

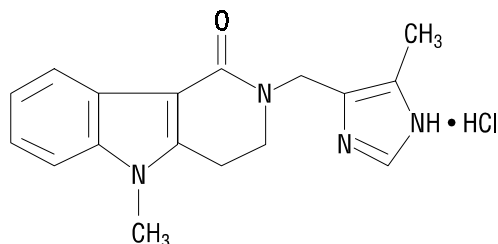
LOTRONEX[®]
(alosecron hydrochloride)
Tablets

WARNING: Serious gastrointestinal adverse events, some fatal, have been reported with the use of LOTRONEX. These events, including ischemic colitis and serious complications of constipation, have resulted in hospitalization, blood transfusion, surgery, and death.

- Only physicians who have enrolled in GlaxoSmithKline's Prescribing Program for LOTRONEX, based on their attestation of qualifications and acceptance of responsibilities, should prescribe LOTRONEX (see DOSAGE AND ADMINISTRATION and HOW SUPPLIED).
- LOTRONEX is indicated only for women with severe diarrhea-predominant IBS who have failed to respond to conventional therapy (see INDICATIONS AND USAGE). Less than 5 percent of IBS is considered severe. Before receiving the initial prescription for LOTRONEX, the patient must read and sign the Patient-Physician Agreement (see PRECAUTIONS: Information for Patients).
- LOTRONEX should be discontinued immediately in patients who develop constipation or symptoms of ischemic colitis. Physicians should instruct patients to immediately report constipation or symptoms of ischemic colitis. LOTRONEX should not be resumed in patients who develop ischemic colitis. Physicians should instruct patients who report constipation to immediately contact them if the constipation does not resolve after discontinuation of LOTRONEX. Patients with resolved constipation should resume LOTRONEX only on the advice of their treating physician.

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:

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LOTRONEX Tablets for oral administration contain 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 blue film-coat contains hydroxypropyl methylcellulose, titanium dioxide, triacetin, and indigo carmine.

CLINICAL PHARMACOLOGY:

Pharmacodynamics: Mechanism of Action: Alosetron is a potent and selective 5-HT₃ receptor antagonist. 5-HT₃ receptors are nonselective 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 irritable bowel syndrome (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, IBS patients 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.

In healthy volunteers and IBS patients, 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 IBS patients, multiple oral doses 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-dependant 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 orally twice daily. This decrease was not statistically significant. In another study utilizing alosetron 1 mg 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.

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Pharmacokinetics: The pharmacokinetics of alosetron have been studied after single oral doses ranging from 0.05 mg 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 doses ranging from 1 mg twice daily to 8 mg twice daily.

Absorption: Alosetron is 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 occurs at 1 hour. In young women, the mean peak plasma concentration is approximately 9 ng/mL, with a similar time to peak.

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).

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 4000 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 IBS patients confirmed that alosetron clearance is minimally influenced by doses up to 8 mg.

Renal elimination of unchanged alosetron accounts for only 6% of the dose. Renal clearance is approximately 94 mL/min.

Alosetron is extensively metabolized in humans. The biological activity of these metabolites is unknown. A mass balance study was performed utilizing an orally administered dose of unlabeled and ¹⁴C-labeled alosetron. This study indicates that on a molar basis, alosetron metabolites reach additive peak plasma concentrations 9-fold greater than alosetron and that the additive metabolite AUCs are 13-fold greater than alosetron's AUC. Plasma radioactivity declined with a half-life 2-fold longer than that of alosetron, indicating the presence of circulating metabolites. Approximately 73% of the radiolabeled dose was recovered in urine with another 24% of the dose recovered in feces. Only 7% of the dose was recovered as unchanged drug. At least 13 metabolites have been detected in urine. The predominant product in urine was a 6-hydroxy metabolite (15% of the dose). This metabolite was secondarily metabolized to a glucuronide that was also present in urine (14% of the dose). Smaller amounts of the 6-hydroxy metabolite and the 6-O-glucuronide also appear to be present in feces. A bis-oxidized dicarbonyl accounted for 14% of the dose and its monocarbonyl precursor accounted for another 4% in urine and 6% in feces. No other urinary metabolite accounted for more than 4% of the dose. Glucuronide or sulfate conjugates of unchanged alosetron were not detected in urine.

