Lotronex advertisement.

[s.l.]: [s.n.], 2000

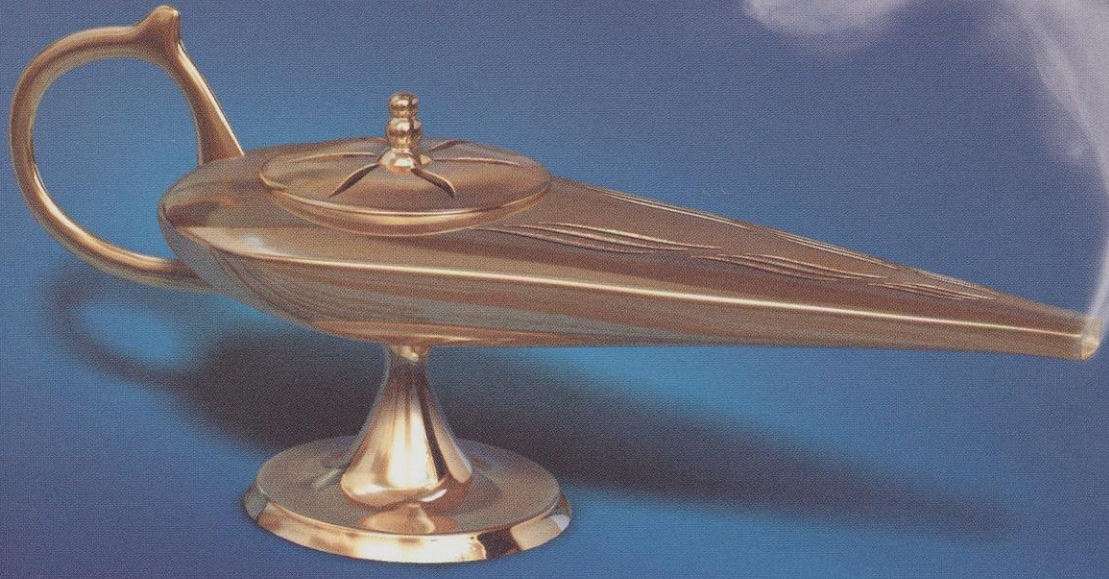
NOW AVAILABLE

FOR WOMEN WITH DIARRHEA-PREDOMINANT IRRITABLE BOWEL SYNDROME

NEW

LOTRONEX™

alosetron HCl tablets



One tablet (1 mg) b.i.d. for relief of IBS pain and discomfort, urgency, and frequency

LOTRONEX is indicated for the treatment of irritable bowel syndrome (IBS) in female patients whose predominant bowel symptom is diarrhea. Safety and effectiveness in men have not been established. Constipation was a frequent (28%) adverse event. LOTRONEX should not be used in constipation-predominant patients or those currently constipated. Management of constipation with usual care, including laxatives, fiber, or a brief interruption of therapy, may be considered. Acute ischemic colitis was infrequently (0.1% to 1%) reported; a causal relationship has not been established, nor have risk factors been identified. There were no cases reported after 12 months of treatment with LOTRONEX. If symptoms of ischemic colitis occur, LOTRONEX should be discontinued and the patient promptly evaluated. Safety and effectiveness in men and efficacy beyond 12 weeks have not been established.

www.lotronex.com

Please see Brief Summary of Prescribing Information for LOTRONEX at the end of this advertisement.

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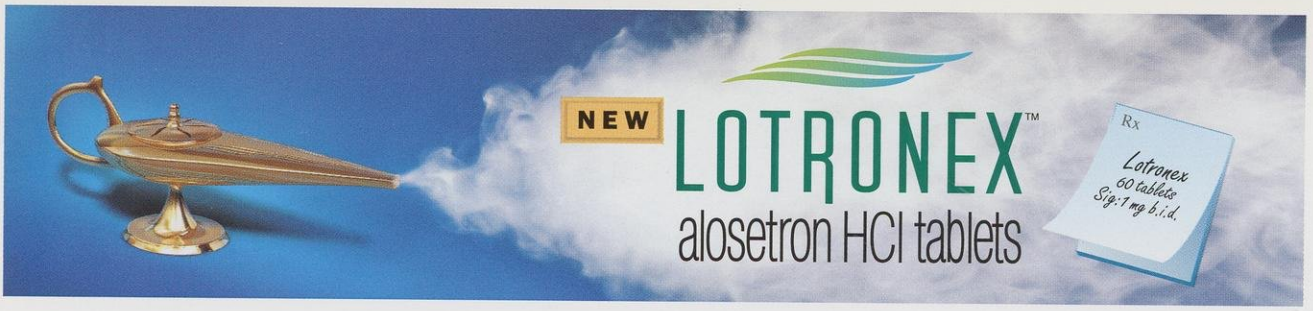

BRIEF SUMMARY

LOTRONEX™ (alosetron hydrochloride) Tablets

The following is a brief summary only; see full prescribing information for complete product information.

INDICATIONS AND USAGE: LOTRONEX is indicated for the treatment of irritable bowel syndrome (IBS) in women whose predominant bowel symptom is diarrhea.

The safety and effectiveness of LOTRONEX in men have not been established.

CONTRAINDICATIONS: LOTRONEX is contraindicated in patients known to have hypersensitivity to any component of the product.

WARNINGS: Acute ischemic colitis was infrequently* reported in patients receiving LOTRONEX in 3-month clinical trials. The reported cases resolved over several days to weeks without sequelae or complications following supportive management. A causal association between treatment with LOTRONEX and acute colitis has not been established, nor have risk factors been identified. LOTRONEX should be discontinued in patients experiencing rectal bleeding and a sudden worsening of abdominal pain. These patients should be promptly evaluated and appropriate diagnostic testing considered.

