



PRESCRIBING INFORMATION
P189503001

LOTROXEX®
(alosecron hydrochloride)
Tablets

2000010704

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Tablets



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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LOTROXEX safely and effectively. See full prescribing information for LOTROXEX.

LOTROXEX (alosecron 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 LOTROXEX. These events, including ischemic colitis and serious complications of constipation, have resulted in hospitalization and, rarely, blood transfusion, surgery, and death.

- LOTROXEX is indicated only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have not responded adequately to conventional therapy. (1)
- Discontinue LOTROXEX immediately in patients who develop constipation or symptoms of ischemic colitis. Do not resume LOTROXEX in patients who develop ischemic colitis. (2.1, 5.1, 5.2)

INDICATIONS AND USAGE

LOTROXEX is a selective serotonin 5-HT₃ antagonist indicated only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have:

- chronic IBS symptoms (generally lasting 6 months or longer),
- had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and
- not responded adequately to conventional therapy. (1)

Severe IBS includes diarrhea and 1 or more of the following:

- frequent and severe abdominal pain/discomfort,
- frequent bowel urgency or fecal incontinence,
- disability or restriction of daily activities due to IBS. (1)

DOSAGE AND ADMINISTRATION

- Starting dose is 0.5 mg twice a day (2.1)
- May increase dose to 1 mg twice a day after 4 weeks if starting dosage is well tolerated but does not adequately control IBS symptoms (2.1)
- Discontinue LOTROXEX 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)

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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)
- Concomitant use of fluvoxamine (4.3)

WARNINGS AND PRECAUTIONS

- Serious Complications of Constipation: May occur in some patients without warning. Includes 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 LOTROXEX 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 LOTROXEX immediately if signs of ischemic colitis occur, such as rectal bleeding, bloody diarrhea, or new or worsening abdominal pain. (5.2)

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 Sebelo at 1-844-732-3521 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 alosecron. Use with fluvoxamine is contraindicated. (4.3, 7.1)
- CYP3A4 inhibitors: Use with caution in combination due to increased exposure of alosecron. (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)

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FULL PRESCRIBING INFORMATION

WARNING: SERIOUS GASTROINTESTINAL ADVERSE REACTIONS

Infrequent but serious gastrointestinal adverse reactions have been reported with the use of LOTROXEX. These events, including ischemic colitis and serious complications of constipation, have resulted in hospitalization, and rarely, blood transfusion, surgery, and death.

- LOTROXEX 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)*].
- LOTROXEX should be discontinued immediately in patients who develop constipation or symptoms of ischemic colitis. Patients should immediately report constipation or symptoms of ischemic colitis to their prescriber. LOTROXEX should not be resumed in patients who develop ischemic colitis. Patients who have constipation should immediately contact their prescriber if the constipation does not resolve after LOTROXEX is discontinued. Patients with resolved constipation should resume LOTROXEX only on the advice of their treating prescriber [see *Dosage and Administration (2.1), Warnings and Precautions (5.1), (5.2)*].

1 INDICATIONS AND USAGE

LOTROXEX 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 LOTROXEX, 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 LOTROXEX in men.

DOSAGE AND ADMINISTRATION

2.1 Adult Patients

To lower the risk of constipation, LOTROXEX should be started at a dosage of 0.5 mg twice a day. Patients who become constipated at this dosage should stop taking LOTROXEX until the constipation resolves. They may be restarted at 0.5 mg once a day. If constipation recurs at the lower dose, LOTROXEX 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. LOTROXEX 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.

LOTROXEX can be taken with or without food [see *Clinical Pharmacology (12.3)*].

LOTROXEX should be discontinued immediately in patients who develop constipation or signs of ischemic colitis. LOTROXEX 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 LOTROXEX 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 LOTROXEX is prescribed for these patients [see *Warnings and Precautions (5.1)*].