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In studies of Japanese men, an N-desmethyl metabolite was found circulating in plasma in all subjects and accounted for up to 30% of the dose in one subject when alosetron was administered with food. The clinical significance of this finding is unknown.

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% (see PRECAUTIONS: Drug Interactions).

Population Subgroups: Age: 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. However, this effect was not consistently observed in men (see WARNINGS).

Gender: Plasma concentrations are 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).

Reduced Hepatic Function: No pharmacokinetic data are available in this patient group (see PRECAUTIONS: Hepatic Insufficiency and DOSAGE AND ADMINISTRATION: Patients with Hepatic Impairment).

Reduced Renal Function: 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 kinetics and the effect of end-stage renal disease have not been assessed (see DOSAGE AND ADMINISTRATION: Patients with Renal Impairment).

CLINICAL TRIALS: LOTRONEX 1 mg twice daily was studied in two 12-week U.S. multicenter, randomized, double-blind, placebo-controlled trials of identical design (Studies 1 and 2) 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.

There were a total of 633 women on LOTRONEX and 640 on placebo, about two thirds with 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.

Women with Severe Diarrhea-Predominant IBS: LOTRONEX is indicated only for women with severe diarrhea-predominant IBS (see INDICATIONS AND USAGE). The indication has been narrowed to this group of severely affected patients because serious gastrointestinal adverse events, some fatal, have been reported with the use of LOTRONEX. The following prospective and retrospective analyses support efficacy of LOTRONEX in this subset of the population that was studied in clinical trials.

In two 12-week, randomized, double-blind, placebo-controlled clinical trials of women with diarrhea-predominant IBS and bowel urgency on at least 50% of days at entry (Studies 3 and 4), there were a total of 778 women on LOTRONEX and 515 on placebo. Patients on LOTRONEX had

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significant increases over placebo (13% to 16%) in the median percentage of days with urgency control.

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 to 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 to 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 to 1% of placebo patients.

Efficacy in men has not been established.

INDICATIONS AND USAGE: Because of serious gastrointestinal adverse events, some fatal, reported with use of this drug, 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
- failed to respond 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

Less than 5 percent of IBS is considered severe.

In men, the safety and effectiveness of LOTRONEX have not been established (see CLINICAL TRIALS).

CONTRAINDICATIONS:

LOTRONEX **should not be initiated** in patients with constipation (see WARNINGS).

LOTRONEX is contraindicated in patients:

- With a history of chronic or severe constipation or with a history of sequelae from constipation.
- With a history of intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforation, and/or adhesions.
- With a history of ischemic colitis, impaired intestinal circulation, thrombophlebitis, or hypercoagulable state.
- With current or a history of Crohn's disease or ulcerative colitis.
- With active diverticulitis or a history of diverticulitis.

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- Who are unable to understand or comply with the Patient-Physician Agreement.
- With known hypersensitivity to any component of the product.

WARNINGS: (See **BOXED WARNING** and **DOSAGE AND ADMINISTRATION**.)

Some patients have experienced serious complications of constipation or ischemic colitis without warning.

Constipation: Serious complications of constipation, including obstruction, perforation, impaction, toxic megacolon, secondary colonic ischemia, and death have been reported with use of LOTRONEX. In some cases these complications have required intestinal surgery, including colectomy. **In IBS clinical trials, the incidence of serious complications of constipation in women was approximately 1 per 1,000 patients, but approximately 10% of patients on LOTRONEX withdrew prematurely because of constipation.** 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**).

Ischemic Colitis: 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 2 per 1,000 patients (95% confidence interval 1 to 3) over 3 months and was 3 per 1,000 patients (95% confidence interval 1 to 4) over 6 months. Patient experience in controlled clinical trials is insufficient to estimate the incidence of ischemic colitis in patients taking LOTRONEX for longer than 6 months.**

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.

PRECAUTIONS:

Information for Patients: Patients should be fully counseled on and understand the risks and benefits of LOTRONEX before an initial prescription is written.

