DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

APR 28 2000

Michele M. Hardy
Director, Advertising Policy
Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, North Carolina 27709

RE: **LOTRONEX (alosetron hydrochloride) Tablets**
NDA 21-107
MACMIS ID # 8772

Dear Ms. Hardy:

This letter concerns the dissemination of violative promotional materials by Glaxo Wellcome, Inc. (Glaxo) for Lotronex (alosetron hydrochloride) Tablets. The materials consist of a Formulary Kit [Lot 186RO], which includes a Sales Brochure, a Slide Kit, and a Sell Sheet. The Division of Drug Marketing, Advertising and Communication (DDMAC), has determined that the materials violate the Federal Food, Drug, and Cosmetic Act because they contain unsubstantiated Health-Related Quality of Life (HQRL), productivity and economic claims. The violations we have identified and described below are not exhaustive, and our objections extend to all other Lotronex materials containing similar claims.

1. Unsubstantiated Health-Related Quality of Life (HRQL) Claims

The Lotronex Formulary Kit states that the condition of Irritable Bowel Syndrome (IBS) negatively affects the HRQL for IBS patients and suggests that treatment with Lotronex has a positive effect on the HQRL of IBS patients. These representations are misleading because they are not based on substantial evidence, and overstate the effect of Lotronex on the HRQL of IBS patients. Examples of misleading HRQL claims from the Lotronex Formulary Kit follow.

The representation that *IBS "affects quality of life as much or more than diabetes and clinical depression"*[1] and the implication that Lotronex would improve the quality of life of IBS patients, is unsubstantiated. The Wells[2] article, referenced to support this representation, fails to evaluate the effects of Lotronex on HRQL.

The representation that IBS *"impacts sleep, diet, work, leisure, travel, and sexual functioning,"*[3] and the implication that Lotronex treatment can improve these outcomes in IBS patients is misleading because it is unsupported by the reference cited. This representation is based on an article describing a study by Whitehead et. al (1996),[4] and on the results of the Landmark Survey[5] sponsored by Glaxo. The Whitehead study and the Landmark Survey, however, both fail to evaluate the effect of Lotronex in IBS patients.

2. Unsubstantiated Economic Impact Claims

The Lotronex Formulary Kit implies that Lotronex reduces or eliminates the economic burden of disease [IBS] by presenting information about the economic burden of IBS and presenting information about the efficacy and safety of Lotronex. For example, the Sales Brochure (page 7) contains a section on the "Economic Impact" [of IBS]:

> *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. 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).*
>
> *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 drug costs associated with IBS, including prescription drug expenditures, or indirect costs such as lost wages. Accordingly, it is likely an underestimate of the true economic cost of IBS in US patients.*

The presentation of the economic burden of IBS, together with efficacy claims for Lotronex, suggests that Lotronex has a positive impact on reducing the economic

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1 This claim is found on the "IBS Facts" Page of the Formulary Kit, and on page 6 of the Sales Brochure in the Formulary Kit.

2 Wells NEJ, Hahn BA, Whorwell PJ. Clinical economics review: irritable bowel syndrome. *Aliment Pharmacol Ther*, 1997; 1:1019-1030.

3 This claim appears both on the inside flap of the Lotronex Formulary Kit, and on page 5 of the Sales Brochure portion of the Formulary Kit.

4 Whitehead WE, Burnett VK, Cook EW, Taub E. Impact of irritable bowel syndrome on quality of life. *Dig Dis Sci*, 1996; 41:2248-2253.

5 Data on file (Irritable bowel syndrome in American women, a landmark survey, July 1999), Glaxo Wellcome Inc.

burden of IBS. This presentation, however, lacks adequate evidence and is misleading because the Talley study[6], referenced by Glaxo in support, does not evaluate the impact of Lotronex on the economic burden of IBS.

3. Unsubstantiated Productivity Claims

The Lotronex Formulary Kit presents information on the impact of IBS on work absenteeism and implies that Lotronex has a positive impact on increasing the productivity of IBS patients and reducing the costs of absenteeism. For example, page 6 of the Sales Brochure contains the following information:

> *In a survey-based study comprising responses from a random sample of over 5000 U.S. 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. 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 U.S., 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. (Hahn et al.)*
>
> *A 1999 U.S. 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 information is supported by two studies.[7,8] However, neither of these studies evaluated the impact of Lotronex on productivity.

5. Overstated Efficacy Claims

Glaxo, in the Product Facts Section of the Formulary Guide, under the header "*Multisymptom Relief,*" claims that *"[Lotronex] relieves symptoms identified by...women with IBS as most bothersome...abdominal pain, urgency, frequency, bloating, and mucus."* This claim overstates the efficacy of Lotronex, since

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6 Talley, NJ, Gabriel SE, Harmsen WS, Zinsmeister AR, Evans RW. Medical costs in community subjects with irritable bowel syndrome. *Gastroenterology.* 1995;109:1736-1741.

7 Drossman, DA. Review article: an integrated approach to the irritable bowel syndrome. *Aliment Pharmacol Ther.* 1999;13 (Suppl 2):3-14.

8 Hahn 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.

Lotronex has not been proven to affect the symptoms of bloating or mucus in IBS patients.

6. Lack of Drug Interactions with Haloperidol

Glaxo's claim that Lotronex does not interact with haloperidol [in IBS patients] is misleading, because it is not based on substantial evidence. For example, the Formulary Slide Kit (Slide No. 33), claims that "Lotronex also had no effect on the metabolism of haloperidol, " and references a study by Gupta et. al. (1995).[9] The Gupta study, however, is inadequate to support the haloperidol claim because it was not designed to measure the effect of Lotronex on haloperidol in IBS patients at the Lotronex dose approved for use in IBS patients. The Gupta study measured the pharmacokinetics of haloperidol in 13 schizophrenic patients (not IBS patients) over a period of 56 days (not 12 weeks), at one-half the approved dose of Lotronex (1mg/daily rather than 1 mg/twice daily) as indicated for the treatment of IBS.

7. Misrepresentation of CNS Adverse Effects

The Lotronex Formulary Kit contains an Executive Summary Sheet that states that "LOTRONEX [patients] reported no significant difference versus placebo in CNS adverse events (dizziness, sleep or depressive disorders, visual disturbances) versus patients in the placebo group." This claim is misleading because it fails to disclose that the actual CNS adverse event rates experienced by Lotronex patients were higher than placebo. For example, sleep disorders occurred in 3% of the Lotronex patients vs. 2% placebo; depression occurred in 2% of Lotronex patients vs. 1% placebo. Failure to provide this additional information relative to the adverse event profile claim suggests that the Lotronex is safer than has actually been demonstrated.

8. Lack of Fair Balance

The presentation of the risk information within the Safety Section of the Sales Brochure in the Lotronex Formulary Kit lacks fair balance. This section uses highlighted large-font graphics to emphasize the low CNS adverse event frequencies of Lotronex and the favorable long-term safety information for Lotronex, but "buries" important risk information within long bodies of text. Important warnings, such as "Lotronex should be discontinued in patients experiencing rectal bleeding and a sudden worsening of abdominal pain," and "Lotronex should not be used in patients who are currently constipated or whose predominant bowel symptom is constipation," are minimized and hidden within the

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9 Gupta, Kanka, Metz, et al. The effect of alosetron (a new 5-HT3 receptor antagonist) on the pharmacokinetics of haloperidol in schizophrenic patients. [*J. Clin Pharmacol* 1995; 35:202-207.]

text of the Safety Section.

