CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-107

FINAL PRINTED LABELING

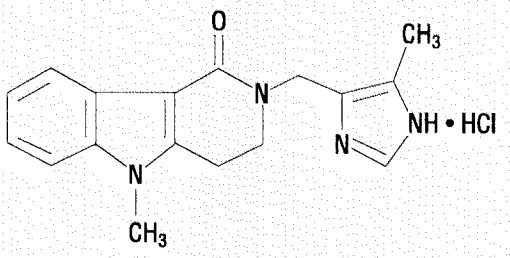
PRODUCT INFORMATION

LOTRONEX™

(alosetron hydrochloride)

Tablets

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: $C_{17}H_{18}N_4O \cdot HCl$, 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 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 $5HT_3$-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.

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 ^{14}C-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 two-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.

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 PRECAUTIONS: Geriatric Use and DOSAGE AND ADMINISTRATION: Geriatric Patients).

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: Two 12-week treatment, multi-center, double-blind, placebo-controlled, dose-ranging studies were conducted to determine the dosage of oral LOTRONEX for subsequent evaluation in efficacy studies.

In women, of the doses studied, 1 mg of LOTRONEX twice daily was significantly more effective than placebo in providing relief of IBS pain and discomfort, decreasing the proportion of days with urgency, decreasing stool frequency, and producing firmer stools. Efficacy in men,, as assessed by producing adequate relief of IBS pain and discomfort, was not demonstrated at any dose of LOTRONEX.

The efficacy and safety of 1 mg of oral LOTRONEX twice daily for 12 weeks was studied in two US multi-center, double-blind, placebo-controlled trials of identical design (Studies 1 and 2) in non-constipated women with IBS meeting the Rome Criteria (see Appendix) for at least 6 months. For enrollment into the studies, patients were required to meet entry pain and stool consistency criteria. An average pain score of at least mild pain, as collected during a two-week screening period, was required. Women with severe pain were excluded. An entry stool consistency requirement was also incorporated to target women whose predominant bowel symptom was diarrhea or in which diarrhea was a prominent feature in their alternating pattern. Women with a history of severe constipation were excluded. Men were not studied.

The primary efficacy measure in these studies was the woman's weekly assessment of adequate relief of IBS pain and discomfort. Key secondary measures included percentage of days with urgency and daily assessment of stool frequency and consistency. Study 1 enrolled 647 women (71% diarrhea-predominant, 28% alternating between diarrhea and constipation, and 1% constipation-predominant) while Study 2 enrolled 626 women (71% diarrhea-predominant, 27% alternating between diarrhea and constipation, and 2% constipation-predominant). At entry into the studies, most women reported mild to moderate pain intensity and stool consistency of formed to loose.

In both trials, LOTRONEX 1 mg administered twice daily was significantly more effective than placebo in providing relief of IBS pain and discomfort.

In both Study 1 and Study 2, the beneficial effect on IBS pain and discomfort was demonstrated only in women with diarrhea-predominant IBS. Data in Figures 1 and 2 are presented for this subgroup. In Study 1, significantly more women reported relief of their abdominal pain and discomfort within 1 week of starting alosetron therapy than those who received placebo (Figure 1) start. In Study 2, this treatment effect was observed within

4 weeks (Figure 2). Once attained, significant treatment effect persisted throughout the remainder of the treatment period. Upon discontinuing LOTRONEX, symptoms returned. Within one week after discontinuing therapy, there was no difference between placebo and alosetron-treated women.

Figure 1: Percentage of Women (Diarrhea-Predominant) Reporting Relief of IBS Pain and Discomfort in Study 1

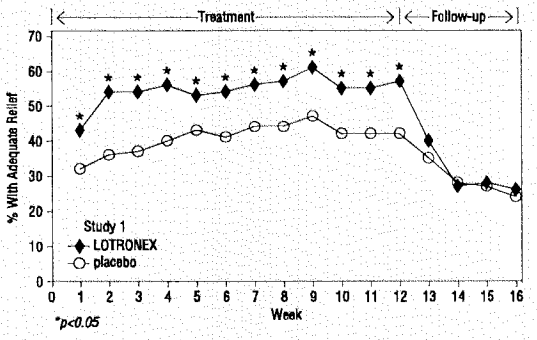
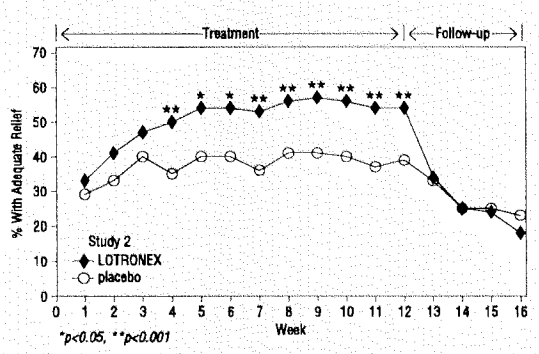


Figure 2: Percentage of Women (Diarrhea-Predominant) Reporting Relief of IBS Pain and Discomfort in Study 2



In each study, women who received LOTRONEX reported a significant decrease in the percentage of days with urgency as compared to those who received placebo. Treatment with LOTRONEX also resulted in firmer stools and a significant decrease in stool frequency.

Significant improvement of these symptoms occurred within the first week of treatment and persisted throughout the 12 weeks of therapy. Upon discontinuance of treatment these symptoms returned. Within one week after discontinuing therapy, there was no difference between placebo and alosetron-treated patients. The efficacy of LOTRONEX for treatment longer than 12 weeks has not been established.

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)

*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 labeling 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$^{\pm}$) 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.

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).

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% of 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.

DOSAGE AND ADMINISTRATION:

Usual Dose in Adults: The recommended adult dosage of LOTRONEX is 1 mg taken orally twice daily with or without food. Individual patients who experience constipation may need to interrupt treatment (see WARNINGS and ADVERSE REACTIONS: Gastrointestinal).

Pediatric Patients: No studies have been conducted in patients less than 18 years of age (see PRECAUTIONS: Pediatric Use).

Geriatric Patients: No dosage adjustment is recommended for elderly patients (65 years of age and older) (see CLINICAL PHARMACOLOGY: Population Subgroups: Age and PRECAUTIONS: Geriatric Use).

Patients with Renal Impairment: No dosage adjustment is recommended for patients with renal impairment (creatinine clearance 4 to 56 mL/min) (see CLINICAL PHARMACOLOGY: Reduced Renal Function).

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

HOW SUPPLIED: LOTRONEX Tablets, 1 mg (1.124 mg alosetron HCl equivalent to 1 mg alosetron), are blue, oval, film-coated tablets engraved with GX CT1 on one face in bottles