2.2 Patients with Hepatic Impairment

LOTROXEX is extensively metabolized by the liver, and increased exposure to LOTROXEX is likely to occur in patients with hepatic impairment. Increased drug exposure may increase the risk of serious adverse reactions. LOTROXEX 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)*].

DOSAGE FORMS AND STRENGTHS

0.5 mg and 1 mg tablets

LOTROXEX Tablets, 0.5 mg (0.562 mg alosecron HCl equivalent to 0.5 mg alosecron), are white, oval, film-coated tablets debossed with GX E1 on one face.

LOTROXEX Tablets, 1 mg (1.124 mg alosecron HCl equivalent to 1 mg alosecron), are blue, oval, film-coated tablets debossed with GX CT1 on one face.

4 CONTRAINDICATIONS

4.1 Constipation

LOTROXEX should not be initiated in patients with constipation [see *Warnings and Precautions (5.1)*].

4.2 History of Severe Bowel or Hepatic Disorders

LOTROXEX 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 Concomitant Use of Fluvoxamine

Concomitant administration of LOTROXEX with fluvoxamine is contraindicated. Fluvoxamine, a known strong inhibitor of CYP1A2, has been shown to increase mean alosecron 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 LOTROXEX 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 LOTROXEX 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.

LOTROXEX 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 LOTROXEX 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 LOTROXEX 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 LOTROXEX for longer than 6 months.

LOTROXEX 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 LOTROXEX should not be resumed in patients who develop ischemic colitis.

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)*]
 - 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 LOTROXEX twice daily for 8 to 24 weeks. The adverse reactions

in Table 1 were reported in 1% or more of patients who received LOTROXEX and occurred more frequently on LOTROXEX than on placebo. A statistically significant difference was observed for constipation in patients treated with LOTROXEX compared to placebo (p<0.0001).

Table 1. Adverse Reactions Reported in ≥1% of Patients with Irritable Bowel Syndrome and More Frequently on LOTROXEX 1 mg Twice Daily Than Placebo

Body System Adverse Reaction	Placebo (n = 2,363)	LOTROXEX 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 LOTROXEX [see *Warnings and Precautions (5.1)*]. In clinical studies constipation was reported in approximately 29% of patients with IBS treated with LOTROXEX 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 LOTROXEX 1 mg twice daily withdrew from the studies due to constipation. Although the number of patients with IBS treated with LOTROXEX 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 LOTROXEX 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 LOTROXEX 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 LOTROXEX.

Hepatic: A similar incidence in elevation of ALT (>2-fold) was seen in patients receiving LOTROXEX 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 LOTROXEX was reported in a 12-week study. A causal association with LOTROXEX 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 LOTROXEX 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 LOTROXEX and occurred more frequently with LOTROXEX than with placebo. Other events reported in 3% or more of patients who received LOTROXEX and occurring more frequently with LOTROXEX 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 LOTROXEX Than Placebo

Adverse Reaction	Placebo (n = 176)	LOTROXEX 0.5 mg once daily (n = 175)	LOTROXEX 1 mg once daily (n = 172)	LOTROXEX 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 LOTROXEX and occurring more frequently with LOTROXEX than with placebo included constipation (14% and 10% of patients taking LOTROXEX 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 LOTROXEX and occurring more frequently with LOTROXEX 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 LOTROXEX 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 LOTROXEX 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 LOTROXEX: During its assessment in clinical trials, multiple and single doses of LOTROXEX were administered, resulting in 11,874 subject exposures in 86 completed clinical studies. The conditions, dosages, and duration of exposure to LOTROXEX 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 LOTROXEX, occurred in at least 2 patients, and occurred at a greater frequency during treatment with LOTROXEX 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 LOTROXEX and occurring at a greater frequency in patients treated with LOTROXEX 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 LOTROXEX, 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.

Hepatology/Tract and Pancreas: *Rare:* Abnormal bilirubin levels and cholelystibitis.