Glaxo should immediately cease distribution of these and other similar promotional materials for Lotronex that contain the same or similar claims or presentations. Glaxo should submit a written response to DDMAC on or before May 15, 1999, describing its intent and plans to comply with the above. In its letter to DDMAC, Glaxo should include a list of materials discontinued and the date on which these materials were discontinued.

If you have any questions or comments, please contact the undersigned by facsimile at (301) 594-6759, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 17-B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official. In all future correspondence regarding this particular matter, please refer to MACMIS ID # 8772.

Sincerely,

/S/

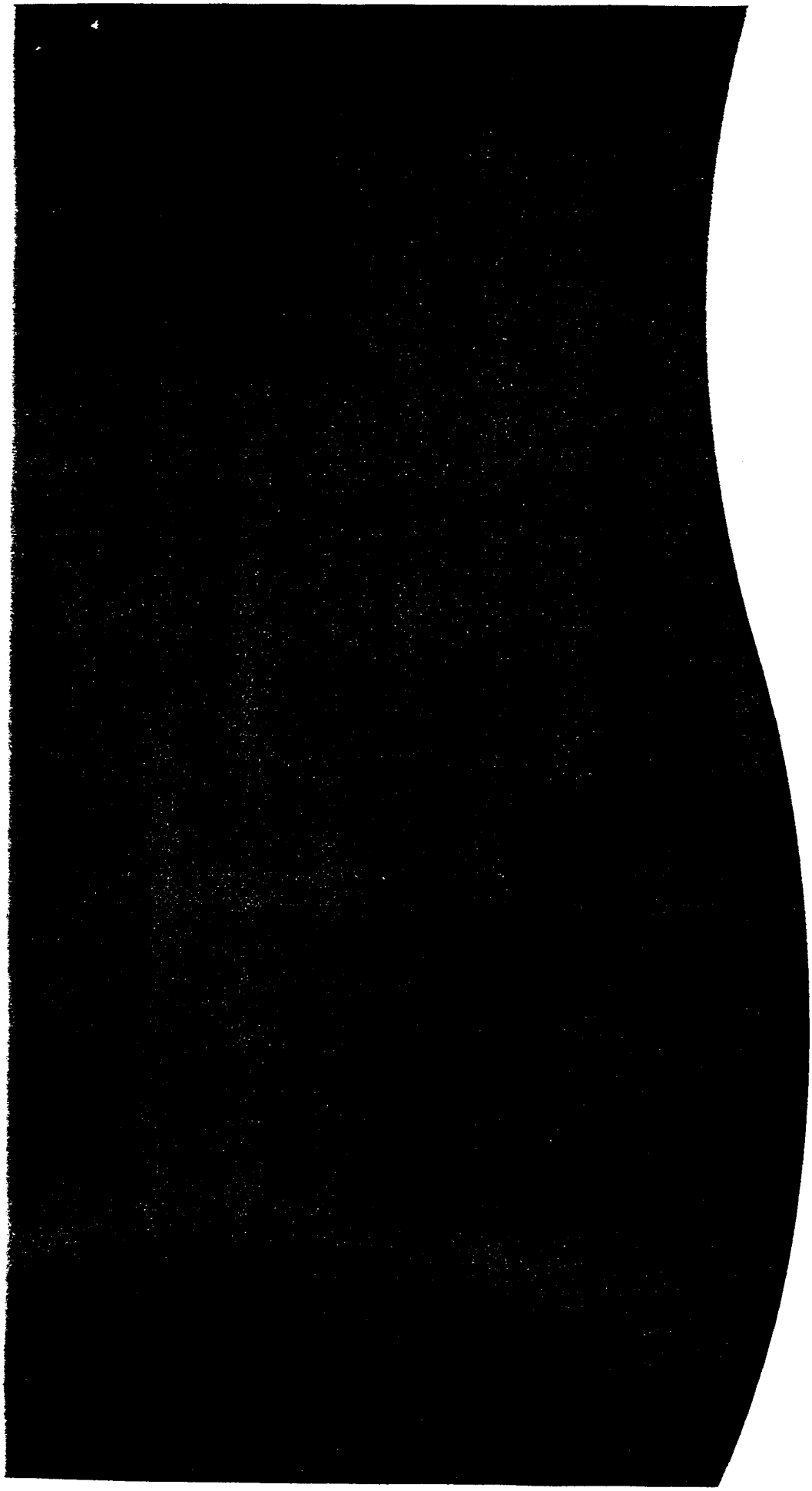
Patricia Kuker Staub, R.Ph., JD
Regulatory Reviewer
Division of Drug Marketing,
Advertising and Communications

LOTRONEX™

alosetron HCl tablets

Formulary Kit

GlaxoWellcome



LOTRONEX™

alosetron HCl tablets

www.lotronex.com

Formulary Kit Contents

Tabbed items

Executive Summary
Summary of the cost burden irritable bowel syndrome (IBS) places on health plans and employers as well as a description of LOTRONEX

Irritable Bowel Syndrome (IBS): Facts and Figures
Facts on IBS pathophysiology and epidemiology in an easy-to-read, bullet-point format

Product Facts-LOTRONEX ™ (alosetron HCl):
A Novel Treatment Approach for Women with Diarrhea-Predominant IBS
Fact sheet on efficacy, mode of action, and safety profile of LOTRONEX in an easy-to-read, bullet-point format

The American Hospital Formulary Service (AHFS) Product Information Form
Modified version of standard AHFS form

Summaries From Scientific Journals
Brief summaries of key scientific articles on IBS

Complete Prescribing Information

Sell Sheet for LOTRONEX
Supply and dosing information

Managing IBS
IBS Matters℠ is available to patients, providers, health plans, and employers to educate them about IBS and how to manage it (includes toll-free number for more information)

IBS Information Resources
Articles from scientific journals and Web sites on LOTRONEX and IBS

