LOTRONEX™ (alosetron HCl) for the Management of Irritable Bowel Syndrome in Women Whose Predominant Bowel Symptom Is Diarrhea

LOTRONEX™
alosetron HCl tablets

GlaxoWellcome

LOTRONEX™ (alosetron HCl) Table of Contents

Introduction

Irritable Bowel Syndrome (IBS) is a common, chronic medical disorder with far-reaching impact on many affected patients and on society. Its core symptom—chronic abdominal pain or discomfort, associated with altered bowel function (diarrhea, constipation, or alternating bouts of each)—can be seriously debilitating and can be associated with marked impairment of patients' quality of life and productivity.[1] IBS also has significant economic consequences, estimated at $8 billion annually in direct medical expenditures (excluding outpatient medications).[2]

Current treatment of IBS has been challenging for many physicians and IBS sufferers alike. While there are several pharmacologic agents available, they generally target only one symptom of IBS, and patients may need to take more than one medication to control their symptoms.[3,4]

Today, important strides have been made that may improve management of IBS. These include:

- Steps toward precise symptom-based diagnostic criteria (e.g., Rome criteria)
- Enhanced understanding of the role of the enteric nervous system and the neurotransmitter serotonin in regulating intestinal motility and visceral hypersensitivity and how these processes may be related to IBS
- LOTRONEX™ (alosetron HCl)—a selective 5-hydroxytryptamine-3 (5-HT_3) receptor antagonist is indicated for the management of Irritable Bowel Syndrome (IBS) in women whose predominant bowel symptom is diarrhea. Efficacy and safety in men have not been established

This publication is intended to serve as a resource guide for healthcare professionals who treat patients with IBS. It includes a concise overview of the disease as well as a useful summary of available information on LOTRONEX.

Irritable Bowel Syndrome (IBS)

Prevalence

IBS is estimated to occur in up to 20% of the US population.[5,6] It is diagnosed more than three times as frequently in women as in men.[7] Whatever the reason for the difference, the disorder is a major women's health issue.

Although the condition occurs in adult patients of all ages, prevalence appears to be age-associated, peaking in women during the prime reproductive years and declining thereafter. The age distribution of IBS is shown in Figure 1.[5]

The prevalence of IBS in the US population ranks the disorder among other major chronic diseases. As illustrated in Figure 2, IBS occurs at a higher rate than hypertension, asthma, diabetes, and congestive heart failure.[6,8,9]

FIGURE 1

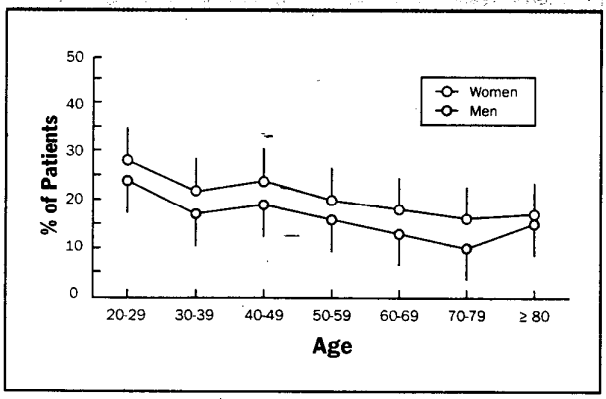


Figure 1. Age-specific prevalence of IBS. Adapted with permission from Talley NJ, et al. *Am J Epidemiol.* 1995;142:76-83.

Medical Visits. IBS is among the most frequently seen disorders in US medical settings.[10] It has been estimated that IBS accounts for more than 3.5 million physician visits each year.[11] According to a 1994 survey, 25% of people with IBS reported

FIGURE 2

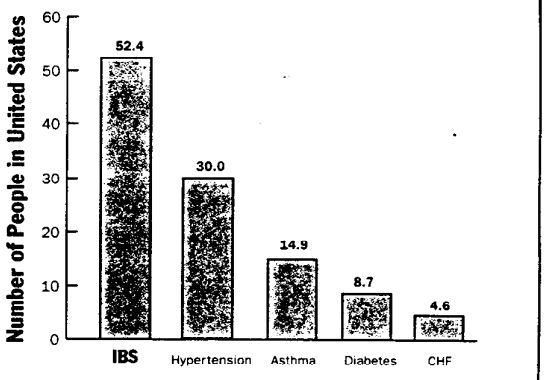


Figure 2. Comparative US prevalence of major chronic diseases. Data from US Census Bureau, *Statistical Abstract of the United States*, 1998; American Heart Association, *1999 Heart and Stroke Statistical Update*; Camilleri M, Choi M-G, *Aliment Pharmacol Ther.* 1997;11:3-15. IBS figure approximated by taking 20% of the 1995 US population (in millions).

IBS occurs at a higher rate than hypertension, asthma, diabetes, and congestive heart failure

physician visits in the prior year, as compared with 8% of those without IBS.[2] It is the most common diagnosis encountered by practicing gastroenterologists in the United States,[12] representing 26% of all patients[13] and up to 50% of outpatient referrals to gastroenterologists.[14] In fact, IBS is among the top 10 diagnoses made by US physicians in any specialty.[13]

Although IBS affects up to 20% of the population, it has been reported that only 25% seek medical care.[5] It is unclear as to why the other 75% do not consult their physicians. A 1990 survey revealed that less than half of those with IBS symptoms had ever seen a doctor for their condition.[15]

Clinical Features

IBS is a medical disorder with a variety of symptoms and presentations. IBS is characterized by abdominal pain associated with abnormal bowel motility. These symptoms can occur simultaneously or sequentially, and in numerous combinations.

Abdominal Pain. Chronically recurring abdominal pain or discomfort is the hallmark symptom of IBS. It is usually characterized as crampy in nature or as a generalized ache with superimposed periods of abdominal cramping.[14] The pain of IBS is typically relieved by defecation.[10] A recent study of symptom patterns in patients with diagnosed IBS found abdominal pain and/or discomfort to be a predominant finding, reported by patients on 1 out of every 3 days on average.[16]

Altered Bowel Function. Patients with IBS may experience diarrhea, constipation, or diarrhea that alternates with constipation. They may thus be classified into 1 of 3 subgroups: diarrhea predominant, constipation predominant, or alternating constipation and diarrhea.

Chronically recurring abdominal pain or discomfort is the hallmark symptom of IBS

In their epidemiologic study of patients with IBS, Talley and colleagues found that many patients with IBS experience diarrhea, either as their predominant symptom or as a concurrent/alternating symptom.[5]

Other GI Symptoms. Other GI symptoms experienced by patients with IBS include urgency to defecate, feelings of incomplete evacuation, sensations of abdominal distention and bloating, and passage of mucus.[5,10,17,18]

Comorbidities

A strong association between IBS and anxiety and depression has been noted.[19] Additionally, there is an increased prevalence of chronic pelvic pain[20] and fibromyalgia (FM) in patients with Irritable Bowel Syndrome.[21]

Course/Chronicity

IBS is a chronic disease in which symptoms typically wax and wane for many years.[14] Hahn and associates evaluated the frequency and severity of symptoms in a group of 59 adults with IBS.[16] The investigators' symptom data were captured by way of a touch-tone telephone system accessed by the patients on a daily basis for a period of 12 weeks. In this study, the majority of patients with IBS reported experiencing frequent symptoms, i.e., at least one episode of symptoms on over 50% of reported days, repeatedly cycling between symptomatic days and symptom-free days. The majority of symptoms were reported to be moderate to severe in intensity.

IBS is a chronic disease in which symptoms can be debilitating

Impact of IBS

Quality of Life. IBS can be associated with marked decrements in a variety of aspects of affected patients' quality of life (QOL). These may include diet, work, leisure activities, sexual functioning, and sleep.[22,23]

Two of several standardized instruments used to evaluate QOL in patients with IBS are the Irritable Bowel Syndrome Quality of Life Questionnaire (IBS QOL) and the Medical Outcomes Study Short Form (SF-36™). The first was developed specifically for IBS, while the second is more general. Hahn and associates administered the IBS QOL to 2 groups of patients with IBS—in California (n=126) and Tennessee (n=122)—and to a group of 37 control subjects without IBS.[24] The result is illustrated in Figure 3. Comparison of mean scores demonstrates lower QOL in patients with IBS in every assessment domain as compared to control subjects.

FIGURE 3

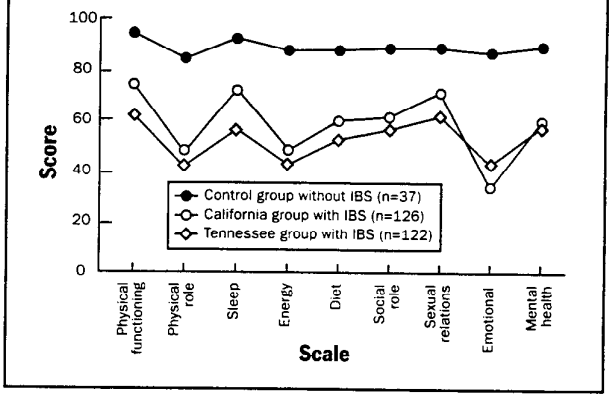


Figure 3. Mean scores on IBS QOL in 2 groups of patients with IBS and control subjects. Higher values denote better QOL. Adapted with permission from Hahn BA, et al. *Aliment Pharmacol Ther.* 1997;11:547-552.