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, equilibrium function disorders, disturbances of sense of taste, and disorders of cognition, 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.

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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 LOTROXEX 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 LOTROXEX.

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

Neurological: Headache. *Skin:* Rash.

7 DRUG INTERACTIONS

In vivo data suggest that alosecron 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 alosecron.

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 alosecron 1 mg on the last day. Fluvoxamine increased mean alosecron plasma concentrations (AUC) approximately 6-fold and prolonged the half-life by approximately 3-fold. Concomitant administration of alosecron and fluvoxamine is contraindicated [see *Contraindications (4.3)*].

Concomitant administration of alosecron 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 alosecron 1 mg on the last day. Ketoconazole increased mean alosecron plasma concentrations (AUC) by 25%. Caution should be used when alosecron and ketoconazole are administered concomitantly. Coadministration of alosecron 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 alosecron 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 alosecron 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, alosecron inhibited CYP enzymes 1A2 (60%) and 2E1 (50%). In an *in vivo* metabolic probe study, alosecron did not inhibit CYP2E1 but did produce 30% inhibition of both CYP1A2 and N-acetyltransferase. Although not studied with alosecron, 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 alosecron had no clinically significant effect on plasma concentrations of the oral contraceptive agents ethinyl estradiol and levonorgestrel (CYP3A4 substrates). A clinical interaction study was conducted with alosecron and the CYP3A4 substrate cisapride. No significant effects on cisapride metabolism or QT interval were noted. The effects of alosecron 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 alosecron will inhibit the hepatic metabolic clearance of drugs metabolized by the CYP enzymes 2C9, 2C19, or 2E1.

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Absorption: Alosetron was rapidly absorbed after oral administration with a mean absolute bioavailability of approximately 50% to 60% (approximate range, 30% to >90%). After administration of radiolabeled alosetron, only 1% of the dose was recovered in the feces as unchanged drug. Following oral administration of a 1 mg alosetron dose to young men, a peak plasma concentration of approximately 5 ng/mL occurred at 1 hour. In young women, the mean peak plasma concentration was approximately 9 ng/mL, with a similar time to peak.

Plasma concentrations were 30% to 50% lower and less variable in men compared to women given the same oral dose. Population pharmacokinetic analysis in IBS patients confirmed that alosetron concentrations were influenced by gender (27% lower in men).

Food Effects: Alosetron absorption is decreased by approximately 25% by co-administration with food, with a mean delay in time to peak concentration of 15 minutes [see *Dosage and Administration* (2.1)].

Distribution: Alosetron demonstrates a volume of distribution of approximately 65 to 95 L. Plasma protein binding is 82% over a concentration range of 20 to 4,000 ng/mL.

Metabolism and Elimination: Plasma concentrations of alosetron increase proportionately with increasing single oral doses up to 8 mg and more than proportionately at a single oral dose of 16 mg. Twice-daily oral dosing of alosetron does not result in accumulation. The terminal elimination half-life of alosetron is approximately 1.5 hours (plasma clearance is approximately 600 mL/min). Population pharmacokinetic analysis in patients with IBS confirmed that alosetron clearance is minimally influenced by doses up to 8 mg.

Renal elimination of unchanged alosetron accounts for only 13% of the dose. Renal clearance is approximately 112 mL/min.