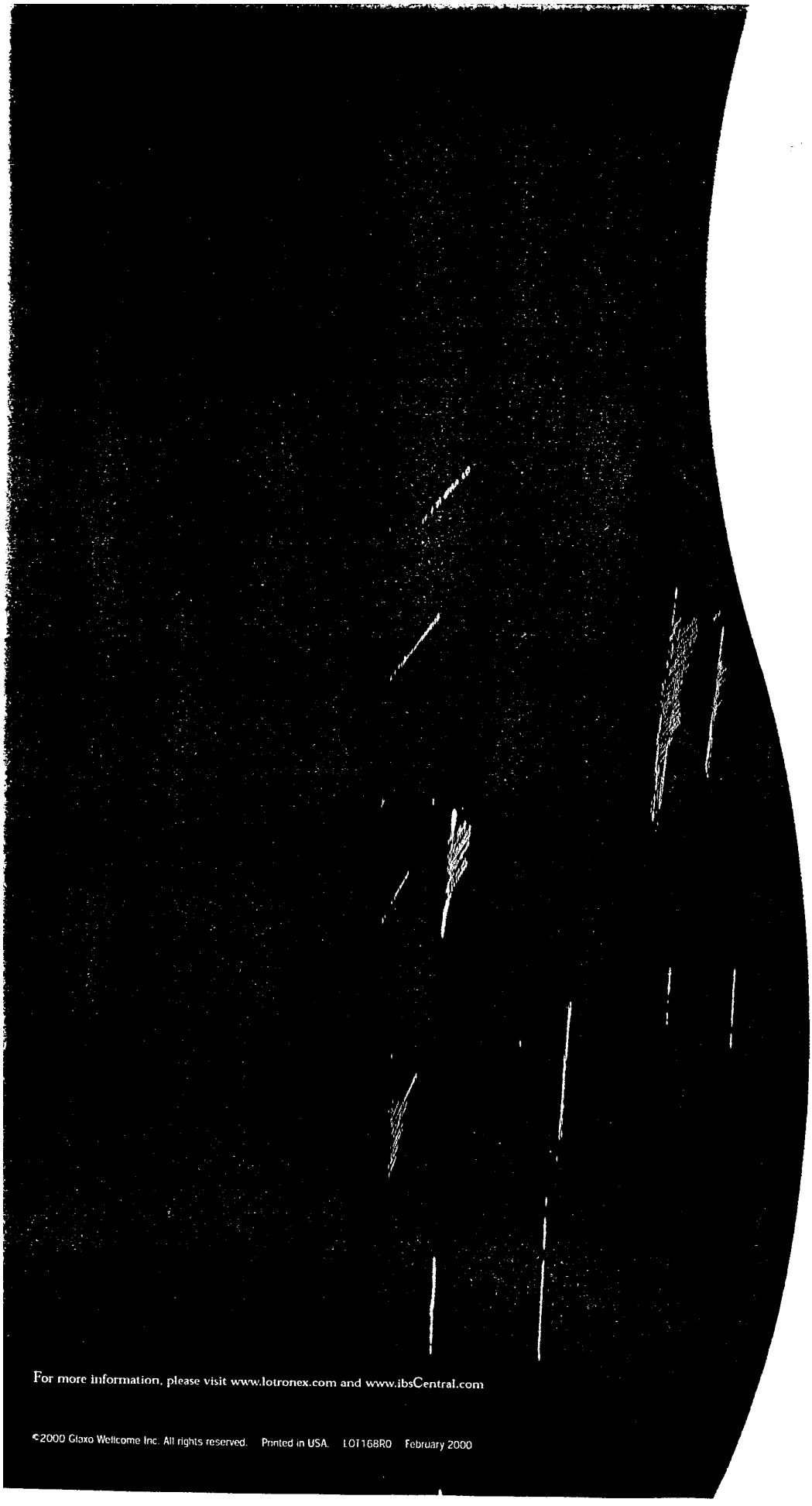
Boxed items

IBS, Managed Markets, and LOTRONEX
Slides with speakers' notes on the economic burden of IBS on plans, their members, and their employer-customers, and clinical data on LOTRONEX

LOTRONEX in the Management of Irritable Bowel Syndrome in Female Patients Whose Predominant Bowel Symptom is Diarrhea
Monograph on IBS and LOTRONEX, including charts and graphs of clinical trial results

IBS Diagnostic Checklist
Checklist on IBS indicators and clues that might suggest that patient symptoms require further exploration of any existing organic diseases

Please consult accompanying complete Prescribing Information.



For more information, please visit www.lotronex.com and www.ibsCentral.com

 Printed in USA. LOT168R0 February 2000

GlaxoWellcome

Glaxo Wellcome Inc.
Research Triangle Park, NC 27709
www.glaxowellcome.com

Formulary Kit
Executive Summary

This kit has been developed to help you evaluate LOTRONEX™ (alosetron HCl) during your formulary review process. Inside you will find detailed information on the substantial direct and indirect costs associated with irritable bowel syndrome (IBS). The kit also describes LOTRONEX, providing information on its indication, mode of action, performance in clinical trials, and safety profile.

The following is a broad overview of information available in the kit, which is also available on the World Wide Web at: www.formkit.com. (More information on IBS is available at www.ibsCentral.com or www.lotronex.com)

The Cost Burden of IBS

Managed Care Organizations and employers are already absorbing high costs of IBS diagnosis and care. Diagnosis is a challenge, as there are no pathophysiologic markers to indicate the presence of IBS.[1,2] IBS accounts for an estimated $8 billion annual expense in physician visits, (excluding medications).[3] According to *IBS in American Women: A Landmark Survey*, respondents reported that it took an average of more than three years and contact with three physicians before IBS was correctly diagnosed.[4] (Data presented are from the 1999 *IBS in American Women* telephone survey, funded by Glaxo Wellcome, the largest, most comprehensive national survey ever done on IBS.)*

Because of IBS, employers lose productivity, either through absenteeism or reduced on-the-job productivity. A published study shows that individuals with IBS miss 13.4 workdays per year while those without IBS miss only 4.9 workdays per year.[5] In a typical 1-month period[6]:

On average, employees reported 3 reduced workdays per month

30% of individuals with IBS were absent from work at least 1 day per month

46% reduced their work hours

A Novel Treatment Approach

LOTRONEX is the first medication proven in large-scale clinical trials to relieve multiple symptoms in women with diarrhea-predominant IBS.† In clinical trials, LOTRONEX offered significantly greater relief of abdominal pain and discomfort, urgency, and frequency than placebo.† These symptoms were ranked by women with diarrhea-predominant IBS as the most bothersome.‡ The safety and effectiveness of LOTRONEX in men have not been established.

* The survey was conducted by a national public opinion research organization in July-August 1999. The survey included over 1000 women with diagnosed IBS, more than 1000 women in the general public, and over 700 healthcare professionals.

† Versus placebo in two well-controlled trials with several endpoints representing multiple symptom relief.

‡ Versus placebo in two well-controlled trials in 1273 nonconstipated female patients.

Please consult accompanying complete Prescribing Information.

LOTRONEX™
alosetron HCl tablets

Executive Summary

Modulates the Enteric Nervous System (ENS)

As a neuroenteric modulator (NEM), LOTRONEX™ (alosetron HCl) blocks serotonin receptors ($5\text{-}HT_3$) in the enteric nervous system (ENS) of the GI tract—potentially modulating signals that control perception of pain and GI motility. $5\text{-}HT_3$ receptors are distributed on the enteric neurons of the gastrointestinal tract as well as other peripheral and central locations. Blocking these $5\text{-}HT_3$ serotonin receptors helps regulate the processes that may influence IBS: visceral sensitivity and motor activity. Although the cause of IBS is unknown, research strongly suggests these processes lead to symptoms such as the pain, urgency and frequency experienced by individuals with IBS. The mechanism and site of action of alosetron have not been fully established.

Proven multisymptom relief in clinical trials

LOTRONEX 1 mg b.i.d. has been tested in two phase III, 12-week, placebo-controlled clinical trials involving over 1273 nonconstipated female patients. (Efficacy beyond 12 weeks has not been established.)

Relief of pain and discomfort: Significantly more women with diarrhea-predominant IBS experienced relief of pain and discomfort in 1 and 4 weeks in studies 1 and 2, respectively.

Relief of urgency: Patients receiving LOTRONEX experienced greater reduction in bowel urgency than the placebo group.

Relief of frequency: Stool frequency was significantly reduced in patients receiving LOTRONEX.

