

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 21-107/S002

Trade Name: Lotronex Tablets

Generic Name: alosetron hydrochloride

Sponsor: GlaxoWellcome, Inc.

Approval Date: August 11, 2000

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APPLICATION NUMBER:
NDA 21-107/S002

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Approvable Letter	
Labeling	
Medical Review(s)	X
Chemistry Review(s)	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/ Biopharmaceutics Review(s)	
Administrative/Correspondence Document(s)	X

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APPLICATION NUMBER:
NDA 21-107/S002

APPROVAL LETTER

NDA 21-107/S-002

Glaxo Wellcome, Inc.
Attention: Mark Baumgartner
Product Director, Regulatory Affairs
Five Moore Drive
Research Triangle Park, NC 27709

AUG 11 2000

Dear Mr. Baumgartner:

Please refer to your supplemental new drug application dated July 17, 2000, received July 18, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lotronex™ (alosetron hydrochloride) Tablets.

We also refer to our correspondence dated August 4, 2000, in which we notified GlaxoWellcome that Pursuant to 21 C.F.R. Part 208, and based on information from post-marketing experience, FDA has determined that Lotronex™ (alosetron hydrochloride) poses a serious and significant public health concern requiring distribution of a Medication Guide.

We acknowledge receipt of your submissions dated July 18, 28; August 09, 10, and 11, 2000.

This supplemental new drug application provides for changes to the approved labeling, which includes changes to the package insert text and the immediate carton and container labels. In addition, your submission includes proposals for a new Patient Medication Guide, as well as "Dear HealthCare Practitioner" and "Dear Pharmacist" letters.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. In addition, we concur with your proposed "Dear HealthCare Practitioner" and "Dear Pharmacist" letters. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted August 11, 2000, Patient Medication Guide submitted August 11, 2000, immediate container and carton labels submitted August 10, 2000).

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved

supplement NDA 21-107/S-002." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Paul E. Levine, Jr., R.Ph., Regulatory Project Manager, at (301) 827-7310.

Sincerely,

LE 8-11-00

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Archival NDA 21-107

HFD-180/Div. Files

HFD-180/P.Levine

HFD-180/L.Talarico

S.Aurecchia

H.Gallo-Torres

S.Kress

HF-1/J. Henney

HF-22/B.Hubbard

HFD-001/J.Woodcock

HFD-40/B.Temple

R.Varsaci

HFD-103/F.Houn

V.Raczkowski

HF-11/C.Lorraine

HF-2/MedWatch (with labeling)

HFD-002/ORM (with labeling)

HFD-103/ADRA (with labeling)

HFD-42/N.Ostrove

K.Lechter

P.Staub

HFD-440/M.Dempsey

HFI-20/Press Office (with labeling)

HFD-400/OPDRA (with labeling)

HFD-613/OGD (with labeling)

HFD-21/ACS (with labeling)

HFD-095/DDMS-IMT (with labeling)

HFD-820/DNDC Division Director

DISTRICT OFFICE

Drafted by: PEL-08/11/00

Initialed by: JB-08/11/00

final: August 11, 2000

filename: Lotronex MedGuide-Labeling AP Ltr 081100.doc

APPROVAL (AP)

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APPLICATION NUMBER:
NDA 21-107/S002

LABELING

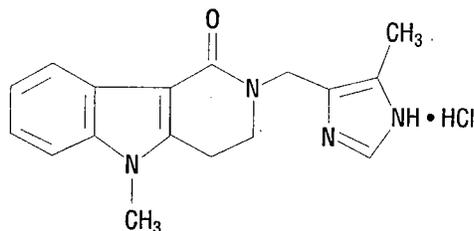
LOTRONEX[®]
(alosecron hydrochloride)
Tablets

WARNING: Serious gastrointestinal adverse events, some fatal, have been reported with the use of LOTRONEX. These events, including ischemic colitis and serious complications of constipation, have resulted in hospitalization, blood transfusion, surgery, and death.