A study with ¹⁴C-labeled alosetron in Caucasian males (n = 3) and females (n = 3) and an Asian male (n = 1) showed similar serum metabolite profiles. Unchanged alosetron was the major component in serum, with other metabolites being present at low concentrations, none amounting to more than 15% of the unmetabolized alosetron concentration. The circulating metabolites were identified as 6-hydroxy glucuronide, 6-hydroxy sulphate, 7-hydroxy sulphate, hydroxymethyl imidazole, and mono- and bis-oxygenated imidazole derivatives of alosetron. The metabolites are unlikely to contribute to the biological activity of alosetron. Of the circulating Phase I metabolites, only the hydroxymethyl imidazole has weak pharmacological activity, around 10-fold less potent than alosetron. Total recovery of radioactivity in the excreta was 85 ± 6%. The majority of the radiolabeled dose is excreted in the urine (74 ± 5%). The major urinary metabolites were the 6-hydroxy glucuronide and the mono- and bis-oxygenated imidazole derivatives of alosetron. 11 ± 4% of the radiolabeled dose was excreted in the feces with less than 1% of the dose being excreted as the unchanged alosetron.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In 2-year oral studies, alosetron was not carcinogenic in mice at doses up to 30 mg/kg/day or in rats at doses up to 40 mg/kg/day. These doses are about 60 to 160 times, respectively, the recommended human dose of alosetron of 2 mg/day (1 mg twice daily) based on body surface area. Alosetron was not genotoxic in the Ames tests, the mouse lymphoma cell (L5178Y/TK⁺) forward gene mutation test, the human lymphocyte chromosome aberration test, the ex vivo rat hepatocyte unscheduled DNA synthesis (UDS) test, or the *in vivo* rat micronucleus test for mutagenicity. Alosetron at oral doses up to 40 mg/kg/day (about 160 times the recommended daily human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male or female rats.

14 CLINICAL STUDIES

14.1 Dose-Ranging Study

Data from a dose-ranging study of women (n = 85) who received LOTRONEX 0.5 mg twice daily indicated that the incidence of constipation (14%) was lower than that experienced by women receiving 1 mg twice daily (29%). Therefore, to lower the risk of constipation, LOTRONEX should be started at a dosage of 0.5 mg twice a day. The efficacy of the 0.5 mg twice-daily dosage in treating severe diarrhea-predominant IBS has not been adequately evaluated in clinical trials. [See *Dosage and Administration* (2.1)]

14.2 Efficacy Studies

LOTRONEX has been studied in women with IBS in five 12-week US multicenter, randomized, double-blind, placebo-controlled clinical studies.

Table 3. Efficacy Studies Conducted in Women with Irritable Bowel Syndrome (IBS)

Study	Patient Population	Placebo (n)	LOTRONEX Dose (n)
1 and 2	Non-constipated women with IBS	(640)	1 mg twice daily (633)
3 and 4	Women with severe diarrhea predominant IBS (defined as bowel urgency ≥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 Criteria¹ for at least 6 months. Women with severe pain or a history of severe constipation were excluded. A 2-week run-in period established baseline IBS symptoms.

About two thirds of the women had diarrhea-predominant IBS. Compared with placebo, 10% to 19% more women with diarrhea-predominant IBS who received LOTRONEX had adequate relief of IBS abdominal pain and discomfort during each month of the study.

Studies in Women with Severe Diarrhea-Predominant Irritable Bowel Syndrome: LOTRONEX is indicated only for women with severe diarrhea-predominant IBS [see *Indications and Usage* (1)]. The efficacy of LOTRONEX in this subset of the women studied in clinical trials is supported by prospective and retrospective analyses.

Prospective Analyses: Studies 3 and 4 were conducted in women with diarrhea-predominant IBS and bowel urgency on at least 50% of days at entry. Women receiving LOTRONEX had significant increases over placebo (13% to 16%) in the median percentage of days with urgency control.

The lower gastrointestinal functions of stool consistency, stool frequency, and sense of incomplete evacuation were also evaluated by patients' daily reports. Stool consistency was evaluated on a scale of 1 to 5 (1 = very hard, 2 = hard, 3 = formed, 4 = loose, and 5 = watery).

At baseline, average stool consistency was approximately 4 (loose) for both treatment groups. During the 12 weeks of treatment, the average stool consistency decreased to approximately 3.0 (formed) for patients who received LOTRONEX and 3.5 for the patients who received placebo in the 2 studies. At baseline, average stool frequency was approximately 3.2 per day for both treatment groups. During the 12 weeks of treatment, the average daily stool frequency decreased to approximately 2.1 and 2.2 for patients receiving LOTRONEX and 2.7 and 2.8 for patients receiving placebo in the 2 studies.