Onset of multisymptom relief

Patients 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. When LOTRONEX was discontinued, symptoms returned within 1 week.

Favorable safety profile

LOTRONEX was generally well tolerated in clinical trials of more than 2000 patients. The most frequent adverse event versus placebo was constipation (28% vs 5%). LOTRONEX should not be used in IBS patients who are currently constipated or whose predominant bowel symptom is constipation. Acute ischemic colitis was infreqently (0.1% to 1%) reported in patients receiving LOTRONEX in 3-month clinical trials. A causal association between treatment with LOTRONEX and acute colitis has not been established. Patients using LOTRONEX reported no significant difference versus placebo in CNS adverse events (dizziness, sleep or depressive disorders, visual disturbances) versus patients in the placebo group.[4]

Convenient dosing

Dosage is one tablet (1 mg) b.i.d. with or without food.

Inhibition of major cytochrome P_{450} isoenzymes is unlikely based on in vitro and in vivo data.

By relieving chronic symptoms of IBS, LOTRONEX may help ease the burden of IBS on your plan, employer-customers, and members. For details about the key issues discussed above as well as additional information about IBS management, please review the other formulary kit materials.

Please consult accompanying complete Prescribing Information.

References

1. Sandler RS. Epidemiology of irritable bowel symptom in the United States. *Gastroenterology.* 1990;99:409-415.
2. Thompson WG, Dotevall G, Drossman DA, Heaton KW, Kreuls W. Irritable bowel syndrome: guidelines for the diagnosis. *Gastroenterology Int.* 1989:2:92-95.
3. Talley NJ, Gabriel SE, Harmsen WS, Zinsmeister AR, Evens RW. Medical costs in community subjects with irritable bowel syndrome. *Gastroenterology.* 1995;109:1736-1741.
4. Data on file, Glaxo Wellcome Inc.
5. Drossman DA, Zhiming L, Andruzzi E, et al. US householder survey of functional gastrointestinal disorders: prevalence, sociodemography, and health impact. *Dig Dis Sci.* 1993;38(9):1569-1580.
6. Hahn 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.

For more information, please visit www.lotronex.com or www.ibsCentral.com

Please consult accompanying complete Prescribing Information.

LOTRONEX™
alosetron HCl tablets

 Printed in USA. LOT168R0 February 2000

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Glaxo Wellcome Inc.
Research Triangle Park, NC 27709
www.glaxowellcome.com

Irritable Bowel Syndrome (IBS) Facts and Figures

May Affect up to 20% of US Adults[1,2]

- More prevalent than hypertension, asthma, or diabetes[1-3]
- Affects 3.2 times more women than men[4]
- Often strikes during prime working years[5]

Disrupts Lives Every Day

- Affects quality of life as much or more than diabetes and clinical depression[6]
- Impacts sleep, diet, work, leisure, travel, and sexual functioning[7]

Consumes Healthcare Resources

- Accounts for an estimated $8 billion annual expense in physician visits, procedures, radiology, and lab fees[8]
- Associated with up to 3.5 million physician visits per year[4]
  - 50% to 62% of patients leave the office visit with an established follow-up appointment[9]
- Patients with IBS commonly experience comorbid conditions[10-12]

Reduces Productivity in the Workplace

- A published study shows that patients with IBS miss 13.4 workdays per year while those without IBS miss only 4.9 workdays per year[5]
- In a typical 1-month period, 30% of patients with IBS were absent from work at least 1 day per month[13]

Disease

- A medical condition characterized by cramping abdominal pain or discomfort, along with irregular bowel functions such as diarrhea and/or constipation or urgency
- Chronic, recurring condition—symptoms may be debilitating[13,14]
- Shows no identifiable biochemical or structural abnormalities in the GI system[4,15]

Symptoms

- Surveyed nonconstipated patients with IBS rank abdominal pain, urgency, and frequency as the 3 most bothersome symptoms[16]
- Other IBS symptoms include altered stool form, abdominal distention and bloating, feeling of incomplete evacuation, and relief after defecation[15,17]
- Patients in a survey reported symptoms on over 50% of study days[14]

Emerging Theory of the Basis for IBS

- The enteric nervous system (ENS) of the GI tract contains numerous neurotransmitters, among them serotonin, which may mediate pain transmission and may play a role in visceral hypersensitivity and GI dysmotility[18]
- IBS is characterized by visceral hypersensitivity and hyperactivity of the GI tract, which lead to abnormal sensations of pain and motor activity
- In a pilot study, patients with IBS showed an exaggerated release of serotonin, especially after meals[19]

Treatment Options

- Reducing stress, changing diet
- Multiple symptoms may require multiple medications

References

1. Camilleri M, Choi M-G. Review article: irritable bowel syndrome. *Aliment Pharmacol Ther.* 1997;11:3-15.
2. Lynn RB, Friedman LS. Irritable bowel syndrome. In: Fauci AS, Braunwald E, Isselbacker KJ, et al, eds. *Harrison's Principles of Internal Medicine.* Vol 2. 14th ed. New York, NY: McGraw-Hill; 1998:1646-1648.
3. US Bureau of the Census. *Statistical Abstract of the United States; 1998.* 118th ed. Washington, DC: US Bureau of the Census. 1998.
4. Sandler RS. Epidemiology of irritable bowel syndrome in the United States. *Gastroenterology.* 1990;99:409-415.
5. Drossman DA, Zhiming L, Andruzzi E, et al. US householder survey of functional gastrointestinal disorders: prevalence, sociodemography, and health impact. *Dig Dis Sci.* 1993;38(9):1569-1580.
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8. Talley NJ, Gabriel SM, Harmsen WS, et al. Medical costs in community subjects with irritable bowel syndrome. *Gastroenterology.* 1995;109:1736-1741.
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10. Coremans G, Dapoigny M, Müller-Lissner S, et al. Diagnostic procedures in irritable bowel syndrome. *Digestion.* 1995;56:76-84.
11. Whorwell PJ, McCallum M, Creed FH, Roberts CT. Non-colonic features of irritable bowel syndrome. *Gut.* 1986;27:37-40.
12. Moore J, Barlow D, Jewell D, Kennedy S. Do gastrointestinal symptoms vary with the menstrual cycle? *Brit J Obstet and Gynacol.* 1998;105:1322-1325.
13. Hahn 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.
14. 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.
15. Thompson WG, Dotevall G, Drossman DA, Heaton KW, Kreuis W. Irritable bowel syndrome: guidelines for the diagnosis. *Gastroenterology Int.* 1989; 2: 92-95.
16. Data on file, Glaxo Wellcome Inc.
17. Manning AP, Thompson WG, Heaton KW, Morris AF. Towards positive diagnosis of the irritable bowel. *Br Med J.* 1978;2:653-654.
18. Bueno L, Fioramonti J, Delvaux M, Frexinos J. Mediators and pharmacology of visceral sensitivity: from basic to clinical investigations. *Gastroenterology.* 1997;112:1714-1743.
19. Bearcroft CP, Perrett D, Farthing MJG. Postprandial plasma 5-hydroxytryptamine in diarrhoea predominant irritable bowel syndrome: a pilot study. *Gut.* 1998;42:42-46.

For more information, please visit www.ibsCentral.com

Please consult accompanying complete Prescribing Information.

