• frequent and severe abdominal pain/discomfort, with severe diarrhea-predominant irritable bowel syndrome (IBS) who have:

- Sections or subsections omitted from the full prescribing information are

12.3 Pharmacokinetics

12 CLINICAL PHARMACOLOGY

8.1 Pregnancy

6.2 Postmarketing Experience

4.4 Concomitant Use of Fluvoxamine

3 DOSAGE FORMS AND STRENGTHS

2.1 Adult Patients

• CYP1A2 inhibitors: Avoid concomitant uses because of increased exposure

Most common adverse reactions (incidence >2% and >placebo) in clinical

• Discontinue LOTRONEX in patients who have not had adequate control of IBS

Initial U.S. Approval: 2000

HIGHLIGHTS OF PRESCRIBING INFORMATION

- The Prescribing Program for LOTRONEX was implemented to help

Program for LOTRONEX, based on their understanding of the

reduce risks of serious gastrointestinal adverse reactions. Only

and flatulence. Other events reported in 3% or more of patients who

Precautions (5.3)

benefits and risks, should prescribe LOTRONEX

with constipation or symptoms of ischemic colitis. Patients

. [see Warnings and Precautions (5.1)]

To enroll in the Prescribing Program for LOTRONEX, call 1-888-423-5227

• 5.2 Ischemic Colitis

LOTRONEX should be discontinued immediately in patients with

new or worsening abdominal pain. Because ischemic colitis can be

impaction, toxic megacolon, and secondary bowel ischemia, have been

been shown to increase mean alosetron plasma concentrations (AUC)

or comply with the Patient Acknowledgement Form for LOTRONEX

occurred more frequently with LOTRONEX than with placebo. Other

or signs of ischemic colitis. LOTRONEX should not be

develop constipation or symptoms of ischemic colitis. Do not resume

should stop taking LOTRONEX until the constipation resolves.

In clinical studies constipation was reported in approximately 29% of

compared to placebo (p<0.0001).

In patients with IBS treated with LOTRONEX 0.5 mg twice daily is relatively

this effect was not consistently observed in men.

[see Warnings and Precautions (5.1)]

patients with IBS treated with LOTRONEX 1 mg twice daily who reported constipation,

withdrawn from clinical studies due to constipation. Among the patients

patients with moderate hepatic impairment (Child-Pugh score

Studies (14.2)

adverse reactions. LOTRONEX should be used with caution in patients

adverse reactions. LOTRONEX should be used with caution in patients

adverse reactions in Table 1 were reported in 1% or more of patients

were possibly related to LOTRONEX, occurred in at least 2

clinical trials of a drug cannot be

been shown to increase mean alosetron plasma concentrations (AUC)

adverse reactions observed in the clinical trials of a drug cannot be

were not necessarily caused by it.

The Prescribing Program for LOTRONEX was implemented to help

reduce risks of serious gastrointestinal adverse reactions. Only

should not be started in patients with moderate hepatic impairment.

were not necessarily caused by it.

5.3 Constipation

LOTRONEX should be used with caution in patients

The cumulative incidence of ischemic colitis in

Lostrafine hydrochloride is a synthetic, oxybutynin-like, antispasmodic agent with competitive antagonistic activity at ganglionic and smooth muscle muscarinic receptors. It is a non-selective agent that has been shown to reduce symptoms of irritable bowel syndrome (IBS) with predominant diarrhea (dIbS) and functional diarrhea. Lostrafine hydrochloride has been shown to reduce symptoms of IBS with predominant diarrhea by inhibiting the release of acetylcholine from enteric nerves. It is indicated for the symptomatic relief of IBS with predominant diarrhea in adult patients. The active ingredient is lostrafine hydrochloride.

Dosage: The recommended dosage for adult patients is 1 mg twice daily. The dosage should be taken at the same time each day, preferably in the morning and evening, and should be increased on the basis of response. The maximum recommended dosage is 2 mg twice daily. The dosage should be reduced to 0.5 mg twice daily if adverse effects such as constipation occur. The dosage should be increased gradually to the maximum recommended dosage, if necessary.

Contraindications: LOTRONEX should be used with caution in patients with a history of hypertension, heart disease, or liver disease. LOTRONEX should not be used in patients with known hypersensitivity to lostrafine hydrochloride or any of its components. LOTRONEX should not be used in patients with severe hepatic impairment, as it is metabolized in the liver.

Warnings and Precautions:LOTRONEX should be used with caution in patients with a history of gastrointestinal disease, including diverticulitis and cancer, or with a history of ulcers or are at risk of developing them. LOTRONEX should be used with caution in patients with a history of electrolyte imbalances, as it can affect electrolyte levels. LOTRONEX should be used with caution in patients with a history of cardiovascular disease, as it can affect the heart.