Whitehead and colleagues used the SF-36™ to document QOL status in 3 groups of subjects in the US—patients with medically diagnosed IBS (n=83), patients with symptoms of IBS but who had not consulted a physician (n=165), and asymptomatic controls (n=122).[25] Mean QOL subscale scores are shown in Figure 4. On each subscale shown, QOL was significantly lower among patients with IBS as compared to controls.[25]

A comparison of QOL for patients with IBS with the QOL score of patients with other medical disorders demonstrates similar QOL decrements for IBS, clinical depression, and type 2 diabetes (Figure 5).[26]

FIGURE 4

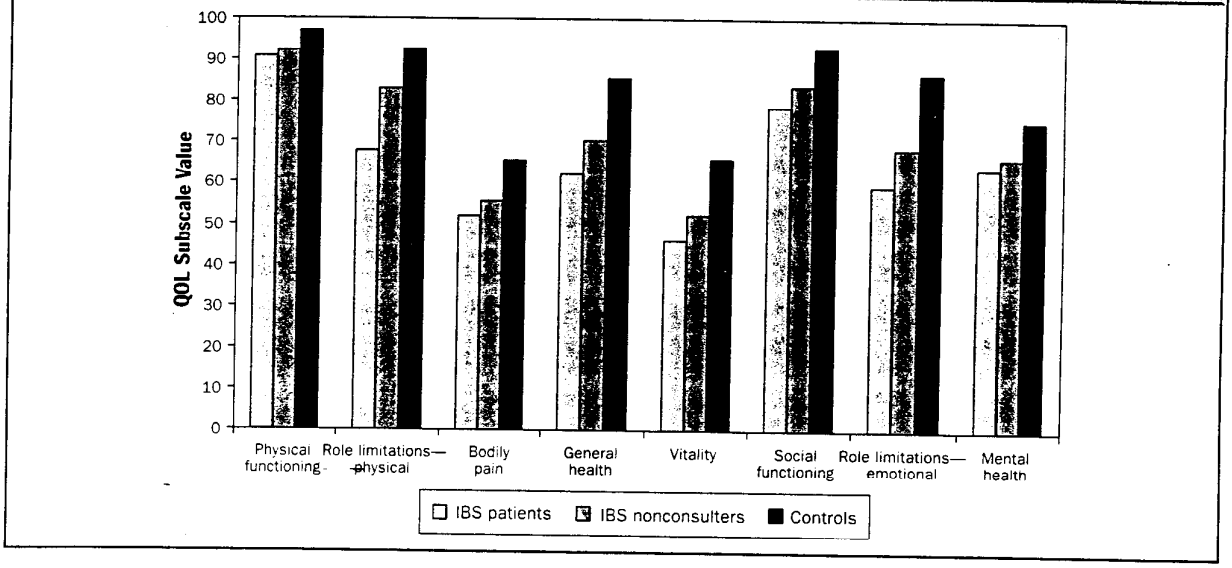


Figure 4. Comparison of mean SF-36™ QOL subscale scores. Higher values denote better QOL. Data from Whitehead WE, et al. *Dig Dis Sci.* 1996;41:2248-2253.

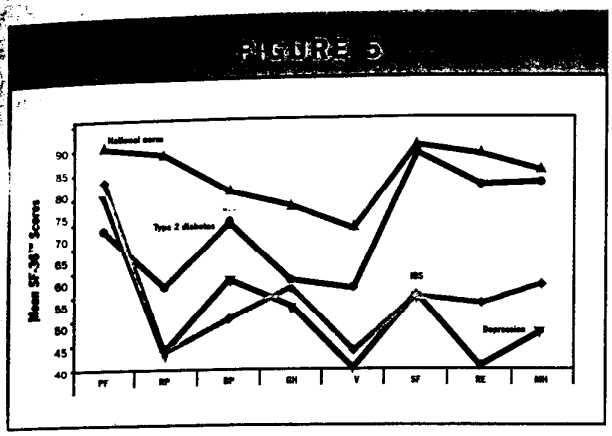


Figure 5. Comparison of QOL scores in patients with diagnosed IBS and patients with other medical conditions. Higher values denote better QOL. PF = physical functioning; RP = role limitations-physical; BP = bodily pain; GH = general health; V = vitality; SF = social functioning; RE = role limitations-emotional; MH = mental health. Adapted with permission from Wells NEJ, et al. *Aliment Pharmacol Ther.* 1997;11:1019-1030.

The functional impairments of IBS may also interfere with patients' careers. A recent postal survey of patients with IBS in the US found that 12% lost or quit a job because of their condition, and 16% turned down offers of promotion or advancement.[1]

Patients with IBS demonstrate reductions in QOL similar to those of patients with depression and type 2 diabetes

Productivity. Another important work-related manifestation of IBS is its impact on productivity. In a survey-based study comprising responses from a random sample of over 5000 US households, Drossman and coworkers documented that people with symptoms consistent with a diagnosis of IBS missed an average of 13.4 work days a year because of IBS symptoms.[15] This was in comparison with fewer than 5 absentee days for workers without symptoms of IBS. A higher proportion of those with IBS symptoms also reported currently being too sick to go to work or school (11.3% vs 4.2% of patients without symptoms).

In another postal survey of patients in the United States, nearly one-third of patients reported missing at least 1 day of work in the previous 4 weeks because of IBS. On average, patients lost nearly 2 days of work and cut back on their workdays 3 days a month because of their IBS.[1]

A 1999 US national survey of 1014 women with IBS found that on average, women with IBS reported being almost 2 times more likely than women without IBS to have missed workdays or schooldays in the past year as a result of illness. This telephone survey, conducted by a national public opinion research organization and funded by Glaxo Wellcome Inc., included more than 1000 women in the general public and over 700 healthcare professionals. It is the largest, most comprehensive national survey ever done on IBS.[27]

Economic Impact. The economic costs of IBS are substantial. Talley and associates reported that, in 1992, patients with IBS in Olmstead County, Minnesota, incurred median direct medical charges (excluding outpatient medications) of $742, which was $313 more than control subjects.[2] Extrapolation of these data to the entire Caucasian population of the United States would result in an estimated $8 billion annually in direct medical costs (excluding outpatient medications).[2]

It should be noted, however, that as staggering as this estimate is, it did not take into account a number of other direct costs associated with IBS, including prescription drug expenditures, or indirect costs such as lost wages.[2] Accordingly, it is likely an underestimate of the true economic cost of IBS in US patients.

People with IBS missed an average of 13.4 workdays a year

Physician and Patient Perspectives

From the standpoint of both the patient and the physician, IBS can be challenging. IBS symptoms can mimic those of other diseases, complicating the diagnosis.[28] The diagnosis is further complicated because symptoms can vary from person to person.[29] Because most medicines generally target 1 IBS symptom, patients often need more than 1 medication, making management more complicated.

In addition to these inherent diagnostic challenges, there is an education gap between patients with IBS and their doctors. The 1999 survey discussed previously revealed that 28% of patients surveyed did not believe that their doctors understood how much pain and discomfort they felt. When asked to rate abdominal pain or discomfort on a scale of 1 to 10, doctors rated the pain or discomfort from IBS for the average patient significantly lower than patients rated their own pain. However, 87% of all doctors acknowledged that physicians need to be better educated about IBS.[27]

Pathophysiology

While the cause of IBS is not known, there is evidence to suggest that a variety of factors may contribute to the symptoms experienced by patients. These include alterations in bowel motor activity, a reduced pain threshold or hypersensitivity of the viscera, and dysregulation of the enteric nervous system.[10,14] With regard to the modulation of the enteric nervous system, the roles of neurotransmitters such as serotonin (5-hydroxytryptamine) are of particular interest.