GlaxoWellcome
Glaxo Wellcome Inc.
Research Triangle Park, NC 27709
www.glaxowellcome.com

Product Facts

Onset of Relief

IBS SYMPTOM	EXPECTED TIME FOR RELIEF
Abdominal pain and discomfort	Within 1 to 4 weeks
Urgency	Within 1 week
Frequency	Within 1 week

Dosing

- One tablet (1 mg) b.i.d. daily with or without food; individual patients who experience constipation may need to interrupt treatment

Drug Interactions

- LOTRONEX is unlikely to inhibit the hepatic clearance of drugs metabolized by the major cytochrome P_{450} isoenzymes, based on in vitro and in vivo data
- Pharmacokinetic studies demonstrate no effect on the metabolism of ethinyl estradiol/levonorgestrel, cisapride, theophylline, or haloperidol[1]
- No studies have been conducted in patients with hepatic impairment

Safety Profile

The most common adverse event versus placebo was constipation (28% vs 5%). LOTRONEX should not be used in patients with IBS who are currently constipated or whose predominant bowel symptom is constipation.

- Occurrences of constipation were generally mild to moderate in intensity and self-limited. Most events resolved spontaneously with continued treatment
- Approximately 9% of patients in the studies required interruption of treatment for a few days; 10% of patients withdrew from the studies due to constipation
- Patients who reported constipation and completed 12-week treatment had pain relief similar to patients without constipation who completed treatment
- Patients who experience constipation may be considered for management with usual care including laxatives, fiber, or a brief interruption of therapy

Acute ischemic colitis was infrequently (0.1% to 1%) reported 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. There were no cases reported after 12 months of treatment with LOTRONEX. LOTRONEX should be discontinued in patients experiencing rectal bleeding and a sudden worsening of abdominal pain. These patients should be promptly evaluated with appropriate diagnostic testing. No significant difference in CNS adverse event frequencies in patients taking LOTRONEX (dizziness, sleep or depressive disorders, visual disturbances) vs placebo.[1]

LOTRONEX is indicated for the treatment of irritable bowel syndrome (IBS) in female patients whose predominant bowel symptom is diarrhea. Safety and effectiveness in men have not been established.

Reference: 1. Data on file, Glaxo Wellcome Inc.

For more information, please visit www.lotronex.com and www.ibsCentral.com

Please consult accompanying complete Prescribing Information.

LOTRONEX™
alosetron HCl tablets
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A Novel Treatment Approach For Women With Diarrhea-Predominant IBS

Modulates the Enteric Nervous System

- 5-HT_3 receptors are extensively distributed on enteric neurons in the GI tract as well as other peripheral and central locations
- Activation of receptors affects regulation of processes related to IBS:
  - visceral pain
  - colonic transit
  - GI secretions
- LOTRONEX, a potent and selective 5-HT_3 receptor antagonist, blocks ENS serotonin, thereby potentially reducing pain and exaggerated motor responses. The mechanism and site of action of alosetron are not fully established.

Multisymptom Relief

- Efficacy proven in two phase III, placebo-controlled, 12-week clinical trials involving 1273 nonconstipated women with IBS
  - Relieves symptoms identified by these women with IBS as most bothersome[1]

IBS SYMPTOMS PATIENTS IDENTIFIED AS MOST BOTHERSOME[1]

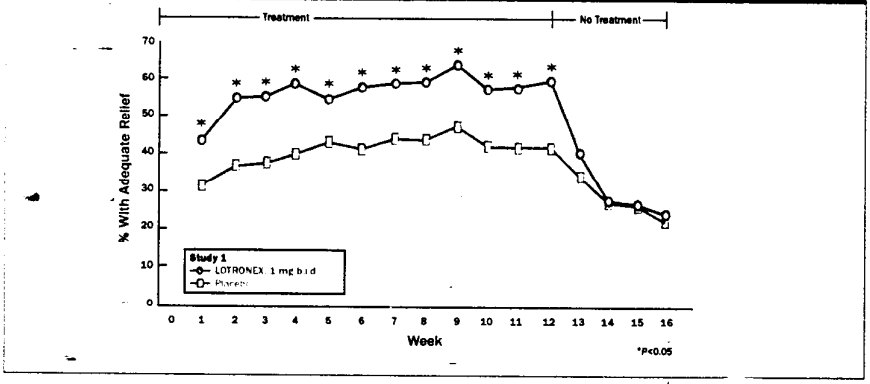
36%	28%	22%	12%	1%
Abdominal pain	Urgency	Frequency	Bloating	Mucus

Results of Clinical Trials

RELIEF OF ABDOMINAL PAIN AND DISCOMFORT

Significantly more women experienced adequate relief of IBS pain and discomfort versus placebo in 1 and 4 weeks in studies 1 and 2, respectively ($P<0.05$).*
Efficacy beyond 12 weeks has not been established.

% OF WOMEN (DIARRHEA-PREDOMINANT) REPORTING RELIEF OF IBS PAIN AND DISCOMFORT IN STUDY 1



RELIEF OF URGENCY

45% greater reduction in bowel urgency versus placebo[1†]

RELIEF OF FREQUENCY

Reduced daily stool frequency by 31% versus placebo[1‡]

*Results of placebo-controlled double-blind multicenter, randomized trials (Study 1: n=647 and Study 2: n=626) in 1273 nonconstipated female patients 18 to 83 years of age. 12-week treatment phase with a 4-week follow-up.

† Reduction in percentage of days with urgency with LOTRONEX from 68.4% (baseline) to 38.1% (at 3 months) vs 72.2% (baseline) to 50% (at 3 months) with placebo.[1]

‡ Reduction with LOTRONEX from 2.89 (baseline) to 2.01 (at 3 months) vs 3.01 (baseline) to 2.65 (at 3 months) with placebo.[1]

Please consult accompanying complete Prescribing Information.

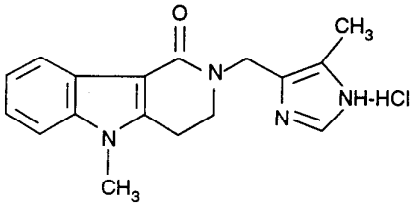
LOTRONEX™
alosetron HCl tablets

Product Facts

American Hospital Formulary Service (AHFS)* Product Information Form

Designed to supplement the official package insert

1. **Date:** February 2000
2. **AHFS Pharmacologic-Therapeutic Category:** selective antagonist of the 5-HT_3 receptor subtype
3. **Generic Name:** alosetron hydrochloride
4. **Source of Supply (List the trade name and manufacturer):** LOTRONEX™ 1-mg Tablets, Glaxo Wellcome Inc.
5. **Structural Formula:**



6. **Physical Properties of the Chemical Entity:**
   (a) Macroscopic appearance: white to beige solid
   (b) Solubility: 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
7. **Excipients:**
   Tablets (1 mg): lactose (anhydrous), magnesium stearate, microcrystalline cellulose, and pregelatinized starch; blue film-coat contains hydroxypropyl methylcellulose, titanium dioxide, triacetin, and indigo carmine.
8. **Chemical Properties:**
   (a) Structurally related to the following available compounds or groups of compounds: Alosetron is a potent and selective serotonin receptor (5-HT_3) antagonist.
   (b) Incompatibilities (If possible, specify whether the incompatibility is physical or chemical, the results of the incompatibility, and concentration tested.): N/A
   (c) Stability of admixture: N/A
   (d) pH range over which chemical is stable in solution: N/A
   (e) pH of parenteral preparation: N/A
   (f) How drug is supplied: Blue, oval, film-coated tablets engraved with GX CT1 on one face in bottles of 60 tablets (NDC 0173-0690-00).
   (g) Expiration date and storage conditions for commercially available preparation (Specify length of time): Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from excessive moisture. Expiration date: 2 years.