Constipation is a frequent and dose-related side effect of treatment with LOTRONEX. LOTRONEX should not be used in IBS patients who are currently constipated or whose predominant bowel symptom is constipation. In clinical studies, 25 to 30% of patients receiving alosetron experienced constipation. For the majority of these patients, constipation was mild to moderate in intensity and self-limited; however, approximately 9% of patients studied required interruption of treatment for a few days and approximately 10% could not tolerate twice daily dosing on a continuous basis and discontinued therapy. Patients experiencing constipation who completed the 12-week treatment period had similar relief of abdominal pain as patients not experiencing constipation who completed the study. Management of constipation with usual care including laxatives, fiber, or with a brief interruption of therapy may be considered (see DOSAGE AND ADMINISTRATION section of full prescribing information).

*Infrequent is defined as occurring in 1/100 to 1/1000 patients.

PRECAUTIONS:

Information for Patients: See the tear-off leaflet at the end of the full prescribing information for Information for the Patient.

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.

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 individual pathways on metabolite kinetics and pharmacodynamic consequences has not been examined.

Hepatic Insufficiency: Due to the extensive hepatic metabolism and first pass metabolism of alosetron and metabolites, increased exposure to alosetron 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 needed.

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: Of all patients who received at least one dose of alosetron in premarketing studies, 211 were 65 years of age and over and 39 were 75 years of age and over. The safety profile of LOTRONEX was similar in older and younger patients.

In two placebo-controlled IBS safety and efficacy trials (Studies 1 and 2), 60 patients 65 years of age and over and 14 patients 75 years of age and over received 1-mg oral doses of LOTRONEX twice daily for up to 12 weeks. In both studies, subgroup analyses showed no evidence of differential treatment effects across the age categories assessed. Other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out (see CLINICAL PHARMACOLOGY: Population Subgroups: Age section of full prescribing information).

ADVERSE REACTIONS: In two large, placebo-controlled clinical trials conducted in the US (Studies 1 and 2), women (18 years of age and older) were treated with 1 mg of LOTRONEX twice-daily for up to 12 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 ($p<0.0001$).

Table 1: Adverse Events Reported in ≥1% Female Patients and More Frequently on LOTRONEX 1 mg B.I.D. than Placebo (Studies 1 and 2)

Body System Adverse Event	LOTRONEX (n = 632)	Placebo (n = 637)
Cardiovascular		
Hypertension	2%	<1%
Ear, Nose, and Throat		
Allergic rhinitis	2%	<1%
Throat and tonsil discomfort and pain	1%	<1%
Bacterial ear, nose, and throat infections	1%	<1%
Gastrointestinal		
Constipation	28%	5%
Nausea	7%	6%
Gastrointestinal discomfort and pain	5%	4%
Abdominal discomfort and pain	5%	3%
Gastrointestinal gaseous symptoms	3%	2%
Viral gastrointestinal infections	3%	2%
Dyspeptic symptoms	3%	1%
Abdominal distention	2%	<1%
Hemorrhoids	2%	<1%
Neurology		
Sleep disorders	3%	2%
Psychiatry		
Depressive disorders	2%	1%

Gastrointestinal: The most frequent adverse event reported by patients treated with LOTRONEX was constipation (see WARNINGS). In clinical studies, constipation was reported in 25 to 30% of patients treated with LOTRONEX 1 mg twice daily for up to 12 weeks (n = 702). This effect was statistically significant compared to placebo ($p<0.0001$). Ten percent (10%) of patients treated with LOTRONEX withdrew from the studies due to constipation. Of the patients reporting constipation, 75% reported a single episode with the mean time to constipation onset of about 3 weeks. Occurrences of constipation were generally mild to moderate in intensity and transient in nature. Most constipation events resolved spontaneously with continued treatment. In studies 1 and 2, 9% of patients treated with LOTRONEX reported constipation and 4 consecutive days with no bowel movement; by protocol, therapy was withheld for 1 to 4 days. Following interruption of treatment, 88% of the affected patients resumed bowel movements within the 4-day period and were able to re-initiate treatment with LOTRONEX.

Hepatic: A similar incidence in elevation of ALT (>3-fold) was seen in patients receiving LOTRONEX or placebo (0.5% vs 0.4%) in studies of 12 weeks' and 12 months' duration. 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: The pattern and frequency of adverse events in a long-term, placebo-controlled safety study in which women with IBS (n = 473) were treated with LOTRONEX 1 mg twice daily for up to 12 months were essentially the same as observed in 12-week safety and effectiveness trials. There were no reports of acute colitis in these alosetron-treated women.

Other Events Observed During the Premarketing Evaluation of LOTRONEX: During its premarketing assessment, multiple and single doses of LOTRONEX were administered resulting in 2574 patient exposures in 46 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.

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 one 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.

Cardiovascular - Infrequent: Arrhythmias.

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

Ear, Nose, and Throat - Infrequent: Nasal signs and symptoms. ***Rare:*** Ear signs and symptoms.

Eyes - Rare: Photophobia.

Gastrointestinal - Infrequent: Ischemic colitis. ***Rare:*** proctitis.

Hepatobiliary Tract and Pancreas - Infrequent: Abnormal bilirubin levels.

Lower Respiratory - Infrequent: Breathing disorders. ***Rare:*** Cough.

Neurological - Rare: Sedation and abnormal dreams.

Non-site Specific - Rare: Allergies, allergic reactions, unusual odors and taste.

Psychiatry - Infrequent: Anxiety.

Reproduction - Infrequent: Menstrual disorders. ***Rare:*** Sexual function disorders.

Skin - Rare: Acne and folliculitis.

Urology - Rare: Urinary infections, polyuria, and diuresis.

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.

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