Bowel Motor Activity. Research suggests IBS is associated with abnormal motor patterns throughout the gut.[14] In particular, patients with IBS demonstrate quantitative differences in gut-motor reactivity and increased sensitivity to stimuli (such as distention) or spontaneous contractions.[10]

In qualitative terms, colonic motility patterns in patients with IBS are not markedly different from those in healthy controls. Transit time, however, is accelerated in some patients with diarrhea-predominant IBS and decelerated in some patients with constipation-predominant IBS.[10]

Visceral Hypersensitivity. While the colonic motor abnormalities of IBS may account for symptoms of diarrhea and constipation, they fail to explain the cardinal symptom of abdominal pain or discomfort experienced by many patients. Studies of visceral sensitivity have been conducted that draw an association between IBS pain and visceral hypersensitivity (hyperalgesia). Specifically, they have demonstrated a lower pain threshold in patients with IBS to balloon distention of the small bowel and colon as well as an increased sensitivity to normal fluctuations in intestinal function (e.g., spontaneous migrating motor complexes). In addition, increased somatic referral of visceral pain has also been reported.[10]

Symptoms may relate to bowel motor activity, a reduced pain threshold or hypersensitivity of the viscera, and dysregulation of the enteric autonomic nervous system, including those functions modulated by 5-hydroxytryptamine

Autonomic Dysregulation. The motor and sensory disruptions of the gut described above are believed to be modulated by the central nervous system (CNS) and the enteric nervous system.[10, 30] Neurotransmitters found in both the brain and gut that regulate motor and sensory activity include serotonin, enkephalins, substance P, and calcitonin.[10]

The underlying disease process of IBS may involve a dysregulation of the enteric nervous system (ENS). Unlike the other components of the peripheral nervous system, the enteric nervous system can perform its basic tasks without input from the brain or spinal cord. For this reason, it has been called a "second brain"—it contains more neurotransmitters and neuromodulators than any other part of the peripheral nervous system.[31]

Serotonin is a critical neurotransmitter in the enteric nervous system. Ninety-five percent of the body's serotonin is contained in the enterochromaffin cells of the gut.[31] Serotonin increases intestinal motility[31] and also has a direct effect on sensory neurons in the intestine.[32] Recent research suggests that, in IBS, exaggerated release of serotonin (and increased numbers of enterochromaffin cells) may cause both the hypersensitivity and the altered bowel habits that are commonly seen in this condition.[33,34]

Diagnosis

Based on recently published guidelines, a diagnosis of IBS can be made with reasonable certainty by means of a good patient history.[35]

Since the 1980s, progress has been made in developing specific symptom-based criteria to assist physicians in diagnosing IBS with more certainty than in the past. The 6 Manning criteria, introduced in 1978, identified the following symptoms as predictive of IBS: pain relieved by defecation; more frequent stools at the onset of pain; looser stools at the onset of pain; visible abdominal distention; passage of mucus; and sensation of incomplete evacuation.[3,6,36]

The Manning criteria were refined to develop even more precise guidelines when, in October 1986, the 13th International Congress of Gastroenterology established a "Working Team" of investigators to develop guidelines for the diagnosis of IBS for presentation in Rome in 1988. One of their objectives was to establish symptom-based criteria using a minimum of diagnostic studies.[35] The Rome Working Team defined IBS as a "group of functional bowel disorders."[18] The "Rome criteria" were revised in 1992 and again in 1999. The latest recommendations, the Rome II criteria, are a simplification of the original criteria for application to clinical practice.[18]

Rome II criteria for diagnosis of IBS

At least 12 weeks (not necessarily consecutive, in the previous 12 months) of abdominal discomfort or pain, having 2 of the following 3 features:

- **Relieved with defecation**
- **Onset associated with a change in stool frequency**
- **Onset associated with a change in stool form (appearance)**

Thompson WG, et al. *Gut.* 1999;45 (Suppl 2):1143-1147.

Symptoms other than pain that the Rome II working team considered to be supportive of a diagnosis of IBS include the following[18]:

- Abnormal stool frequency (≥3/day and <3/week)
- Abnormal stool form (lumpy/hard or loose/watery)

- Abnormal stool passage (feeling of incomplete evacuation)
- Passage of mucus
- Bloating or feeling of abdominal distention

The Rome criteria may not always be definitive. Ruling out red-flag symptoms such as weight loss, rectal bleeding, or anemia and ordering appropriate laboratory studies to confirm the absence of organic disease can assist in making a positive diagnosis of IBS or may suggest an alternative or coexisting diagnosis.[37]

Red-flag symptoms that may suggest a condition other than IBS include[37]:

- Anemia
- Fever
- Persistent diarrhea
- Rectal bleeding
- Severe constipation
- Weight loss
- Nocturnal symptoms
- Family history of GI cancer, inflammatory bowel disease, or celiac disease
- New onset of symptoms in patients <50 years old

Other Tests. A limited number of diagnostic tests may be appropriate to rule out other organic, structural, metabolic, or infectious etiologies of patients' symptoms. These may include hematology and blood-chemistry testing, erythrocyte sedimentation rate, examination of the stool for occult blood, parasites, or ova, imaging studies, and sigmoidoscopy.[6] Laboratory tests can be particularly useful when a patient presents with a red-flag symptom.

For patients <50 years of age who present with typical features of IBS, a CBC is recommended as part of the diagnostic procedure. For patients ≥50 years of age, a colonoscopy or air-contrast barium enema with sigmoidoscopy is recommended.[37]

A diagnosis of IBS can be made with reasonable certainty by means of a good patient history and attention to red-flag symptoms

Treatment

IBS treatment strategies have historically been oriented toward relief of individual symptoms rather than multiple symptoms of IBS. Classes of medications used to treat symptoms of the disorder include the following[14]:

- Bulk-producing agents
- Antispasmodic agents
- Antidiarrheal agents/opiates
- Prokinetic agents
- Antidepressants (tricyclics/SSRIs)
- Anxiolytics

These agents generally target only 1 symptom. IBS sufferers, therefore, may require more than 1 medication to treat multiple symptoms.[3,4] As will be described in the pages that follow, LOTRONEX is a novel treatment approach for women with diarrhea-predominant IBS. LOTRONEX relieves abdominal pain and discomfort, bowel urgency, and stool frequency.

LOTRONEX™ (alosetron HCl)

Description

LOTRONEX™ (alosetron HCl) is a potent and selective receptor 5-HT$_3$ antagonist discovered and developed by scientists and clinicians at GlaxoWellcome Inc. LOTRONEX is a breakthrough approach to treatment for women with diarrhea-predominant IBS. A neuroenteric modulator, LOTRONEX blocks 5-HT$_3$ receptors in the enteric nervous system. It is the first therapy shown in rigorous double-blind, placebo-controlled clinical trials to effectively treat the most troublesome symptoms of diarrhea-predominant IBS in women. In large-scale placebo-controlled studies, therapy with LOTRONEX was associated with relief of abdominal pain and discomfort, significantly reduced bowel urgency and stool frequency, and produced firmer stools in women with diarrhea-predominant IBS.

In two well-controlled, multicenter, 12-week trials, constipation was the most frequently reported adverse event, occurring in 28% of the patients treated with LOTRONEX compared with 5% on placebo.

LOTRONEX offers twice-daily oral dosing without regard to meals. In addition, there is no need for dosage adjustment in elderly patients or those with renal impairment (creatinine clearance 4 to 56 mL/min).

LOTRONEX is chemically 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. Its chemical structure is shown in Figure 6 below.

FIGURE 6

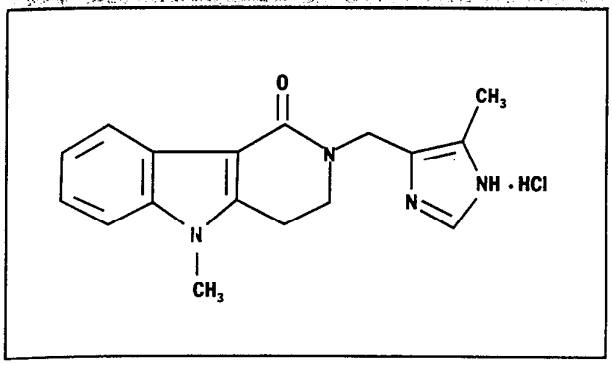


Figure 6. Chemical structure of LOTRONEX.

Pharmacology

Mechanism of Action. LOTRONEX is a potent and selective receptor 5-HT$_3$ antagonist.

5-HT$_3$ receptors are extensively distributed on enteric neurons in the human GI tract as well as other peripheral and central locations. Activation of these receptors is thought to lead to perceptions of visceral pain and to increased intestinal motor and secretory activity.[38] Alosetron HCl, a neuroenteric modulator, inhibits this activation. It has been postulated that neuroenteric modulation through receptor 5-HT$_3$ blockade may reduce the hypersensitivity and exaggerated intestinal motor responses associated with IBS.

Although the site and mechanism of action of alosetron have not been fully established, both preclinical and clinical trials demonstrate a pharmacologic basis for the clinical utility of LOTRONEX in the treatment of women with diarrhea-predominant IBS.

Preclinical Pharmacology Studies. In animal models, colorectal distention has been shown to produce measurable signs of acute visceral pain response,[39] and alosetron has been shown to inhibit the visceral pain response to rectal distention.[40] In addition, alosetron was shown to normalize experimentally induced intestinal hypermotility.[41]

Clinical Pharmacology Studies. 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-dependent 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 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.

5-HT$_3$ receptors are extensively distributed on enteric neurons in the human GI tract as well as other peripheral and central locations.

LOTRONEX™ (alosetron HCl) decreases colonic transit, increases colonic compliance, and increases fluid and electrolyte absorption

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 HCl is rapidly absorbed following oral administration, with peak plasma concentrations occurring approximately 1 hour after ingestion. The drug is incompletely absorbed, however, having an absolute availability of approximately 50% to 60%. Alosetron absorption is decreased 25% by coadministration with food, with a mean delay in time to peak concentration of 15 minutes. This effect is not considered to be clinically significant.

Distribution. The volume of distribution of alosetron HCl ranges from only approximately 65 L 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 patients with IBS confirmed that alosetron clearance is minimally influenced by doses up to 8 mg.