9. **Pharmacologic Properties:**

(a) **Pharmacologically related to the following available compounds or groups of compounds:** pharmacologic class of selective serotonin receptor (5-HT_3) antagonists.

(b) **Site of action:** Serotonin (5-hydroxytryptamine) receptors of the 5-HT_3 subtype are nonselective cation channels that are extensively distributed on enteric neurons in the human gastrointestinal tract, as well as other peripheral and central locations. 5-hydroxytryptamine is found throughout the gastrointestinal tract, located predominantly in the enterochromaffin cells but also in the enteric nervous system.[1] Alosetron is a potent and selective 5-HT_3 receptor antagonist. IBS is characterized by visceral hypersensitivity and hyperactivity of the gastrointestinal tract, which lead to abnormal sensations of abdominal pain and intestinal motor activity. In patients with IBS, the blockade of 5-HT_3 receptors by alosetron potentially reduces pain and exaggerated motor responses. The site of action of alosetron has not been fully established.

(c) **Mechanism of action:** Alosetron is a selective 5-HT_3 receptor antagonist. In healthy volunteers and patients with IBS, alosetron (2 mg twice daily for 8 days) increased colonic transit time. Furthermore, alosetron, in healthy volunteers, also increased basal jejunal water and sodium absorption after a single 4-mg dose. In patients with IBS, alosetron (4 mg twice daily for 6.5 days) significantly increased colonic compliance. Following distention of the rectum, patients with IBS exhibit pain and discomfort at lower volumes than healthy volunteers. In patients with IBS, alosetron reduced pain and exaggerated motor responses, possibly due to blockade of 5-HT_3 receptors. The mechanism of action of alosetron has not been fully established.

(d) **Therapeutically effective serum levels:** N/A

(e) **Toxic serum levels:** Not established in humans. There is no specific antidote for overdose of LOTRONEX™ (alosetron HCl). 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. Symptoms of acute toxicity in female mice and female rats were generated with 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). Symptoms of acute toxicity were labored respiration, subdued behavior, ataxia, tremors and convulsions.

Lethal serum levels: Single oral doses of LOTRONEX of 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.

Subcutaneous: N/A

(f) **Onset of action:** 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.

(g) **Duration of action:** N/A

(h) **Distribution to body tissues:** Alosetron demonstrates a volume of distribution of approximately 65 to 95 L. Plasma protein binding is 82% over a concentration range of 20-4000 ng/mL.

(i) **Does it pass the placental barrier?** LOTRONEX has a Pregnancy Category B rating. 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 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.

(j) Does it pass into the spinal fluid? Yes.

(k) Does it appear in the milk of 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.

(l) Metabolism (Include site and extent of metabolism): Alosetron is extensively metabolized in humans. The biological activity of these metabolites is not known. 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 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 in 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%.

(m) Excretion:

(1) Plasma clearance (oral): 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 dosing of alosetron does not result in accumulation. The terminal elimination half-life of alosetron is approximately 1.5 hours (plasma clearance is approximately 600 mL/min). Population pharmacokinetic analysis in patients with IBS confirmed that alosetron clearance is minimally influenced by doses up to 8 mg. Renal elimination of unchanged alosetron accounts for only 6% of the dose. Renal clearance is approximately 94 mL/min.

(2) The percentage of a single subcutaneously administered dose excreted as metabolite or unchanged drug in 24 hours: N/A

10. Evidence of Teratogenicity (List animals tested): Pregnancy Category B rating

Subcutaneous: N/A

Oral: Teratology 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 human dose based on body surface area). These studies revealed no evidence of impaired fertility or harm to the fetus due to LOTRONEX.

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.

11. **Method of Administration:** Oral

Usual Recommended Dosage: The recommended adult dosage of LOTRONEX is 1 tablet (1 mg) taken orally twice-daily with or without food. Individual patients who experience constipation may need to interrupt treatment.

Dose Adjustment: No dosage adjustment is recommended for elderly patients (65 years of age and older). No dosage adjustment is recommended for patients with renal impairment (creatinine clearance 4-56 mL/min.). No studies have been conducted in patients with hepatic impairment.

12. **Dosing for Pediatric and Elderly Patients:**

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

Elderly Patients: The dosage recommendation for the elderly is the same as for the general population.

Drug Interactions: In vitro human liver microsome studies and an in vitro 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 has 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 cytochrome P_{450} (CYP) drug metabolizing enzyme 3A. Alosetron 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.

13. **Any Additional Dosage Forms Investigated:** No.

ENCLOSURE: PRODUCT INFORMATION FOR LOTRONEX™ (alosetron HCl)

Reference: 1. Bearcroft CP, Perrett D, Farthing MJG. Postprandial plasma 5-hydroxytryptamine in diarrhoea predominant irritable bowel syndrome: a pilot study. *Gut.* 1998;42:42-46.

For more information, please visit www.lotronex.com and www.ibsCentral.com

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Summaries From Scientific Journals

There is a growing recognition in scientific journals that IBS—often a debilitating disease—places a heavy burden on the healthcare system and on individuals with IBS. Published material ranges from primers on IBS to data on new treatment options. Printed below are brief summaries of key articles published in scientific journals. These articles provide background information on IBS.

IBS Background

Camilleri M, Choi M-G. **Review article: irritable bowel syndrome.** *Aliment Pharmacol Ther.* 1997;11:3-15.

Summary- Camilleri and Choi present a broad overview of irritable bowel syndrome, a disease that's most commonly diagnosed by gastroenterologists and one that makes a large economic impact on healthcare utilization and productivity due to absenteeism. The authors examine the epidemiology of IBS, citing numerous studies conducted worldwide to pinpoint the prevalence of the disease: more women are affected than men; individuals aged 30-64 have a higher incidence of IBS symptoms than individuals over 65. Only 10% of people with irritable bowel, the authors note, present for medical care or evaluation, while many people with IBS live with their symptoms for several years. While the cause of IBS is unknown, the authors provide information on mechanisms that lead to symptoms, including abnormal motor function and abnormal visceral perception. In discussing treatment, they present an algorithm that is designed to avoid unnecessary diagnostic procedures in patients with suspected IBS. The algorithm includes initial evaluation, suggesting strategies to rule out organic disease. The algorithm branches out into several symptom subgroups, each requiring a different treatment approach. The authors conclude with a brief look to the future of IBS treatment via neuroenteric modulation.

IBS Epidemiology and Costs

Everhart JE, Renault PF. **Irritable bowel syndrome in office-based practice in the United States.** *Gastroenterology.* 1991;100:998-1005.