PHYSICIANS MUST:

- Be enrolled in GlaxoSmithKline's Prescribing Program for LOTRONEX based on their attestation of qualifications and acceptance of responsibilities. To enroll in the GlaxoSmithKline Prescribing Program for LOTRONEX call 1-888-825-5249 or visit www.LOTRONEX.com.
- Counsel the patient about the risks and benefits of LOTRONEX, in the patients for whom LOTRONEX is indicated, and discuss the impact of IBS symptoms on the patient's life.
- Give the patient a copy of the Medication Guide, which outlines the risks and benefits of LOTRONEX, and instruct the patient to carefully read the Medication Guide. Answer all

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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 with the patient, answer all questions, and confirm that the patient has signed the Agreement.
- Sign the Patient-Physician Agreement, give a copy of the signed Agreement to the patient, and put the original in the patient's medical record.
- Provide each patient with appropriate instructions for taking LOTRONEX.

Copies of the Patient-Physician Agreement and additional copies of the Medication Guide are available by contacting GlaxoSmithKline at 1-888-825-5249 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. Immediately 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~~ Stop taking LOTRONEX and contact their physician if LOTRONEX does not adequately control IBS symptoms after 4 weeks of taking 1 tablet twice a day.

Drug Interactions: In vitro human liver microsome studies and an in vivo metabolic probe study demonstrated that alosetron did not inhibit CYP enzymes 2D6, 3A4, 2C9, or 2C19. In vitro, at total drug concentrations 27-fold higher than peak plasma concentrations observed with the 1-mg dosage, 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 effect 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 major CYP enzyme 3A4, as well as the CYP enzymes 2D6, 2C9, 2C19, 2E1, or 1A2.

Alosetron does not appear to induce the major cytochrome P450 (CYP) 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.

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Because alosetron is metabolized by a variety of hepatic CYP drug-metabolizing enzymes, inducers or inhibitors of these enzymes may change the clearance of alosetron. The effect of induction or inhibition of these pathways on exposure to alosetron and its metabolites is not known.

Hepatic Insufficiency: Due to the extensive hepatic metabolism of alosetron, increased exposure to alosetron and/or its metabolites is likely to occur in patients with hepatic insufficiency.

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, respectively, about 60 to 160 times 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.

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

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.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Postmarketing experience suggests that elderly patients may be at greater risk for complications of constipation (see WARNINGS).

ADVERSE REACTIONS: Table 1 summarizes adverse events 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 events 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).

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Table 1: Adverse Events Reported in $\geq 1\%$ of IBS Patients and More Frequently on LOTRONEX 1 mg B.I.D. than Placebo

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

Gastrointestinal: Constipation is a frequent and dose-related side effect of treatment with LOTRONEX (see WARNINGS). In clinical studies constipation was reported in approximately 29% of IBS patients 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 IBS patients 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). In Studies 1 and 2, 9% of patients treated with LOTRONEX reported constipation and 4 consecutive days with no bowel movement (see CLINICAL TRIALS). 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 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.

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

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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 events were classified using a standardized coding dictionary. Only those events that an investigator believed were possibly related to alosetron, occurred in at least 2 patients, and occurred at a greater frequency during treatment with LOTRONEX than during placebo administration are presented. Serious adverse events occurring in at least 1 patient for which an investigator believed there was reasonable possibility that the event was related to alosetron treatment and which occurred at a greater frequency in 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 events are those occurring on one or more occasion in 1/100 to 1/1000 patients; *Rare* adverse events are those occurring on one or more occasion in fewer than 1/1000 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, hemorrhage, and lymphatic signs and symptoms.

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 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. **Rare:** Viral respiratory infections.

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.

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Non-site Specific: Infrequent: Malaise and fatigue, cramps, pain, temperature regulation disturbances. **Rare:** General signs and symptoms, non-specific conditions, 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.

Postmarketing Experience: 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: Constipation, ileus, impaction, obstruction, perforation, ulceration, ischemic colitis, small bowel mesenteric ischemia (see WARNINGS).

Neurological: Headache.

Skin: Rash.