- Only physicians who have enrolled in GlaxoSmithKline's Prescribing Program for LOTRONEX, based on their attestation of qualifications and acceptance of responsibilities, should prescribe LOTRONEX (see DOSAGE AND ADMINISTRATION and HOW SUPPLIED).
- LOTRONEX is indicated only for women with severe diarrhea-predominant IBS who have failed to respond to conventional therapy (see INDICATIONS AND USAGE). Less than 5 percent of IBS is considered severe. Before receiving the initial prescription for LOTRONEX, the patient must read and sign the Patient-Physician Agreement (see PRECAUTIONS: Information for Patients).
- LOTRONEX should be discontinued immediately in patients who develop constipation or symptoms of ischemic colitis. Physicians should instruct patients to immediately report constipation or symptoms of ischemic colitis. LOTRONEX should not be resumed in patients who develop ischemic colitis. Physicians should instruct patients who report constipation to immediately contact them if the constipation does not resolve after discontinuation of LOTRONEX. Patients with resolved constipation should resume LOTRONEX only on the advice of their treating physician.

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: C₁₇H₁₈N₄O•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:

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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-dependant reduction in the flare response seen after intradermal injection of serotonin. Urinary 6- β -hydroxycortisol excretion decreased by 52% in elderly subjects after 27.5 days of alosetron 2 mg orally twice daily. This decrease was not statistically significant. In another study utilizing alosetron 1 mg orally twice daily for 4 days, there was a significant decrease in urinary 6- β -hydroxycortisol excretion. However, there was no change in the ratio of 6- β -hydroxycortisol to cortisol, indicating a possible decrease in cortisol production. The clinical significance of these findings is unknown.

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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 ¹⁴C-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 2-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.

LOTRONEX[®] (alosecron hydrochloride) Tablets

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 WARNINGS).

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: LOTRONEX 1 mg twice daily was studied in two 12-week U.S. multicenter, randomized, double-blind, placebo-controlled trials of identical design (Studies 1 and 2) in non-constipated women with IBS meeting the Rome Criteria¹ for at least 6 months. Women with severe pain or a history of severe constipation were excluded. A 2-week run-in period established baseline IBS symptoms.

There were a total of 633 women on LOTRONEX and 640 on placebo, about two thirds with diarrhea-predominant IBS. Compared with placebo, 10% to 19% more women with diarrhea-predominant IBS who received LOTRONEX had adequate relief of IBS abdominal pain and discomfort during each month of the study.

Women with Severe Diarrhea-Predominant IBS: LOTRONEX is indicated only for women with severe diarrhea-predominant IBS (see INDICATIONS AND USAGE). The indication has been narrowed to this group of severely affected patients because serious gastrointestinal adverse events, some fatal, have been reported with the use of LOTRONEX. The following prospective and retrospective analyses support efficacy of LOTRONEX in this subset of the population that was studied in clinical trials.

In two 12-week, randomized, double-blind, placebo-controlled clinical trials of women with diarrhea-predominant IBS and bowel urgency on at least 50% of days at entry (Studies 3 and 4), there were a total of 778 women on LOTRONEX and 515 on placebo. Patients on LOTRONEX had

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significant increases over placebo (13% to 16%) in the median percentage of days with urgency control.

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

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

Efficacy in men has not been established.

INDICATIONS AND USAGE: Because of serious gastrointestinal adverse events, some fatal, reported with use of this drug, LOTRONEX is indicated only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have:

- chronic IBS symptoms (generally lasting 6 months or longer),
- had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and
- failed to respond to conventional therapy.

Diarrhea-predominant IBS is severe if it includes diarrhea and one or more of the following:

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

Less than 5 percent of IBS is considered severe.

In men, the safety and effectiveness of LOTRONEX have not been established (see CLINICAL TRIALS).

CONTRAINDICATIONS:

LOTRONEX **should not be initiated** in patients with constipation (see WARNINGS).