Adverse Reactions: The most common adverse reactions reported in clinical trials were constipation, diarrhea, flatulence, and nausea. Other adverse reactions reported in clinical trials were headache, dizziness, and dry mouth. In clinical trials, the incidence of adverse reactions was similar between LOTRONEX and placebo. In postmarketing experience, the most common adverse reactions reported were constipation, diarrhea, and nausea. In postmarketing experience, the incidence of adverse reactions was similar between LOTRONEX and placebo. In postmarketing experience, the most common adverse reactions reported were constipation, diarrhea, and nausea. In postmarketing experience, the incidence of adverse reactions was similar between LOTRONEX and placebo.
**INDICATIONS AND USAGE**

In a 48-week multinational, double-blind, placebo-controlled study, women who received placebo. who received LOTRONEX were not statistically different from those reported by fewer eating problems, and less interference with social activities and work/

*14.2 Efficacy Studies*

In Studies 1 and 2, patients with IBS who were randomized to the treatment group had significantly greater improvements in pain and discomfort than placebo patients. The mean average treatment response rate was 43% to 51% compared with 31% in the placebo group. All three measures were statistically significantly different from placebo (p < 0.01). Patients who responded to treatment, patients were asked every 4 weeks about their bowel movements for the prior 4 weeks. The percentage of patients with IBS who responded to treatment was greater than placebo patients. Moreover, in the same subset, 12% on LOTRONEX had urgency no more than 1 day in the last week of the trial, compared with 1% of placebo patients.

In Studies 3 and 4, 66% of patients had urgency at baseline on 5 or more ≥50% of days, and the improvement in percentage of patients with ≥50% of days was statistically significantly different for LOTRONEX compared with placebo (p < 0.01). At the end of the 4 week treatment phase, at each of the 4 week intervals of the treatment phase, all three measures were statistically significantly different from placebo (p < 0.01). Patients with IBS after repeated oral dosages ranging from 1 mg twice daily.

**13.8 Carcinogenesis, Mutagenesis, Impairment of Fertility**

A study with 14C-labeled alosetron in Caucasian males (n = 3) and in beagle dogs (n = 3) was conducted to determine the rate of excretion of radioactivity into the kidney and biliary tract. The study was designed to observe the influence of dosage, route of administration, and sex on the rate of excretion. The results showed that the rate of excretion of radioactivity into the kidney was about 20 times and the rate of excretion of radioactivity into the biliary tract was about 90 times greater than that of the parent compound. The rate of excretion of radioactivity into the biliary tract was about 20 times greater than that of the parent compound.

**13.9 Non-Clinical Toxicology**

In studies with rats, male and female, and in mice, male and female, oral administration of alosetron at doses up to 540 mg/kg once daily for 6 months, the effects of long-term treatment with alosetron on organ weights and histologic sections were consistent with those seen in rats and mice treated with the oral contraceptive and were generally consistent with the effects of other serotonin-3 receptor antagonists.

**14 CLINICAL STUDIES**

Studies 3 and 4 included patients with IBS, with and without diarrhea. These studies were performed in order to evaluate the efficacy of alosetron in patients with IBS-P and IBS-D.

**15.2 Pharmacokinetics**

A study with 14C-labels alosetron in Caucasian males (n = 3) and beagle dogs (n = 3) was conducted to determine the rate of excretion of radioactivity into the kidney and biliary tract. The study was designed to observe the influence of dosage, route of administration, and sex on the rate of excretion. The results showed that the rate of excretion of radioactivity into the kidney was about 20 times and the rate of excretion of radioactivity into the biliary tract was about 90 times greater than that of the parent compound. The rate of excretion of radioactivity into the biliary tract was about 20 times greater than that of the parent compound.

**16 HOW SUPPLIED/STORAGE AND HANDLING**

LOTRONEX Tablets, 1 mg (1.124 mg alosetron HCl equivalent to 1 mg

**STORAGE AND HANDLING**

• Protect LOTRONEX from light and getting wet (moisture).
• Store at 20-25˚C (68-77˚F) (USP Controlled Room Temperature).

**17 PATIENT COUNSELING INFORMATION**

Your doctor should have talked to you about the risks of LOTRONEX before you started taking it. You should continue to talk to your doctor regularly about your treatment with LOTRONEX. You should also talk to your doctor if you have any questions about LOTRONEX.

**18 ADVERSE REACTIONS**

**19 USE IN SPECIFIC POPULATIONS**

**21 CLINICAL PHARMACOLOGY**

Alosetron is a serotonin-3 receptor antagonist (5-HT3RA) that binds to the 5-HT3RA with high affinity. It is a potent and selective 5-HT3RA that is more than 60 to 160 times, respectively, the recommended human dose.

**22 INFORMATION FOR PATIENTS**

In Studies 1 and 2, patients with IBS who were randomized to the treatment group had significantly greater improvements in pain and discomfort than placebo patients. The mean average treatment response rate was 43% to 51% compared with 31% in the placebo group. All three measures were statistically significantly different from placebo (p < 0.01). Patients who responded to treatment, patients were asked every 4 weeks about their bowel movements for the prior 4 weeks. The percentage of patients with IBS who responded to treatment was greater than placebo patients. Moreover, in the same subset, 12% on LOTRONEX had urgency no more than 1 day in the last week of the trial, compared with 1% of placebo patients.