Summary- Everhart and Renault used data from National Ambulatory Medical Care Surveys (NAMCS) of office-based physicians to estimate the frequency of physician office visits and patterns of treatment for the diagnosis of irritable bowel syndrome. Their analysis showed that the overall rate of visits with the diagnosis of irritable bowel syndrome in the 1980-81 and 1985 surveys were 10.6 per thousand. Women had over twice the rate of visits than men. For both sexes the rates of office visits rose until middle age. The data also show that IBS was the leading diagnosis among digestive diseases diagnosed by gastroenterologists and the seventh-leading diagnosis among all physicians. One out of 2 office visits of patients with IBS led to a subsequent appointment.

Sandler RS. **Epidemiology of irritable bowel syndrome in the United States.** *Gastroenterology.* 1990;99:409-415.

Summary- Sandler used data from six large, systematic national health surveys to examine the epidemiology of irritable bowel syndrome in the United States. He analyzed the following data bases: National Health Interview Survey, Second National Health and Nutrition Examination Survey, National Ambulatory Medical Care Survey, National Disease and

Therapeutic Index, National Hospital Discharge Survey, the Commission on Professional and Hospital Activities. He found that IBS is a common condition in the United States and its impact on the health care system is significant. Among the supporting data for his conclusions were findings like: IBS symptoms account for between 2.4 and 3.5 million physician visits annually. In addition, rates for women were more than 3 times those for men. And, IBS occurred most often during the prime working years—ages 45 to 64.

IBS Symptom Patterns

Hahn B, Watson M, Yan S, Gunput D, Heuijerjans J. **Irritable bowel syndrome symptom patterns: frequency, duration, severity.** *Dig Dis Sci.* 1998;43(12):2715-2718.

Summary- During a 12-week study conducted in the United States, the United Kingdom, and The Netherlands, Hahn and colleagues established that irritable bowel syndrome is a burdensome, chronic, multisymptom condition.

Using an interactive telephone data entry system to report daily symptoms, 59 patients completed the study, logging the minimum required 70 days of symptom reporting. The data show that the majority of patients experienced at least one symptom on 50% of the days. (Individual symptoms were reported on less than 50% of the days, indicating that symptoms sometimes occurred sequentially rather than always simultaneously.) On average, patients reported pain/discomfort on 33% of days, bloating on 28% of days, altered stool form or stool passage on 25% and 18% of days, respectively, and mucus on 7% of days. Although the duration of symptoms was relatively short, intensity was moderately severe on the majority of reported days. Patients experienced an "episode" (defined as a period of days with symptoms bounded by one or more symptom-free days) on an average of 12.4 times during the study. Episode duration varied greatly among patients.

S's From Scientific Journals

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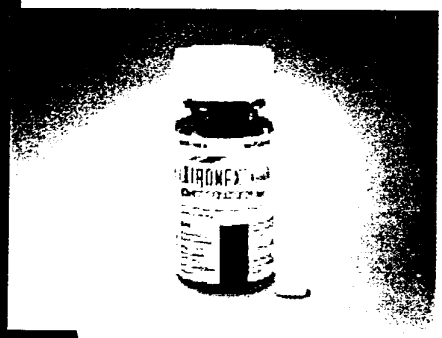
FOR WOMEN WITH DIARRHEA-PREDOMINANT
IRRITABLE BOWEL SYNDROME

Proven Multisymptom Relief

Sell Sheet for LOTRONEX® (alosetron HCl)



One tablet (1 mg) b.i.d.

SUPPLIED BY:	Glaxo Wellcome Inc.
DISTRIBUTED BY:	Glaxo Wellcome Inc.
PRODUCT NAME:	LOTRONEX™ (alosetron hydrochloride)
PACKAGE SIZE:	60 1-mg tablets per bottle
NDC NUMBER:	NDC 0173-0690-00
MINIMUM ORDER QUANTITY:	Direct Accounts: Please order in full-case quantities
UNIT:	50 cc cameo blue bottle
CASE QUANTITY:	48 units
CASE DIMENSIONS:	$9\frac{3}{4}$" x $6\frac{1}{2}$" x $7\frac{3}{4}$"
CASE WEIGHT:	$4\frac{1}{4}$ lb
DATED ITEM:	24 months
PRESCRIPTION LEGEND:	Yes
SPECIAL STORAGE REQUIREMENTS:	Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from excessive moisture.
REFRIGERATION REQUIRED:	No
INITIAL STOCKING TERMS:	See your Glaxo Wellcome Trade Relations Manager or Wholesale Representative
DISTRIBUTION:	To Glaxo Wellcome Inc. Direct Accounts
RETURNED GOODS:	See Glaxo Wellcome Inc. Return Goods Policy

Individual patients who experience constipation may need to interrupt treatment.

LOTRONEX™
alosetron HCl tablets

FOR WOMEN WITH DIARRHEA-PREDOMINANT
IRRITABLE BOWEL SYNDROME

Relief from pain and discomfort, urgency, and frequency

Sell Sheet for LOTRONEX® (alosetron HCl)

LOTRONEX™
alosetron HCl tablets

Neuroenteric Modulator (NEM)

- A potent and selective serotonin receptor ($5\text{-}HT_3$) antagonist that modulates the enteric nervous system, which may lead to reduced pain and reduced hypermotility; mechanism and site of action have not been fully established
- Relieves abdominal pain and discomfort within 1 to 4 weeks
- Significantly reduced bowel urgency and stool frequency—within 1 week
- Relief, once achieved, continues throughout treatment—symptoms return when LOTRONEX is discontinued
- Favorable safety profile and generally well-tolerated
- Convenient, 1 tablet (1 mg) b.i.d. dosing

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

For more information, please visit www.lotronex.com and www.ibsCentral.com

Please consult accompanying complete Prescribing Information.

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Managing IBS

Tools for Identifying and Managing the Costs of a Frequently Misunderstood and Often Debilitating Disease

Irritable Bowel Syndrome (IBS) often strikes adults during their prime working years,[1] bringing with it characteristic symptoms of lower abdominal pain or discomfort, associated with change in bowel function such as diarrhea, constipation, or both; urgent or difficult bowel movements; or bloating.

Clearly, this disease, which affects three times more women than men,[2] impacts employers as well as managed care plans. Both plans and employers are bearing the costs of diagnosis and treatment of IBS. For example:

- A published study shows that individuals with IBS miss 13.4 workdays per year while those without IBS miss only 4.9 workdays per year[1]
- Employees with IBS reduce their working hours on average 3 days a month[3]
- 30% of individuals with IBS were absent from work at least 1 day per month[3]
- 46% reduced their work hours or were absent from work[3]
- IBS is the 7th leading diagnosis among all physicians[4]
- Individuals with IBS incurred 73% more direct healthcare costs than those without IBS[5]
- Wo n [illegible]th IBS report nearly double the number of abdominal surgeries than those witho [illegible][5]*

But what do[illegible] really cost an individual employer or managed care plan? And, what can an employer or managed care plan do to contain costs while providing better care for those suffering from IBS?

Glaxo Wellcome has developed the following program to help answer these questions and provide a foundation for an effective strategy to manage IBS for employees and plan members:

IBS Matters[SM] - A Program for Managing IBS

IBS Matters provides the basis for patients, providers, and health plans to forge a partnership and improve the care and management of IBS. The program offers strategies to:

- Educate employees, members, and network physicians about IBS and available treatment approaches
- Identify and understand the costs of IBS
- Make appropriate IBS care and treatment approaches accessible to employees and members

**IBS in American Women: A Landmark Survey*, is a telephone survey conducted by a national public opinion research organization in July-August 1999. It is the largest, most comprehensive survey on IBS ever conducted in the United States. Over 1000 women diagnosed with IBS, more than 1000 women in the general public, and over 700 healthcare professionals were included. This survey was funded by Glaxo Wellcome Inc.