LOTRONEX can be taken with or without food

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 monocar-

bonyl 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 P_{450} (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. Studies in various subgroups of renally impaired subjects have indicated that alosetron HCl concentrations are not significantly affected by impaired renal function. Accordingly, dosage adjustments are not necessary in patients with renal impairment (creatinine clearance of 4 to 56 mL/min). In some studies in healthy male or female volunteers, plasma concentrations were elevated by approximately 40% in individuals 65 years of age and older compared with young adults. Plasma concentrations are 30% to 50% lower and less variable in men compared to women given the same oral dose. Population pharmacokinetic analysis in patients with IBS confirmed that alosetron concentrations were influenced by gender (27% lower in men). No studies have been conducted in patients with impaired hepatic function.

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

Pharmacokinetic studies demonstrate no effect on the metabolism of levonorgestrel/ethinyl estradiol, cisapride, haloperidol, or theophylline

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 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 P_{450} (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.

Levonorgestrel/ethinyl estradiol (oral contraceptive). The effect of concomitant administration of LOTRONEX™ (alosetron HCl) and a typical monophasic oral contraceptive (levonorgestrel/ethinyl estradiol) was studied in an open trial in healthy female subjects. Plasma concentrations of levonorgestrel and of ethinyl estradiol were not significantly affected.

Cisapride. A randomized, placebo-controlled, double-blind study was conducted of the combination of LOTRONEX and cisapride—a CYP3A4 substrate that has been associated with prolonged QT intervals and ventricular arrhythmias. Twelve healthy volunteers received cisapride 20 mg 4 times daily plus LOTRONEX 1 mg twice daily or placebo twice daily in crossover fashion. There were no significant alterations in cisapride pharmacokinetics or in QT intervals associated with concurrent administration of LOTRONEX.

Haloperidol. In a randomized, placebo-controlled trial, patients undergoing haloperidol therapy received concomitant LOTRONEX (1 mg daily) for 2 weeks. Serial blood samples assayed by high-performance liquid chromatography demonstrated no pharmacokinetic interactions.[38]

Theophylline. In a randomized, double-blind trial with a crossover design, healthy subjects received (alone and in combination for periods of 16 days) LOTRONEX 1 mg twice daily and theophylline 200 mg twice daily. No clinically significant alterations in theophylline were observed with combination therapy.

Efficacy

Clinical Trials

Two 12-week treatment, multicenter, double-blind, placebo-controlled, dose-ranging studies were conducted to determine the dosage of oral LOTRONEX™ (alosetron HCl) 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 clinical efficacy of LOTRONEX was further evaluated in 2 well-controlled studies involving a total of 1273 nonconstipated women with IBS. For purposes of this discussion, these studies will be designated as Study 1 and Study 2.

Female nonconstipated patients with IBS (18 years or older) were enrolled in these studies based on meeting the Rome I criteria for at least 6 months[38]:

- Abdominal pain or discomfort that was relieved with defecation and/or associated with a change in stool frequency and/or consistency

-AND-

- 2 or more of the following at least a quarter of occasions or days (protocol defined as at least 2 days per week)

- Altered stool frequency (defined as >3 bowel movements daily or <3 bowel movements weekly)

- Altered stool form (lumpy/hard or loose/watery)

- Altered stool passage (straining, urgency, or feeling of incomplete evacuation), passage of mucus, and/or bloating or feeling of abdominal distention.

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 2-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 whom diarrhea was a prominent feature of an

alternating pattern. Women with a history of severe constipation were excluded. Men were not studied.

The clinical effectiveness of LOTRONEX has been evaluated in 2 well-controlled studies involving a total of 1273 nonconstipated women with IBS

Design. Each was a randomized, double-blind, placebo-controlled, parallel-group trial, and was conducted in the United States.[38] The common design of the 2 studies is illustrated in Figure 7.[38]

FIGURE 7

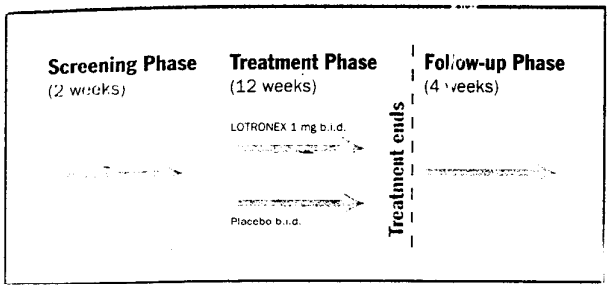


Figure 7. Study 1 and Study 2 design.

During the screening, treatment, and follow-up periods, symptom data were captured daily via an electronic, touch-tone telephone based system.

Efficacy Measures. The primary measure of efficacy in Study 1 and Study 2 was adequate relief of IBS pain and discomfort, as assessed by study subjects. On a weekly basis during the treatment phase, patients responded either *"yes"* or *"no"* to the question, "In the past 7 days, have you had adequate relief of your irritable bowel syndrome pain and discomfort?"[38]

Secondary Efficacy Measures. Key secondary measures of efficacy in these studies included percentage of days with urgency and daily assessment of stool frequency and stool consistency.[38]

Most Bothersome Symptoms of IBS: The Patient's Viewpoint. Hallmark symptoms of IBS include chronic recurring abdominal pain or discomfort, altered bowel function, urgency, feelings of bloating, and the passage of mucus. During the clinical development program for LOTRONEX, 2 surveys were conducted among nonconstipated patients with IBS to assess which of the various IBS symptoms they considered most bothersome.[38] On random days about 2 months apart, patients were asked the following question and could choose one answer:

When your Irritable Bowel Syndrome is active, which of the following symptoms bothers you the most?

- *Abdominal pain*
- *Urgency*
- *Bloating*
- *Mucus*
- *Number of bowel movements*

Results, which were captured electronically, are shown below (Figures 8 and 9). In each survey, the majority of patients rated abdominal pain as their most bothersome symptom, followed by urgency and stool frequency.[38]

FIGURE 8

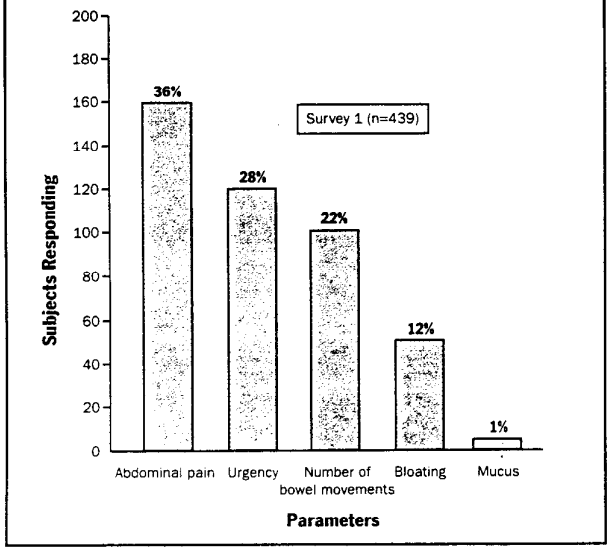


Figure 8. Most bothersome symptoms of IBS: Survey 1.

FIGURE 9

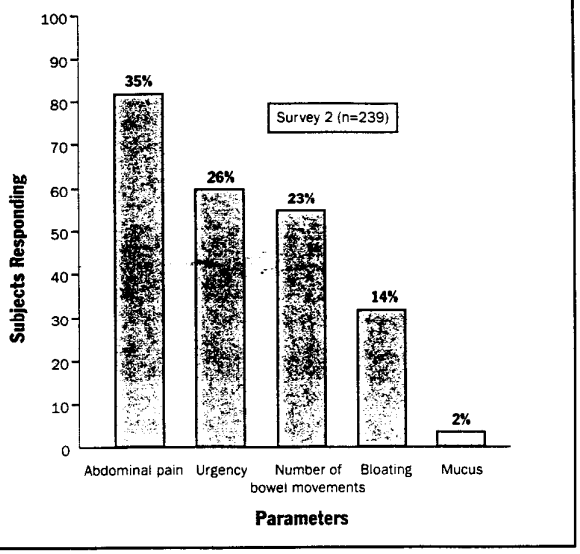


Figure 9. Most bothersome symptoms of IBS: Survey 2.

Patient Characteristics. A total of 1273 nonconstipated female patients with IBS were randomized to treatment in these 2 studies.[38] Demographics and baseline characteristics are provided in Table 1. Baseline demographic characteristics were similar between groups. The median age of the study population was 46 years (age

TABLE 1. PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS FOR PIVOTAL EFFICACY STUDIES (INTENT-TO-TREAT [ITT] POPULATION)

	Study 1		Study 2	
	Placebo	LOTRONEX 1 mg b.i.d.	Placebo	LOTRONEX 1 mg b.i.d.
Subjects randomized	323	324	317	309
Gender (%)				
Female	100	100	100	100
IBS subtype [n (%)]				
Diarrhea-predominant	221 (68)	237 (73)	222 (70)	224 (73)
Alternating	95 (29)	85 (26)	87 (27)	82 (27)
Constipation-predominant	7 (2)	2 (<1)	8 (3)	3 (<1)
Subjects completing [n(%)]	270 (84)	245 (76)	246 (78)	237 (77)
Median age (yr)	45	46	45	46

Data on file, Glaxo Wellcome Inc.