LOTRONEX is contraindicated in patients:

- With a history of chronic or severe constipation or with a history of sequelae from constipation.
- With a history of intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforation, and/or adhesions.
- With a history of ischemic colitis, impaired intestinal circulation, thrombophlebitis, or hypercoagulable state.
- With current or a history of Crohn's disease or ulcerative colitis.
- With active diverticulitis or a history of diverticulitis.

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- Who are unable to understand or comply with the Patient-Physician Agreement.
- With known hypersensitivity to any component of the product.

WARNINGS: (See BOXED WARNING and DOSAGE AND ADMINISTRATION.)

Some patients have experienced serious complications of constipation or ischemic colitis without warning.

Constipation: Serious complications of constipation, including obstruction, perforation, impaction, toxic megacolon, secondary colonic ischemia, and death have been reported with use of LOTRONEX. In some cases these complications have required intestinal surgery, including colectomy. **In IBS clinical trials, the incidence of serious complications of constipation in women was approximately 1 per 1,000 patients, but approximately 10% of patients on LOTRONEX withdrew prematurely because of constipation.** Patients who are elderly, debilitated, or taking additional medications that decrease gastrointestinal motility may be at greater risk for complications of constipation.

LOTRONEX should be discontinued immediately in patients who develop constipation (see BOXED WARNING).

Ischemic Colitis: Ischemic colitis has been reported in patients receiving LOTRONEX in clinical trials as well as during marketed use of the drug. **In IBS clinical trials, the cumulative incidence of ischemic colitis in women receiving LOTRONEX was 2 per 1,000 patients (95% confidence interval 1 to 3) over 3 months and was 3 per 1,000 patients (95% confidence interval 1 to 4) over 6 months. Patient experience in controlled clinical trials is insufficient to estimate the incidence of ischemic colitis in patients taking LOTRONEX for longer than 6 months.**

LOTRONEX should be discontinued immediately in patients with signs of ischemic colitis such as rectal bleeding, bloody diarrhea, or new or worsening abdominal pain. Because ischemic colitis can be life-threatening, patients with signs or symptoms of ischemic colitis should be evaluated promptly and have appropriate diagnostic testing performed. Treatment with LOTRONEX should not be resumed in patients who develop ischemic colitis.

PRECAUTIONS:

Information for Patients: Patients should be fully counseled on and understand the risks and benefits of LOTRONEX before an initial prescription is written.

PHYSICIANS MUST:

- Be enrolled in GlaxoSmithKline's Prescribing Program for LOTRONEX based on their attestation of qualifications and acceptance of responsibilities. To enroll in the GlaxoSmithKline Prescribing Program for LOTRONEX call 1-888-825-5249 or visit www.LOTRONEX.com.
- Counsel the patient about the risks and benefits of LOTRONEX, in the patients for whom LOTRONEX is indicated, and discuss the impact of IBS symptoms on the patient's life.
- Give the patient a copy of the Medication Guide, which outlines the risks and benefits of LOTRONEX, and instruct the patient to carefully read the Medication Guide. Answer all

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questions the patient may have about LOTRONEX. The complete text of the Medication Guide is printed at the end of this document.

- Review the Patient-Physician Agreement with the patient, answer all questions, and confirm that the patient has signed the Agreement.
- Sign the Patient-Physician Agreement, give a copy of the signed Agreement to the patient, and put the original in the patient's medical record.
- Provide each patient with appropriate instructions for taking LOTRONEX.

Copies of the Patient-Physician Agreement and additional copies of the Medication Guide are available by contacting GlaxoSmithKline at 1-888-825-5249 or visiting www.LOTRONEX.com.