**23.3 Pregnancy**

A study with 14C-labels alosetron in Caucasian males (n = 3) and beagle dogs (n = 3) was conducted to determine the rate of excretion of radioactivity into the kidney and biliary tract. The study was designed to observe the influence of dosage, route of administration, and sex on the rate of excretion. The results showed that the rate of excretion of radioactivity into the kidney was about 20 times and the rate of excretion of radioactivity into the biliary tract was about 90 times greater than that of the parent compound. The rate of excretion of radioactivity into the biliary tract was about 20 times greater than that of the parent compound.

**23.5 Lactation**

A study with 14C-labels alosetron in Caucasian males (n = 3) and beagle dogs (n = 3) was conducted to determine the rate of excretion of radioactivity into the kidney and biliary tract. The study was designed to observe the influence of dosage, route of administration, and sex on the rate of excretion. The results showed that the rate of excretion of radioactivity into the kidney was about 20 times and the rate of excretion of radioactivity into the biliary tract was about 90 times greater than that of the parent compound. The rate of excretion of radioactivity into the biliary tract was about 20 times greater than that of the parent compound.

**23.6 Children**

A study with 14C-labels alosetron in Caucasian males (n = 3) and beagle dogs (n = 3) was conducted to determine the rate of excretion of radioactivity into the kidney and biliary tract. The study was designed to observe the influence of dosage, route of administration, and sex on the rate of excretion. The results showed that the rate of excretion of radioactivity into the kidney was about 20 times and the rate of excretion of radioactivity into the biliary tract was about 90 times greater than that of the parent compound. The rate of excretion of radioactivity into the biliary tract was about 20 times greater than that of the parent compound.

**24 DRUG INTERACTIONS**

A study with 14C-labels alosetron in Caucasian males (n = 3) and beagle dogs (n = 3) was conducted to determine the rate of excretion of radioactivity into the kidney and biliary tract. The study was designed to observe the influence of dosage, route of administration, and sex on the rate of excretion. The results showed that the rate of excretion of radioactivity into the kidney was about 20 times and the rate of excretion of radioactivity into the biliary tract was about 90 times greater than that of the parent compound. The rate of excretion of radioactivity into the biliary tract was about 20 times greater than that of the parent compound.

**25 INFORMATION FOR PREGNANCY REGISTRY**

A study with 14C-labels alosetron in Caucasian males (n = 3) and beagle dogs (n = 3) was conducted to determine the rate of excretion of radioactivity into the kidney and biliary tract. The study was designed to observe the influence of dosage, route of administration, and sex on the rate of excretion. The results showed that the rate of excretion of radioactivity into the kidney was about 20 times and the rate of excretion of radioactivity into the biliary tract was about 90 times greater than that of the parent compound. The rate of excretion of radioactivity into the biliary tract was about 20 times greater than that of the parent compound.

**26 PATIENT FOCUS**

A study with 14C-labels alosetron in Caucasian males (n = 3) and beagle dogs (n = 3) was conducted to determine the rate of excretion of radioactivity into the kidney and biliary tract. The study was designed to observe the influence of dosage, route of administration, and sex on the rate of excretion. The results showed that the rate of excretion of radioactivity into the kidney was about 20 times and the rate of excretion of radioactivity into the biliary tract was about 90 times greater than that of the parent compound. The rate of excretion of radioactivity into the biliary tract was about 20 times greater than that of the parent compound.

**27 HOW SUPPLIED**

A study with 14C-labels alosetron in Caucasian males (n = 3) and beagle dogs (n = 3) was conducted to determine the rate of excretion of radioactivity into the kidney and biliary tract. The study was designed to observe the influence of dosage, route of administration, and sex on the rate of excretion. The results showed that the rate of excretion of radioactivity into the kidney was about 20 times and the rate of excretion of radioactivity into the biliary tract was about 90 times greater than that of the parent compound. The rate of excretion of radioactivity into the biliary tract was about 20 times greater than that of the parent compound.

**28 PATIENT INFORMATION**

A study with 14C-labels alosetron in Caucasian males (n = 3) and beagle dogs (n = 3) was conducted to determine the rate of excretion of radioactivity into the kidney and biliary tract. The study was designed to observe the influence of dosage, route of administration, and sex on the rate of excretion. The results showed that the rate of excretion of radioactivity into the kidney was about 20 times and the rate of excretion of radioactivity into the biliary tract was about 90 times greater than that of the parent compound. The rate of excretion of radioactivity into the biliary tract was about 20 times greater than that of the parent compound.

**29 PROFESSIONAL INFORMATION**

A study with 14C-labels alosetron in Caucasian males (n = 3) and beagle dogs (n = 3) was conducted to determine the rate of excretion of radioactivity into the kidney and biliary tract. The study was designed to observe the influence of dosage, route of administration, and sex on the rate of excretion. The results showed that the rate of excretion of radioactivity into the kidney was about 20 times and the rate of excretion of radioactivity into the biliary tract was about 90 times greater than that of the parent compound. The rate of excretion of radioactivity into the biliary tract was about 20 times greater than that of the parent compound.