Please consult accompanying complete Prescribing Information.

ranged from 18 to 83 years), and 90% of subjects were Caucasian.

The efficacy of LOTRONEX™ (alosetron HCl) beyond 12 weeks has not been established

Study 1

Results. In Study 1, the positive effect of LOTRONEX on IBS pain and discomfort was seen only in diarrhea-predominant patients.

When viewed on a weekly basis, significantly more patients reported relief of IBS abdominal pain and discomfort within 1 week of starting therapy with LOTRONEX than with placebo ($P<0.05$) (Figure 10). The significant difference between groups was maintained throughout the 12-week treatment period, but symptoms returned after active treatment was stopped.

FIGURE 10

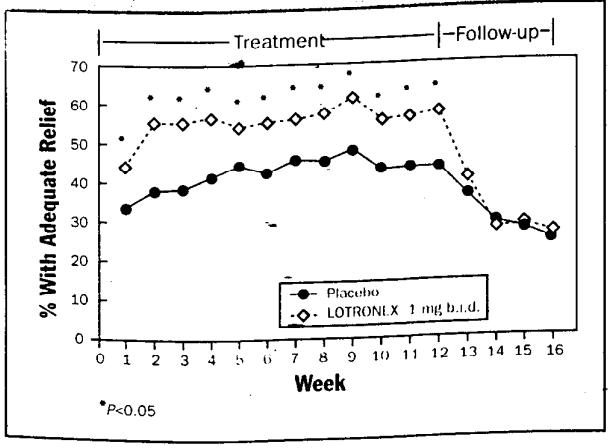


Figure 10. Percentage of patients in Study 1 by treatment group reporting adequate relief of IBS pain and discomfort (subjects with diarrhea-predominant IBS).

Secondary Efficacy Measures. Figures 11A-11C illustrate the weekly data for secondary efficacy measures in women with diarrhea-predominant IBS. Beginning in the first week of treatment, therapy with LOTRONEX was associated with significantly fewer days with urgency, significantly firmer stools, and a significant decrease in frequency of defecation compared with placebo ($P<0.05$). IBS symptoms returned upon discontinuation of LOTRONEX.

In Studies 1 and 2, relief of pain and discomfort was achieved within 1 week and 4 weeks, respectively, and continued throughout treatment

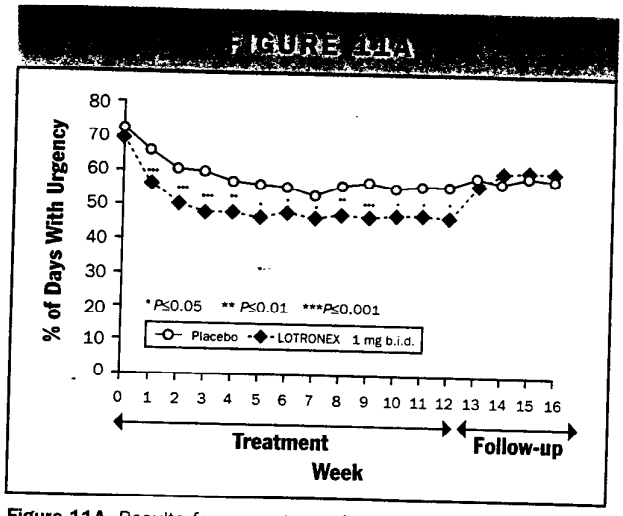


Figure 11A. Results for percentage of days with urgency in Study 1 among patients with diarrhea-predominant IBS.

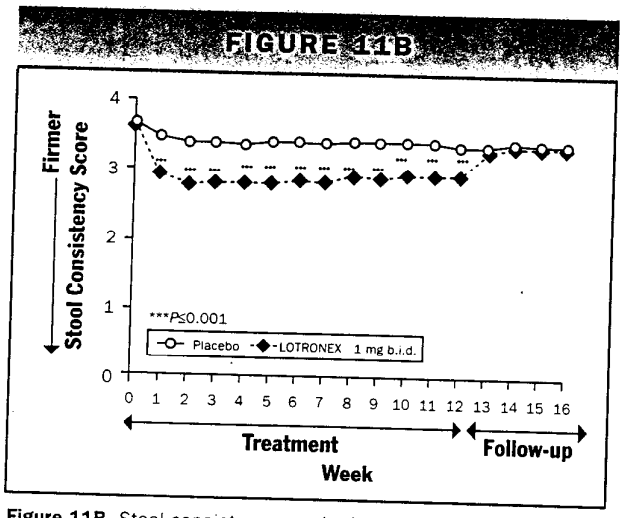


Figure 11B. Stool consistency results in Study 1 among patients with diarrhea-predominant IBS.

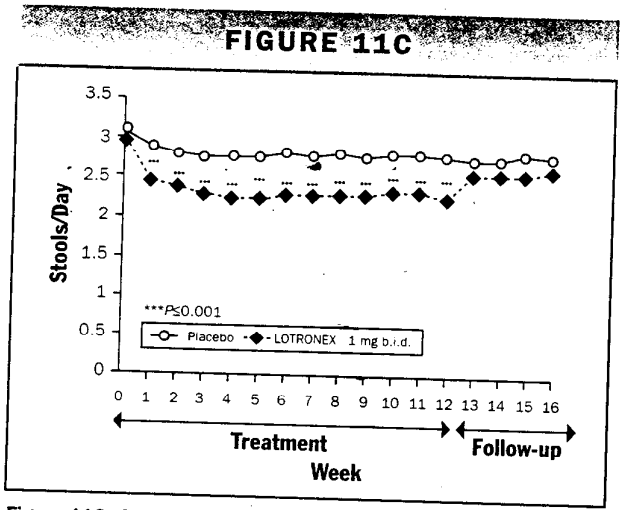


Figure 11C. Stool frequency results in Study 1 among patients with diarrhea-predominant IBS.

Summary of Study 1. In this well-controlled multicenter, double-blind, placebo-controlled study, LOTRONEX™ (alosetron HCl) 1 mg twice daily was significantly more effective than placebo in providing relief of IBS pain and discomfort in women with diarrhea-predominant IBS. This relief was significant within 1 week of initiation of treatment and was maintained throughout the treatment period. In addition to relieving IBS pain and discomfort, LOTRONEX was associated with significant improvements in other symptoms of IBS, resulting in fewer days with urgency, firmer stool consistency, and fewer stools per day. Within 1 week after discontinuing therapy, there was no difference between placebo- and alosetron-treated patients for any of these symptoms.

Study 2

Results. In this study, significantly more women with diarrhea-predominant IBS responded to therapy with

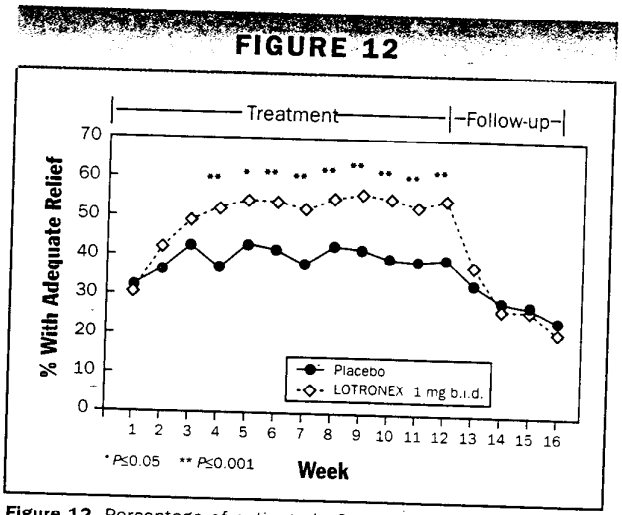


Figure 12. Percentage of patients in Study 2 by treatment group reporting adequate relief of IBS pain and discomfort (subjects with diarrhea-predominant IBS).

LOTRONEX was associated with significant improvement in other symptoms of IBS, resulting in fewer days with urgency, firmer stool consistency, and fewer stools per day within 1 week

LOTRONEX and achieved relief of abdominal pain and discomfort within 4 weeks.

Weekly results, shown in Figure 12, demonstrate a greater percentage of patients treated with LOTRONEX than patients in the placebo group reporting relief of IBS pain and discomfort. This difference between groups attained statistical significance ($P<0.001$) by Week 4, and the significant benefit persisted until LOTRONEX was discontinued. As in the case of the previously discussed study, symptoms returned upon discontinuation of LOTRONEX.

Secondary Efficacy Measures. Figures 13A-13C illustrate the weekly data for secondary measures in women with diarrhea-predominant IBS. Beginning in the first week of therapy, LOTRONEX was associated with significantly fewer days with urgency and significantly firmer stools compared with placebo ($P<0.001$).