DRUG ABUSE AND DEPENDENCE: LOTRONEX has no known potential for abuse or dependence.

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 events. 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 alosetron (see PRECAUTIONS: Drug Interactions). Single oral doses of LOTRONEX at 15 mg/kg in female mice and 60 mg/kg in female rats (30 and 240 times, respectively, the recommended human dose based on body surface area) were lethal. Symptoms of acute toxicity were labored respiration, subdued behavior, ataxia, tremors, and convulsions.

DOSAGE AND ADMINISTRATION:

For safety reasons, LOTRONEX is approved with marketing restrictions. Only physicians who attest to the following qualifications and accept the following responsibilities, and on that basis enroll in the GlaxoSmithKline Prescribing Program for LOTRONEX, should prescribe

LOTRONEX. Physicians must attest that they are able and willing to:

- diagnose and treat IBS

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- diagnose and manage ischemic colitis
- diagnose and manage constipation and complications of constipation
- understand the risks and benefits of treatment with LOTRONEX for severe diarrhea-predominant IBS, including the information in the package insert, Medication Guide, and Patient-Physician Agreement
- educate patients on the risks and benefits of treatment with LOTRONEX and 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
- report serious adverse events to GlaxoSmithKline at 1-888-825-5249 or to the Food and Drug Administration's MedWatch Program at 1-800-FDA-1088
- affix program stickers to all prescriptions for LOTRONEX (i.e., the original and all subsequent refill prescriptions). Stickers will be provided as part of the GlaxoSmithKline Prescribing Program for LOTRONEX. No telephone, facsimile, or computerized prescriptions are permitted with this program.

To enroll in the Prescribing Program for LOTRONEX call 1-888-825-5249 or visit www.LOTRONEX.com.

Usual Dose in Adults: For safety reasons, LOTRONEX should be started at a dosage of 1 mg orally once a day for 4 weeks. This dosage may be less constipating than a regimen of 1 mg twice a day (see WARNINGS). If, after 4 weeks, the 1 mg once-a-day dosage is well tolerated but does not adequately control IBS symptoms, then the dosage can be increased to 1 mg twice a day, the dose used in controlled clinical trials (see CLINICAL TRIALS). Although the efficacy of the 1 mg once-a-day dosage in treating diarrhea-predominant IBS has not been evaluated in clinical trials, for safety reasons consideration should be given to continuing this dosage if well tolerated and IBS symptoms in the individual patient are adequately controlled. **LOTRONEX should be discontinued in patients who have not had adequate control of IBS symptoms after 4 weeks of treatment with 1 mg twice a day.**

LOTRONEX should be discontinued immediately in patients who develop constipation or signs of ischemic colitis. LOTRONEX should not be restarted in patients who develop ischemic colitis.

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 (see also Geriatric Patients).

Pediatric Patients: Safety and effectiveness have not been established in pediatric patients (see PRECAUTIONS: Pediatric Use).

Geriatric 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).

Patients with Renal Impairment: There are insufficient data available on the biological activity of the metabolites of LOTRONEX. It is unknown if dosage adjustment is needed in patients with renal impairment (see CLINICAL PHARMACOLOGY: Reduced Renal Function).

LOTRONEX[®] (alosetron hydrochloride) Tablets

Patients with Hepatic Impairment: No studies have been conducted in 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 events. LOTRONEX should be used with caution in patients with hepatic impairment (see PRECAUTIONS: Hepatic Insufficiency and CLINICAL PHARMACOLOGY: Population Subgroups: Reduced Hepatic Function).

LOTRONEX can be taken with or without food.

HOW SUPPLIED: The physician must attest to meeting the qualifications and accepting the responsibilities in the DOSAGE AND ADMINISTRATION section of this package insert and submit this attestation to GlaxoSmithKline to be enrolled in the Prescribing Program for LOTRONEX, which utilizes special program stickers that the enrolled physician will affix to all prescriptions for LOTRONEX (i.e., the original and all subsequent refill prescriptions). No telephone, facsimile, or computerized prescriptions are permitted with this program.

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].

REFERENCE:

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



GlaxoSmithKline

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(Date of issue)

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