PATIENTS WHO ARE PRESCRIBED LOTRONEX SHOULD BE INSTRUCTED TO:

- Read the Medication Guide before starting LOTRONEX and each time they refill their prescription.
- Not start taking LOTRONEX if they are constipated.
- Immediately discontinue LOTRONEX and contact their physician if they become constipated, or have symptoms of ischemic colitis such as new or worsening abdominal pain, bloody diarrhea, or blood in the stool. Immediately contact their physician again if their constipation does not resolve after discontinuation of LOTRONEX. Resume LOTRONEX only if their constipation has resolved and after discussion with and the agreement of their treating physician.
- ~~Stop~~ **Stop** taking LOTRONEX and contact their physician if LOTRONEX does not adequately control IBS symptoms after 4 weeks of taking 1 tablet twice a day.

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.

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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 these pathways on exposure to alosetron and its metabolites is not known.

Hepatic Insufficiency: Due to the extensive hepatic metabolism of alosetron, increased exposure to alosetron and/or its metabolites is likely to occur in patients with hepatic insufficiency.

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

Pregnancy: Teratogenic Effects: Pregnancy Category B. Reproduction studies have been performed in rats at doses up to 40 mg/kg/day (about 160 times the recommended human dose based on body surface area) and rabbits at oral doses up to 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

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: Postmarketing experience suggests that elderly patients may be at greater risk for complications of constipation (see WARNINGS).

ADVERSE REACTIONS: Table 1 summarizes adverse events from 22 repeat-dose studies in patients with IBS who were treated with 1 mg of LOTRONEX twice daily for 8 to 24 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 ($p < 0.0001$).

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Table 1: Adverse Events Reported in $\geq 1\%$ of IBS Patients and More Frequently on LOTRONEX 1 mg B.I.D. than Placebo

Body System Adverse Event	LOTRONEX 1 mg B.I.D. (n = 8,328)	Placebo (n = 2,363)
Gastrointestinal		
Constipation	29%	6%
Abdominal discomfort and pain	7%	4%
Nausea	6%	5%
Gastrointestinal discomfort and pain	5%	3%
Abdominal distention	2%	1%
Regurgitation and reflux	2%	2%
Hemorrhoids	2%	1%

Gastrointestinal: Constipation is a frequent and dose-related side effect of treatment with LOTRONEX (see WARNINGS). In clinical studies constipation was reported in approximately 29% of IBS patients treated with LOTRONEX 1 mg twice daily (n = 9,316). This effect was statistically significant compared to placebo (p<0.0001). Eleven percent (11%) of patients treated with LOTRONEX 1 mg twice daily withdrew from the studies due to constipation. Although the number of IBS patients treated with LOTRONEX 0.5 mg twice daily is relatively small (n = 243), only 11% of those patients reported constipation and 4% withdrew from clinical studies due to constipation. Among the patients treated with LOTRONEX 1 mg twice daily who reported constipation, 75% reported a single episode and most reports of constipation (70%) occurred during the first month of treatment with the median time to first report of constipation onset of 8 days. Occurrences of constipation in clinical trials were generally mild to moderate in intensity, transient in nature, and resolved either spontaneously with continued treatment or with an interruption of treatment. However, serious complications of constipation have been reported in clinical studies and in postmarketing experience (see BOXED WARNING and WARNINGS). In Studies 1 and 2, 9% of patients treated with LOTRONEX reported constipation and 4 consecutive days with no bowel movement (see CLINICAL TRIALS). Following interruption of treatment, 78% of the affected patients resumed bowel movements within a 2-day period and were able to re-initiate treatment with LOTRONEX.

Hepatic: A similar incidence in elevation of ALT (>2 fold) was seen in patients receiving LOTRONEX or placebo (1.0% vs. 1.2%). 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: Patient experience in controlled clinical trials is insufficient to estimate the incidence of ischemic colitis in patients taking LOTRONEX for longer than 6 months.

Other Events Observed During Clinical Evaluation of LOTRONEX: During its assessment in clinical trials, multiple and single doses of LOTRONEX were administered resulting in 11,874

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subject-exposures in 86 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 and other indications.