Summary. In this double-blind, placebo-controlled, multicenter study, therapy with LOTRONEX significantly relieved abdominal pain and discomfort in women with diarrhea-

FIGURE 13A

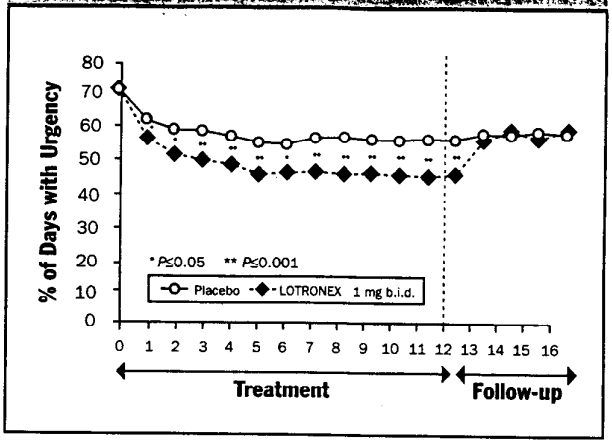


Figure 13A. Results for percentage of days with urgency in Study 2 among patients with diarrhea-predominant IBS.

FIGURE 13B

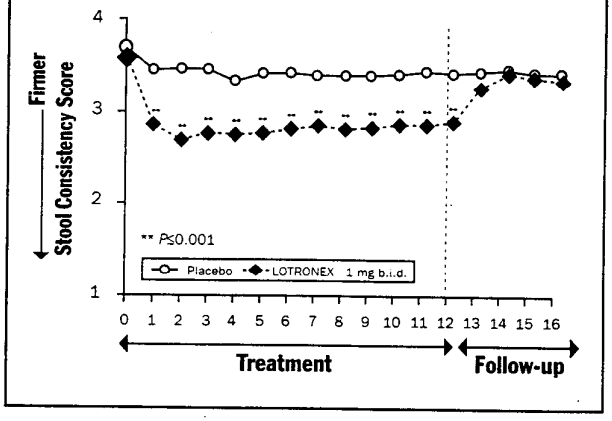


Figure 13B. Stool consistency results in Study 2 among patients with diarrhea-predominant IBS.

FIGURE 13C

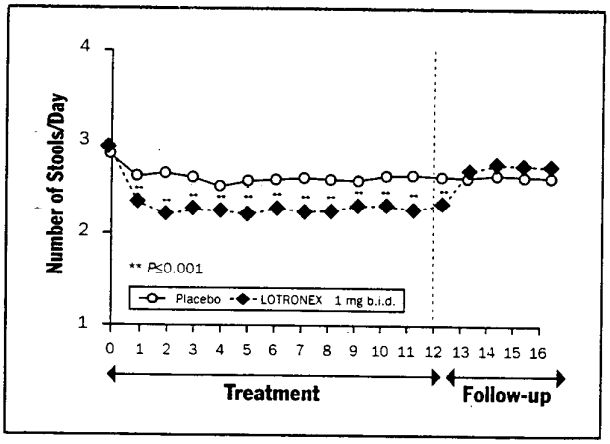


Figure 13C. Stool frequency results in Study 2 among patients with diarrhea-predominant IBS.

predominant IBS. The onset of relief of IBS pain and discomfort occurred within 4 weeks of initiation of treatment, and relief persisted for the duration of therapy. Other benefits observed in this study were significant reductions in urgency, stool consistency, and stool frequency seen within the first week. The benefits of LOTRONEX™ (alosetron HCl) diminished 1 week after treatment was stopped.

Summary: Study 1 and 2

The magnitude and comparability of results from these 2 rigorous clinical trials clearly demonstrate that LOTRONEX, at a dosage of 1 mg twice daily, effectively relieves IBS pain and discomfort, reduces urgency, and improves stool consistency and stool frequency in women with diarrhea-predominant IBS. The onset of effect was seen within 1 to 4 weeks, persisted throughout treatment, and diminished within 1 week of discontinuing therapy. Efficacy beyond 12 weeks has not been established.

Safety Information

Indications and Contraindications

Indications. 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 (0.1% to 1%) 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 patients with IBS 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. Patients who experience constipation while receiving LOTRONEX may be considered for management with usual care including laxatives, fiber, or a brief interruption of therapy (see DOSAGE AND ADMINISTRATION).

Precautions

Information for Patients. A patient leaflet appears at the end of the complete Prescribing Information for LOTRONEX. Healthcare professionals are encouraged to provide this patient information whenever they dispense prescriptions or provide samples to patients.

Drug Interactions. See previous section on page 15.

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 b.i.d.) 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 or general 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™ (alosetron HCl) 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 profiles of LOTRONEX were 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.

Adverse Events

In Study 1 and Study 2 (described previously), 632 women were treated with LOTRONEX, 1 mg twice daily, for up to 12 weeks. LOTRONEX in these studies was generally well tolerated. (See Table 2.)

One exception was constipation, which occurred at a higher rate in patients treated with LOTRONEX (28%) than in placebo-treated patients (5%). Constipation is an expected pharmacologic effect of the 5-HT_3 receptor antagonist class due to a slowing of colonic motility. 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 female IBS patients (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.

Laboratory Evaluations. In patients treated with LOTRONEX for up to 12 months, there have been no meaningful differences compared with placebo in the frequency of laboratory abnormalities.

Similar pattern and frequency of adverse events in 12-week and 12-month studies in women with IBS

Summary

LOTRONEX™ (alosetron HCl) 1 mg twice daily has a favorable safety profile in women with diarrhea-predominant IBS. Constipation is a frequent and dose-related side effect of treatment. LOTRONEX should not be used in IBS patients who are currently constipated or whose predominant bowel symptom is constipation. Individual patients who experience constipation while taking LOTRONEX may need to interrupt treatment. Acute ischemic colitis was reported infrequently (0.1% to 1%) in patients receiving LOTRONEX in 3-month clinical trials. 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 sudden worsening of abdominal pain. These patients should be promptly evaluated with appropriate diagnostic testing. No significant differences in CNS adverse event frequencies (dizziness, sleep or depressive disorders, visual disturbances) compared to placebo have been reported. LOTRONEX was generally well-tolerated compared with placebo. Safety and efficacy in men have not been established.

No significant differences in CNS adverse event frequencies versus placebo

Please consult accompanying complete Prescribing Information.

TABLE 2: TREATMENT-EMERGENT ADVERSE EVENTS IN STUDY 1 AND STUDY 2 OCCURRING IN AT LEAST 2% OF PATIENTS TREATED WITH LOTRONEX, AND OCCURRING MORE FREQUENTLY WITH LOTRONEX 1 mg b.i.d. THAN WITH PLACEBO (%)

Adverse Event	LOTRONEX (n=632)	Placebo (n=637)
Any Adverse Event	74[38]	66[38]
Gastrointestinal		
Constipation	28*	5
Nausea	7	6
GI discomfort and pain	5	4
Abdominal discomfort and pain	5	3
GI gaseous symptoms	3	2
Viral GI infections	3	2
Dyspeptic symptoms	3	1
Abdominal distention	2	<1
Hemorrhoids	2	<1
Ear, Nose, and Throat		
Allergic rhinitis	2	<1
Tonsil and throat discomfort and pain	1	<1
Bacterial ear, nose, and throat infections	1	<1
Neurology		
Sleep disorders	3	2
Cardiovascular		
Hypertension	2	<1
Psychiatry		
Depressive disorders	2	1

*$P<0.0001$.

Dosage and Administration

Dosage and Administration

Usual Dose in Adults. The recommended adult dosage of LOTRONEX™ (alosetron HCl) is 1 tablet (1 mg) taken orally twice daily with or without food. Individual patients who experience constipation may need to interrupt treatment.

The effectiveness of LOTRONEX in females with diarrhea predominant IBS (18 years of age and older) was demonstrated in 2 placebo-controlled studies in which 1 mg was given twice daily for 12 weeks. Safety and efficacy in males have not been established.

Pediatric Patients. No studies have been conducted in patients less than 18 years of age.

Geriatric Patients. No dosage adjustment is recommended for elderly patients (65 years of age or older).

Patients With Renal Impairment. No dosage adjustment is recommended for patients with renal impairment (creatinine clearance 4 to 56 mL/min).

Patients With Hepatic Impairment. No studies have been conducted in patients with hepatic impairment.

How Supplied

LOTRONEX is supplied as blue, oval, film-coated tablets engraved with GXCT1 on one face, containing alosetron HCl equivalent to 1 mg alosetron HCl.

The recommended adult dosage of LOTRONEX is a single, 1-mg tablet taken orally twice daily

Conclusions

LOTRONEX is a potent and selective 5-HT_3 receptor antagonist indicated for the treatment of Irritable Bowel Syndrome (IBS) in women whose predominant bowel symptom is diarrhea. LOTRONEX is a novel treatment approach for women with diarrhea-predominant IBS—a chronic, recurrent, and challenging medical condition which has a large impact on the US population. Safety and effectiveness of LOTRONEX in men have not been established.