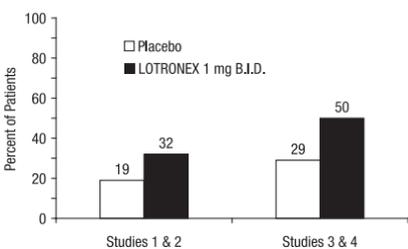
There was no consistent effect upon the sense of incomplete evacuation during the 12 weeks of treatment for patients receiving LOTRONEX as compared to patients receiving placebo in either study.

Study 5 was conducted in women with severe diarrhea-predominant IBS and 1 or more of the following: frequent and severe abdominal pain or discomfort, frequent bowel urgency or fecal incontinence, disability or restriction of daily activities due to IBS. To evaluate the proportion of patients who responded to treatment, patients were asked every 4 weeks to compare their IBS symptoms during the previous month of treatment with how they usually felt during the 3 months prior to the study using an ordered 7-point scale (substantially worse to substantially improved). A responder was defined as a subject who reported moderate or substantial improvement on this global improvement scale (GIS). At Week 12, all three groups receiving LOTRONEX had significantly greater percentages of GIS responders compared to the placebo group (43% to 51% vs. 31%) using a Last Observation Carried Forward (LOCF) analysis. It should be noted that approximately 4% of subjects in each LOTRONEX dose group who were classified as responders using this approach were observed only through week 4. At each of the 4 week intervals of the treatment phase, all three dosages of LOTRONEX provided improvement in the average adequate relief rate of IBS pain and discomfort, stool consistency, stool frequency, and sense of urgency compared with placebo.

Retrospective Analyses: In analyses of patients from Studies 1 and 2 who had diarrhea-predominant IBS and indicated their baseline run-in IBS symptoms were severe at the start of the trial, LOTRONEX provided greater adequate relief of IBS pain and discomfort than placebo. In further analyses of Studies 1 and 2, 57% of patients had urgency at baseline on 5 or more days per week. In this subset, 32% of patients on LOTRONEX had urgency no more than 1 day in the last week of the trial, compared with 19% of patients on placebo.

In Studies 3 and 4, 66% of patients had urgency at baseline on 5 or more days per week. In this subset, 50% of patients on LOTRONEX had urgency no more than 1 day in the last week of the trial, compared with 29% of patients on placebo. Moreover, in the same subset, 12% on LOTRONEX had urgency no more than 2 days per week in any of the 12 weeks on treatment compared with 1% of placebo patients.

Figure 1. Percent of Patients with Urgency on >5 Days/Week at Baseline Who Improved to No More Than 1 Day in the Final Week



In Studies 1 and 2, patient-reported subjective outcomes related to IBS were assessed by questionnaires obtained at baseline and week 12. Patients in the more severe subset who received LOTRONEX reported less difficulty sleeping, less tiredness, fewer eating problems, and less interference with social activities and work/main activities due to IBS symptoms or problems compared to those who received placebo. Change in the impact of IBS symptoms and problems on emotional and mental distress and on physical and sexual activity in women who received LOTRONEX were not statistically different from those reported by women who received placebo.

14.3 Long-Term Use

In a 48-week multinational, double-blind, placebo-controlled study, LOTRONEX 1 mg twice daily was evaluated in 714 women with non-constipated IBS. A retrospective analysis of the subset of women with severe diarrhea-predominant IBS (urgency on at least 10 days during the 2-week baseline period) was performed. Of the 417 patients with severe diarrhea-predominant IBS, 62% completed the trial.