IBS Matters℠ also introduces tools to implement these strategies. Some highlights:

IBS-The Productivity Problem No One Wants to Think About

A CD-ROM containing information on how IBS affects workers and the workplace

IBS-Understanding the Costs

A CD-ROM containing information on IBS...its impacts and opportunities for improving care

IBS Screener

A self-administered quiz to help determine whether symptoms are consistent with IBS

IBS Symptom Diary

A tool employees and plan members can use to keep track of daily symptoms, which is valuable information for physicians making diagnosis and treatment decisions

The program also features:

Tools for Customers

A Basis for IBS Management
The Hidden Costs of IBS
Implementation Tips

Tools for Consumers

What Is IBS?
Managing Your IBS
Talking With Your Doctor About IBS

Tools for Healthcare Providers

Patient History and Symptom Summary
What Patients Want to Know About IBS

For more information on strategies and tools for managing IBS, call 1-800-TALK2GLAXO, visit web sites www.formkit.com, or www.ibsCentral.com, or contact your Glaxo Wellcome account manager.

Keeping Employers, Plans, Providers, and Patients Informed...
A Service of Glaxo Wellcome

References

1. Drossman DA, Zhiming L, Andruzzi E, et al. US householder survey of functional gastrointestinal disorders: prevalence, sociodemography, and health impact. *Dig Dis Sci.* 1993;38:1569-1580.
2. Sandler RS. Epidemiology of irritable bowel syndrome in the United States. *Gastroenterology.* 1990;99:409-415.
3. Hahn BA, Yan S, Strassels S. Impact of irritable bowel syndrome on quality of life and resource utilization in the United States and United Kingdom. *Digestion.* 1999;60:77-81.
4. Everhart JE, Renault PF. Irritable bowel syndrome in office based practice in the United States. *Gastroenterology.* 1991;100:998-1005.
5. Talley NJ, Gabriel SM, Harmsen WS, Zinsmeister AR, Evans RW. Medical costs in community subjects with irritable bowel syndrome. *Gastroenterology.* 1995;109:1736-1741.
6. Data on file, Glaxo Wellcome Inc.

For more information, please visit www.ibsCentral.com

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IBS Information Resource

Selected Bibliography

Glaxo Wellcome is providing the following as a resource for healthcare professionals to learn more about irritable bowel syndrome and its treatment. For easy reference, the bibliography is divided into scientific journal articles and Web sites. The list of Web sites includes brief content summaries as well as suggestions for continuing to search the Web as a way to learn more about IBS.

Scientific Journal Articles

Irritable Bowel Syndrome—Background

Camilleri M, Choi M-G. Review article: irritable bowel syndrome. *Aliment Pharmacol Ther.* 1997;11:3-15.

Everhart JE, Renault PF. Irritable bowel syndrome in office-based practice in the United States. *Gastroenterology.* 1991;100:998-1005.

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.

Sandler RS. Epidemiology of irritable bowel syndrome in the United States. *Gastroenterology.* 1990;99:409-415.

Web Sites

American Academy of Family Physicians
www.aafp.org/patientinfo/bowel.html
"Information from your Family Doctor." Patient information organized by "What IBS is and what to do about it."

American Digestive Health Foundation
www.gastro.org/adhf/dhi.html
Information on the Foundation's Functional Gastrointestinal Disorders Education Campaign. The campaign includes outreach activities for the medical profession, consumers, and managed care organizations.

American Gastroenterological Association
www.gastro.org/ibs.html
In the "public" section of this Web site...information on IBS that may be suitable for distribution to patients. It focuses on causes, symptoms, diagnosis, diet, and stress.

American WholeHealth, Inc. Library
www.americanwholehealth.com/library/ibs/ibs.htm
Links to articles and research on irritable bowel syndrome.

GLAXO WELLCOME:

www.healthylives.com General information on IBS as well as other diseases.
www.ibsCentral.com Information on IBS.

Continued on other side.

International Foundation for Functional Gastrointestinal Disorders
www.iffgd.org

An events calendar with information on numerous IBS support groups. IFFGD is a not-for-profit education and research organization with a mission to inform, assist, and support people affected by functional gastrointestinal disorders or bowel incontinence.

Irritable Bowel Syndrome Frequently Asked Questions
www.angelfire.com/il/ibshelp

Personal accounts of individuals with IBS and research by scientists at UCLA Medical Center. The question and answer format defines IBS, and covers questions on symptoms, medical facts, diagnosis, and management.

The National Digestive Diseases Information Clearinghouse
www.niddk.nih.gov/health/digest/pubs/irrbowel/irrbowel.htm

Information on IBS causes, symptoms, diagnosis, treatment, and comorbidity. It also offers general information on how the digestive system works. Presented as a service of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

University of North Carolina Center for Functional GI & Motility Disorders
www.med.unc.edu/medicine/fgidc/

Up-to-date information on functional GI disorders for both the professional and the patient, as well as information on the Center and its training and research.

Links to Additional IBS Web Sites

The IBS Page available at www.ibspage.com or www.panix.com/~ibs/

List of additional sources of IBS information on the Web.

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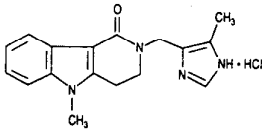
www.glaxowellcome.com

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.

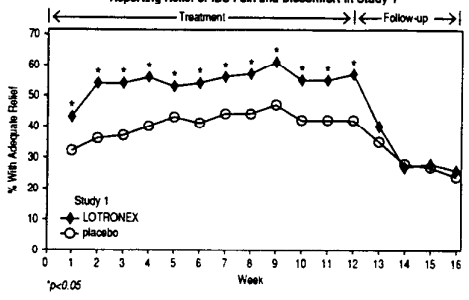
The efficacy and safety of 1 mg of oral LOTRONEX twice daily for 12 weeks was studied in two US multi-center, double-blind, placebo-controlled trials of identical design (Studies 1 and 2) in non-constipated women with IBS meeting the Rome Criteria (see Appendix) for at least 6 months. For enrollment 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.

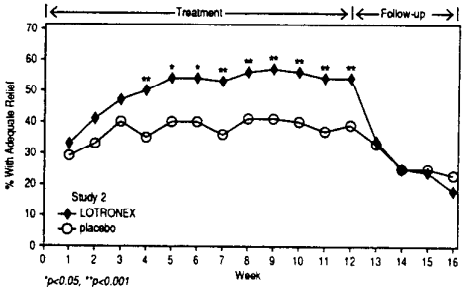
In both Study 1 and Study 2, the beneficial effect on IBS pain and discomfort was demonstrated only in women with diarrhea-predominant IBS. Data in Figures 1 and 2 are presented for this subgroup. In Study 1, significantly more women reported relief of their abdominal pain and discomfort within 1 week 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



*p<0.05

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



*p<0.05, **p<0.001

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

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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

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Complete Prescribing Information

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

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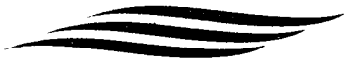

LOTRONEX™

alosetron HCl tablets

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