Clinical trials have demonstrated that LOTRONEX has a favorable safety profile and is generally well tolerated. The most common adverse event was constipation (28% vs 5% with placebo). LOTRONEX should not be used in IBS patients who are currently constipated or whose predominant bowel symptom is constipation. Patients who experience constipation while receiving LOTRONEX may be considered for management with usual care, including fiber, laxatives, or a brief interruption of therapy. Acute ischemic colitis was reported infrequently (0.1% to 1%) in patients receiving LOTRONEX in 3-month clinical trials. LOTRONEX should be discontinued in patients experiencing rectal bleeding and sudden worsening of abdominal pain.

LOTRONEX is the first medication proven in large-scale clinical trials to relieve multiple symptoms of IBS, including abdominal pain and discomfort, bowel urgency, and stool frequency. Women with diarrhea-predominant IBS experienced relief of urgency and frequency within 1 week and relief of pain and discomfort within 1 to 4 weeks. Once achieved, relief continued throughout the treatment period.

Proven multisymptom relief in women with diarrhea-predominant IBS

References

1. Hähn BA, Yan S, Strassels S. Impact of irritable bowel syndrome on quality of life and resource use in the United States and United Kingdom. *Digestion.* 1999;60:77-81.
2. Talley NJ, Gabriel SE, Harmsen WS, Zinsmeister AR, Evans RW. Medical costs in community subjects with irritable bowel syndrome. *Gastroenterology.* 1995;109:1736-1741.
3. Drossman DA. Review article: an integrated approach to the irritable bowel syndrome. *Aliment Pharmacol Ther.* 1999;13(Suppl 2):3-14.
4. Maxwell PR, Mendall MA, Kumar D. Irritable bowel syndrome. *Lancet.* 1997;350:1691-1695.
5. Talley NJ, Zinsmeister AR, Melton LJ III. Irritable bowel syndrome in a community: symptom subgroups, risk factors, and health care utilization. *Am J Epidemiol.* 1995;142:76-83.
6. Camilleri M, Choi M-G. Review article: irritable bowel syndrome. *Aliment Pharmacol Ther.* 1997;11:3-15.
7. Sandler RS. Epidemiology of irritable bowel syndrome in the United States. *Gastroenterology.* 1990;99:409-415.
8. American Heart Association. 1999 Heart and Stroke Statistical Update. Available at: http://www.americanheart.org/statistics/03cardio.html. Accessed on 11/1/99.
9. Census Bureau. *Statistical Abstract of the United States: 1998.* September 25th, 1998.
10. Drossman DA, Whitehead WE, Camilleri M. Irritable bowel syndrome: a technical review for practice guideline development. *Gastroenterology.* 1997;112:2120-2137.
11. Gralnek IM. Health care utilization and economic issues in irritable bowel syndrome. *Eur J Surg Suppl.* 1998;583:73-76.
12. Everhart JE, Renault PF. Irritable bowel syndrome in office-based practice in the United States. *Gastroenterology.* 1991;100:998-1005.
13. Scott-Levin Physician Drug and Diagnosis Audit (PDDA), MAT April 1999.
14. Hasler WL, Owyang C. Irritable bowel syndrome. In: Yamada T, Alpers DH, Owyang C, et al, eds. *Textbook of Gastroenterology.* 2nd ed. Philadelphia, PA: JB Lippincott Co; 1995:1832-1853.
15. Drossman DA, Li Z, Andruzzi E, et al. U.S. householder survey of functional gastrointestinal disorders: prevalence, sociodemography, and health impact. *Dig Dis Sci.* 1993;38:1569-1580.
16. Hahn B, Watson M, Yan S, Gunput D, Heuijerjans J. Irritable bowel syndrome symptom patterns: frequency, duration, and severity. *Dig Dis Sci.* 1998;43:2715-2718.
17. American Gastroenterological Association. AGA Medical Position Statement: Irritable bowel syndrome. *Gastroenterology.* 1997;112:2118-2119.
18. Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Müller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut.* 1999;45 (Suppl 2):1143-1147.
19. Francis CY, Whorwell PJ. The irritable bowel syndrome. *Postgrad Med J.* 1997;73:1-7.
20. Moore J, Barlow D, Jewell D, Kennedy S. Do gastrointestinal symptoms vary with the menstrual cycle? *Br J Obstet Gynaecol.* 1998;105(12):1322-1325.
21. Barton A, Pal B, Whorwell PJ, Marshall D. Increased prevalence of sicca complex and fibromyalgia in patients with irritable bowel syndrome. *Am J Gastroenterol.* 1999;94:1898-1901.
22. Corney RH, Stanton R. Physical symptom severity, psychological and social dysfunction in a series of outpatients with irritable bowel syndrome. *J Psychosomatic Research.* 1990;34:483-491.
23. Mayer EA, Fass R, Fullerton S. Intestinal and extraintestinal symptoms in functional gastrointestinal disorders. *Eur J Surg* Suppl. 1998;583:29-31.
24. Hahn BA, Kirchdoerfer LJ, Fullerton S, Mayer E. Evaluation of a new quality of life questionnaire for patients with irritable bowel syndrome. *Aliment Pharmacol Ther.* 1997;11:547-552.
25. Whitehead WE, Burnett CK, Cook EW III, Taub E. Impact of irritable bowel syndrome on quality of life. *Dig Dis Sci.* 1996;41:2248-2253.
26. Wells NEJ, Hahn BA; Whorwell PJ. Clinical economics review: irritable bowel syndrome. *Aliment Pharmacol Ther.* 1997 Dec;11(6):1019-1030.

27. *Irritable Bowel Syndrome in American Women: A Landmark Survey.* 1999. Performed by Schulman, Ronca, and Bucuvalas, Inc. 1-44.

28. Talley NJ, Phillips SF, Bruce B, Zinsmeister AR, Wiltgen C, Melton LJ. Multisystem complaints in patients with the irritable bowel syndrome and functional dyspepsia. *Eur J Gastroenterol Hepatol.* 1991;3:71-77.

29. Thompson WG, Heaton KW. Functional bowel disorders in apparently healthy people. *Gastroenterology.* 1980;79:283-288.

30. Dalton CB, Drossman DA. Diagnosis and treatment of irritable bowel syndrome. *Am Fam Physician.* 1997;55:875-880.

31. Gershon MD. The enteric nervous system: a second brain. *Hosp Pract.* 1999;34(7):31-52.

32. Bueno L. Fioramonti J, Delvaux M, Frexinos J. Mediators and pharmacology of visceral sensitivity: from basic to clinical investigations. *Gastroenterology.* 1997;112:1714-1743.

33. Ahonen A, Kyosola K, Penttila O. Enterochromaffin cells in macrophages in ulcerative colitis and irritable colon. *Ann Clin Res.* 1976 Feb;8(1):1-7.

34. Bearcroft CP, Perrett D, Farthing MJG. Postprandial plasma 5-hydroxytryptamine in diarrhoea predominant irritable bowel syndrome: a pilot study. *Gut.* 1998;42:42-46.

35. Thompson WG, Dotevall G, Drossman DA, Heaton KW, Kruis W. Irritable bowel syndrome: guidelines for the diagnosis. *Gastroenterology Int.* 1989;2: 92-95.

36. Manning AP, Thompson WG, Heaton KW, Morris AF. Towards positive diagnosis of the irritable bowel. *BMJ.* 1978;2(6138):653-654.

37. Paterson WG, Thompson WG, Vanner SJ, et al. Recommendations for the management of irritable bowel syndrome in family practice. *Can Med Assoc J.* 1999;161: 154-160.

38. Data on file, Glaxo Wellcome Inc.

39. Gershon MD. Review article: roles played by 5-hydroxytryptamine in the physiology of the bowel. *Aliment Pharmacol Ther.* 1999;13 (Suppl 2):15-30.

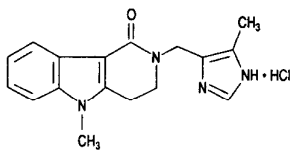
40. Ness TJ, Gebhart GF. Colorectal distension as a noxious visceral stimulus: physiologic and pharmacologic characterization of pseudaffective reflexes in the rat. *Brain Res.* 1988;450: 153-169.

41. Kozlowski CM, Green A, Grundy D, Boissonade FM, Bountra C. The 5-HT_3 receptor antagonist alosetron inhibits the colorectal distension-induced depressor response and spinal c-fos expression in the anaesthetised rat. *Gut.* 2000; 46:474-480.

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 5-HT3 receptors.

In healthy volunteers and IBS patients, alosetron (2 mg orally, twice daily for 8 days) increased colonic transit time without affecting orocecal transit time. In healthy volunteers, alosetron also increased basal jejunal water and sodium absorption after a single 4-mg dose. In IBS patients, multiple oral doses of alosetron (4 mg twice daily for 6.5 days) significantly increased colonic compliance.