LOTRONEX (n = 198) provided a greater average rate of adequate relief of IBS pain and discomfort (52% vs. 41%) and a greater average rate of satisfactory control of bowel urgency (60% vs. 48%) compared with placebo (n = 219). Significant improvement of these symptoms occurred for most of the 48-week treatment period with no evidence of tachyphylaxis.

15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

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 54766-894-03) 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 54766-895-03) with child-resistant closures.

Store at 20-25°C (68-77°F) (USP Controlled Room Temperature). Protect from light and moisture.

LOTRONEX® (alosetron hydrochloride) Tablets

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Prescriber 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 prescriber or a healthcare provider under a prescriber's direction.

Prescribers 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.
- review 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.
- provide each patient with appropriate instructions for taking LOTRONEX.

Additional copies of the Medication Guide are available by contacting Sebelá at 1-844-732-3521 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 prescriber if they become constipated, or have symptoms of ischemic colitis such as new or worsening abdominal pain, bloody diarrhea, or blood in the stool. Contact their prescriber again if their constipation does not resolve after discontinuation of LOTRONEX. Resume LOTRONEX only if their constipation has resolved and after discussion with and the agreement of their treating prescriber.
- stop taking LOTRONEX and contact their prescriber if LOTRONEX does not adequately control IBS symptoms after 4 weeks of taking 1 mg twice a day.

MEDICATION GUIDE LOTRONEX® (LOW-trah-nex) (alosetron hydrochloride) Tablets

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.

What is the most important information I should know about LOTRONEX?

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. Some people have developed serious bowel side effects while taking LOTRONEX. Serious bowel (intestine) side effects can happen suddenly, including the following:
 - **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.
- **Inflammation and injury of the intestines caused by reduced blood flow (ischemic colitis):** Ischemic colitis is caused by reduced blood flow to parts of the large bowel. 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.

Stop taking LOTRONEX and call your doctor or get medical help if you have symptoms of ischemic colitis such as new or worsening stomach-area (abdominal) pain, bloody diarrhea or blood in the stool.

What is LOTRONEX?

LOTRONEX is a prescription medicine used 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.

It is not known if LOTRONEX is safe and effective in men with IBS.

It is not known if LOTRONEX is safe and effective in children.

Who should not take LOTRONEX?

Do not take LOTRONEX if you:

- have constipation or you are constipated most of the time.
- have had a serious problem from constipation. **If you are constipated now, do not start taking LOTRONEX.**
- have had serious bowel blockages.
- have had blood flow problems to your bowels, such as ischemic colitis.
- have had blood clots.
- have had Crohn's disease, ulcerative colitis, diverticulitis, or severe liver disease.
- are taking fluvoxamine (LUVOX).

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.
- any allergies that you have. See the end of the Medication Guide for a complete list of ingredients in LOTRONEX.
- if you have liver problems.
- if you are pregnant or planning to become pregnant. It is not known if LOTRONEX can harm your unborn baby.
- if you are breastfeeding or plan to breastfeed. It is not known if LOTRONEX can harm your baby. Talk to your doctor about the best way to feed your baby if you take LOTRONEX.

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.
- Follow the 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.

What are the possible side effects of LOTRONEX?

LOTRONEX may cause serious side effects, including:
See "What is the most important information I should know about LOTRONEX?"

The most common side effects of LOTRONEX include:

- constipation
 - stomach (abdominal) discomfort and pain
 - nausea
 - intestinal discomfort and pain
- These are not all the possible side effects of LOTRONEX. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store LOTRONEX?

- Store LOTRONEX at room temperature between 68°F to 77°F (20°C to 25°C).
- Protect LOTRONEX from light and moisture.

Keep LOTRONEX and all medicines out of the reach of children.

General information about the safe and effective use of LOTRONEX
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use LOTRONEX for a condition for which it was not prescribed. Do not give LOTRONEX to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about LOTRONEX that is written for healthcare professionals.

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.

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Distributed by:
Sebelá Pharmaceuticals Inc.
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Made in CANADA

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