 86ºF (15ºC to 30ºC).
- 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.lotronex.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.

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

Revised April 2008 LX002A08

17.3 FDA-Approved Patient-Physician Agreement

PATIENT-PHYSICIAN AGREEMENT FOR LOTRONEX

SECTION FOR THE PATIENT

LOTRONEX (alosetron hydrochloride) is only for women with severe irritable bowel syndrome (IBS) whose main problem is diarrhea and who did not get the relief needed from other treatments. LOTRONEX has not been shown to help men with IBS or patients under age 18.

My doctor, or a healthcare provider under a doctor's direction, answered my questions about treatment with LOTRONEX. I have read and I understand the Medication Guide for LOTRONEX, and

- I understand that some patients using LOTRONEX have had serious bowel conditions (ischemic colitis and complications of constipation). I understand that these serious conditions can happen suddenly, and that they may lead to a hospital stay, and in rare cases, blood transfusions, surgery, and death. I also understand that certain patients may be more likely to develop a serious bowel condition while taking LOTRONEX. These include older patients, those who have other health problems and those who take other medicines that may cause constipation.
- My doctor and I agree that my IBS is severe and that other treatments have not given me the relief that I need. I also agree that I meet all of the requirements described in the section of the Medication Guide "What is the most important information I should know about LOTRONEX?" I understand that these requirements help to make sure that LOTRONEX is used only by patients who are likely to have more benefit from treatment than risk.
- I don't have any problems listed in the section of the Medication Guide "Who should not take LOTRONEX?" that prevents me from taking LOTRONEX.
- 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 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 2 times a day.

I understand that LOTRONEX should be prescribed only by doctors who have signed up with the company that makes the drug. Doctors in the program must:

- fully discuss the drug's benefits and risks with each patient.
- sign this agreement with each patient before giving the initial prescription. It is not necessary to sign an agreement more than once.
- use a special sticker on written LOTRONEX prescriptions so that pharmacists know the doctor has signed up. No telephone, facsimile, or computerized prescriptions are permitted with this program. Refills may be written on prescriptions.

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

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

_____

Name of Patient (print)

_____ _____

Signature Date

SECTION FOR THE PHYSICIAN

I am enrolled in the Prescribing Program for LOTRONEX, and I will continue to follow the requirements of the Program.

I, or a healthcare provider under a physician's direction, have given the patient named above:

- a copy of the Medication Guide for LOTRONEX, and instructed the patient to read it carefully before signing this Agreement, and to take it home.
- counseling about the benefits and risks of LOTRONEX.
- appropriate instructions for taking LOTRONEX.
- answers to all of the patient's questions about treatment with LOTRONEX.
- a prescription for LOTRONEX that has the program sticker affixed on it to alert pharmacists I am enrolled in the Prescribing Program for LOTRONEX.

The patient signed the Patient-Physician Agreement in my presence after I counseled the patient, asked if the patient had any questions about treatment with LOTRONEX, and answered all questions to the best of my ability.

_____

Name of Physician (print)

_____ _____

Signature Date

After the patient and the physician sign this Patient-Physician Agreement, give a copy to the patient and put the original signed form in the patient's medical record.

17.4 FDA-Approved Physician Enrollment Form

PRESCRIBING PROGRAM FOR LOTRONEX: PHYSICIAN ENROLLMENT FORM

The Prescribing Program for LOTRONEX was implemented to help reduce risks of serious gastrointestinal adverse reactions, some fatal, associated with this medicine. The program is intended to help physicians and their patients understand the benefits and risks of treatment with LOTRONEX in order to make fully informed decisions.

I wish to participate in the Prescribing Program for LOTRONEX (PPL) and acknowledge that I have read the complete Prescribing Information for LOTRONEX and understand and will follow the requirements of the PPL described below.

- For safety reasons, LOTRONEX is approved only for women with severe, diarrhea-predominant irritable bowel syndrome (D-IBS) who have:
  - chronic IBS 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 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.
- Physicians who enroll in the PPL should be able to diagnose and manage IBS, ischemic colitis, constipation, and complications of constipation, or refer patients to a specialist as needed.
- Patients considering treatment with LOTRONEX must be educated on the benefits and risks of the drug, given a copy of the Medication Guide, instructed to read it, and encouraged to ask questions. The patient may be educated by the enrolled physician or a healthcare provider under a physician's direction.
- After reviewing the Medication Guide prior to the initial prescription, the physician and the patient must both sign the Patient-Physician Agreement form. The original signed form must be placed in the patient's medical record, and a copy given to the patient.
- Program stickers must be affixed to written prescriptions for LOTRONEX (i.e., the original and all subsequent prescriptions). Stickers will be provided as part of the Prometheus Prescribing Program for LOTRONEX. Refills are permitted to be written on prescriptions.
- All prescriptions for LOTRONEX must be written and not transmitted by telephone,

facsimile, or computer.

- Prescribers must report all serious adverse reactions with LOTRONEX to Prometheus at 1-888-423-5227 or to the Food and Drug Administration at 1-800-FDA-1088.

_____

Name of Physician (print)

_____ _____

Signature Date

DEA Number _____

Office Address: _____

_____

_____

Office Phone Number: _____

Office Fax Number: _____

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

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

If you have any questions, please call the Prescribing Program for LOTRONEX at 1-888-423-5227 or visit www.lotronex.com.

TO ENROLL, VISIT WWW.LOTRONEX.COM OR PHONE 1-888-423-5227 OR COMPLETE THIS FORM IN ITS ENTIRETY AND MAIL OR FAX TO THE FOLLOWING ADDRESS:

Prescribing Program for Lotronex
Prometheus Client Services
9410 Carroll Park Drive
San Diego, CA 92121
1-888-423-5227
Fax Number: 1-888-824-0896

Prometheus Laboratories Inc.
San Diego, CA 92121

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