Single oral doses of alosetron administered to healthy men produced a dose-dependent reduction in the flare response seen after intradermal injection of serotonin. Urinary 6-ß-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-ß-hydroxycortisol excretion. However, there was no change in the ratio of 6-ß-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). 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

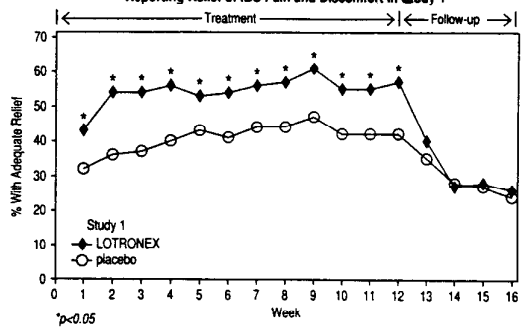
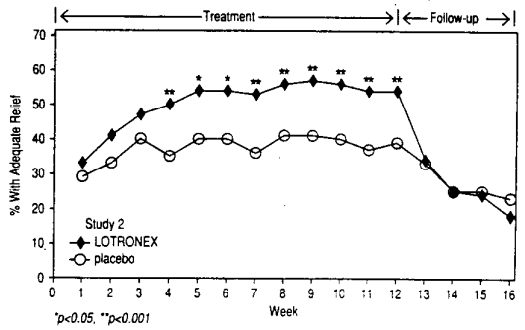


Figure 2: Percentage of Women (Diarrhea-Predominant) Reporting Relief of IBS Pain and Discomfort in Study 2



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$^{+/-}$) 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

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 of 60 tablets (NDC 0173-0690-00).

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

APPENDIX:

Diagnostic Criteria: Irritable Bowel Syndrome (IBS)*
At least three months continuous or recurrent symptoms of:
1. abdominal pain or discomfort which is: (a) relieved with defecation, (b) and/or associated with a change in frequency of stool, (c) and/or associated with a change in consistency of stool;
and
2. two or more of the following, at least a quarter of occasions or days: (a) altered stool frequency, (b) altered stool form (lumpy/hard or loose/watery stool), (c) altered stool passage (straining, urgency, or feeling of incomplete evacuation), (d) passage of mucus, (e) bloating or feeling of abdominal distention.

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

GlaxoWellcome

Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

US Patent No. 5,360,800

February 2000 RL-795

Information for the Patient

LOTRONEX™ (alosetron hydrochloride) Tablets

Read this information carefully before you start taking LOTRONEX (pronounced LOW-trah-nex) Tablets. Read the information included with LOTRONEX each time you refill your prescription, in case something has changed. This information does not take the place of discussions with your doctor.

What is LOTRONEX?

LOTRONEX is a prescription medicine used to treat irritable bowel syndrome (IBS) in women who have diarrhea as their main symptom. LOTRONEX has not been shown to work in men with IBS. IBS has been called by many names including irritable colon and spastic colon. IBS is a medical condition causing cramping abdominal pain, abdominal discomfort, urgency (a sudden need to have a bowel movement), and irregular bowel habits such as diarrhea or constipation.

It is not clear why some people develop IBS. It may be caused by your body's overreaction to a body chemical called serotonin. This overreaction may cause your intestinal system to be overactive. LOTRONEX works by blocking the action of serotonin on the intestinal system. This reduces the cramping abdominal pain, abdominal discomfort, urgency, and diarrhea caused by IBS.

LOTRONEX may not work for every patient who takes it. For women who are helped by LOTRONEX, the medicine works faster in some and slower in others. Some women taking LOTRONEX will have relief from their IBS pain and discomfort within the first week of use. Other women have relief of abdominal pain and discomfort within four weeks of starting LOTRONEX. Within one week, urgency and diarrhea occur less often for some patients. When you stop taking LOTRONEX, IBS symptoms will likely return within one week.

Who should not take LOTRONEX?

You should not start taking LOTRONEX when you are constipated or constipated most of the time.

Do not take LOTRONEX if you are allergic to LOTRONEX or any of its ingredients. The active ingredient in LOTRONEX is alosetron hydrochloride. The inactive ingredients are listed at the end of this leaflet.

LOTRONEX may not be right for you. Tell your doctor if you are:

- constipated most of the time.
- pregnant or plan to become pregnant.
- breast feeding.
- taking or planning to take any other medicines, including those you can get without a prescription.

How should LOTRONEX be taken?

Take LOTRONEX exactly as your doctor prescribes it. You can take LOTRONEX with or without food. If you miss a dose of LOTRONEX, do not double the next dose. Instead, simply go to the next regularly scheduled dosing time and take your normal prescribed dose of LOTRONEX.

What are the possible side effects of LOTRONEX?

If you have a sudden worsening of abdominal pain or if you see blood in your stool (bowel movement), call your doctor right away. These symptoms may be a sign of a serious medical condition.

Constipation is a common side effect of treatment with LOTRONEX. If you become constipated while taking LOTRONEX, call your doctor. Your doctor may tell you to stop taking LOTRONEX or suggest other ways to manage your constipation.

This description of side effects is not complete. Your doctor or pharmacist can give you a more complete list of side effects with LOTRONEX. Talk to your doctor right away about any side effects you have.

Medicines are sometimes prescribed for purposes not listed in patient information leaflets. Do not use LOTRONEX for a condition for which it was not prescribed. Do not share LOTRONEX with other people. As with any medicine, LOTRONEX may be harmful without appropriate medical supervision.

If you have questions about LOTRONEX, ask your doctor or pharmacist. They can show you detailed information about LOTRONEX that was written for health professionals.

Inactive Ingredients: lactose (anhydrous), magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The blue film-coat contains hydroxypropyl methylcellulose, titanium dioxide, triacetin, and indigo carmine.

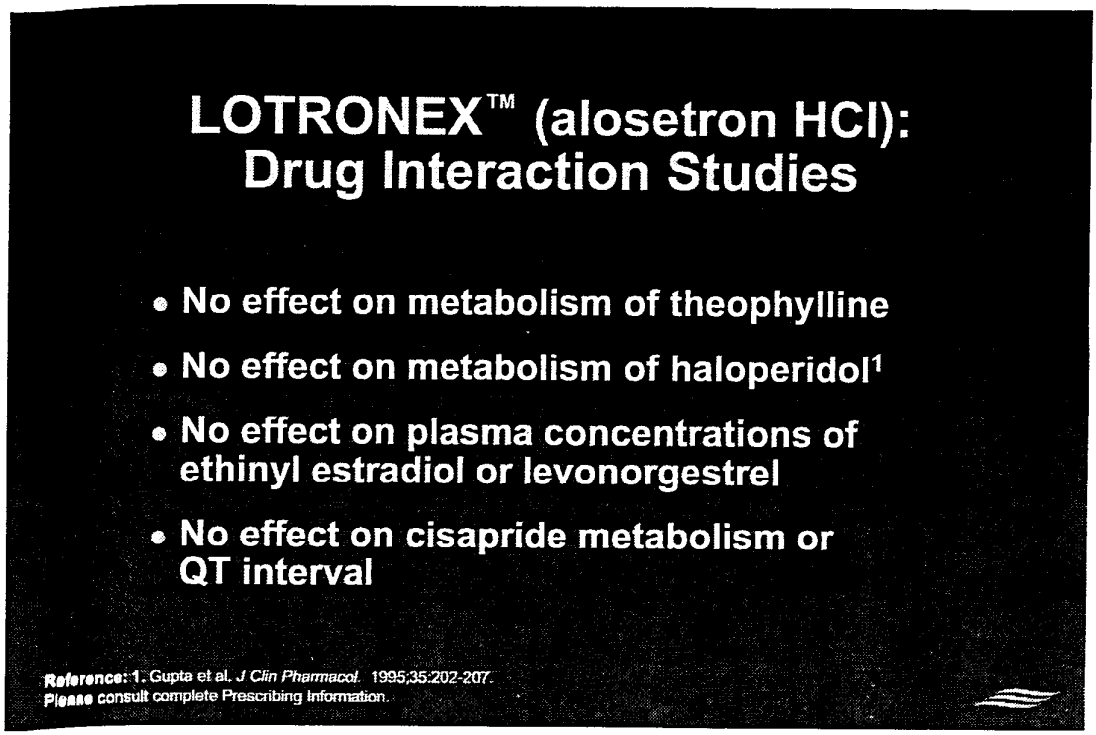
GlaxoWellcome

Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

US Patent No. 5,360,800

© Copyright 2000, Glaxo Wellcome Inc. All rights reserved.

February 2000 RL-795



Based on *in vitro* and *in vivo* studies, it is unlikely that LOTRONEX™ (alosetron HCl) will inhibit the hepatic metabolic clearance of drugs metabolized by the major cytochrome P450 isoenzymes. Therefore, LOTRONEX may also be considered for use with certain multidrug regimens.

No effect on metabolism was observed in a clinical interaction study with theophylline. LOTRONEX also had no effect on the metabolism of haloperidol.[1] Similarly, LOTRONEX had no clinically significant effect on plasma concentrations of oral contraceptive agents ethinyl estradiol and levonorgestrel. Further, no significant effects on cisapride metabolism or QT interval were noted in a clinical interaction study.

Reference:

1. Gupta SK, Kunka RL, Metz A, Lloyd T, Rudolph G, Perel JM. Effect of alosetron (a new 5-HT_3 receptor antagonist) on the pharmacokinetics of haloperidol in schizophrenic patients. *J Clin Pharmacol*. 1995;35:202-207.