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 1 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.

Blood and Lymphatic: *Rare:* Quantitative red cell or hemoglobin defects, hemorrhage, and lymphatic signs and symptoms.

Cardiovascular: *Infrequent:* Tachyarrhythmias. *Rare:* Arrhythmias, increased blood pressure, and extrasystoles.

Drug Interaction, Overdose, and Trauma: *Rare:* Contusions and hematomas.

Ear, Nose, and Throat: *Rare:* Ear, nose, and throat infections; viral ear, nose, and throat infections; and laryngitis.

Endocrine and Metabolic: *Rare:* Disorders of calcium and phosphate metabolism, hyperglycemia, hypothalamus/pituitary hypofunction, hypoglycemia, and fluid disturbances.

Eye: *Rare:* Light sensitivity of eyes.

Gastrointestinal: *Infrequent:* Hyposalivation, dyspeptic symptoms, gastrointestinal spasms, ischemic colitis (see WARNINGS), and gastrointestinal lesions. *Rare:* Abnormal tenderness, colitis, gastrointestinal signs and symptoms, proctitis, diverticulitis, positive fecal occult blood, hyperacidity, decreased gastrointestinal motility and ileus, gastrointestinal obstructions, oral symptoms, gastrointestinal intussusception, gastritis, gastroduodenitis, gastroenteritis, and ulcerative colitis.

Hepatobiliary Tract and Pancreas: *Rare:* Abnormal bilirubin levels and cholecystitis.

Lower Respiratory: *Infrequent:* Breathing disorders. *Rare:* Viral respiratory infections.

Musculoskeletal: *Rare:* Muscle pain; muscle stiffness, tightness and rigidity; and bone and skeletal pain.

Neurological: *Infrequent:* Hypnagogic effects. *Rare:* Memory effects, tremors, dreams, cognitive function disorders, disturbances of sense of taste, disorders of equilibrium, confusion, sedation, and hypoesthesia.

LOTRONEX® (alosetron hydrochloride) Tablets

Non-site Specific: Infrequent: Malaise and fatigue, cramps, pain, temperature regulation disturbances. **Rare:** General signs and symptoms, non-specific conditions, burning sensations, hot and cold sensations, cold sensations, and fungal infections.

Psychiatry: Infrequent: Anxiety. **Rare:** Depressive moods.

Reproduction: Rare: Sexual function disorders, female reproductive tract bleeding and hemorrhage, reproductive infections, and fungal reproductive infections.

Skin: Infrequent: Sweating and urticaria. **Rare:** Hair loss and alopecia; acne and folliculitis; disorders of sweat and sebum; allergic skin reaction; eczema; skin infections; dermatitis and dermatosis; and nail disorders.

Urology: Infrequent: Urinary frequency. **Rare:** Bladder inflammation; polyuria and diuresis; and urinary tract hemorrhage.

Postmarketing Experience: The following events have been identified during use of LOTRONEX in clinical practice. Because they were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to LOTRONEX.

Gastrointestinal: Constipation, ileus, impaction, obstruction, perforation, ulceration, ischemic colitis, small bowel mesenteric ischemia (see WARNINGS).

Neurological: Headache.

Skin: Rash.

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:

For safety reasons, LOTRONEX is approved with marketing restrictions. Only physicians who attest to the following qualifications and accept the following responsibilities, and on that basis enroll in the GlaxoSmithKline Prescribing Program for LOTRONEX, should prescribe

LOTRONEX. Physicians must attest that they are able and willing to:

- diagnose and treat IBS

LOTRONEX[®] (alosetron hydrochloride) Tablets

- diagnose and manage ischemic colitis
- diagnose and manage constipation and complications of constipation
- understand the risks and benefits of treatment with LOTRONEX for severe diarrhea-predominant IBS, including the information in the package insert, Medication Guide, and Patient-Physician Agreement
- educate patients on the risks and benefits of treatment with LOTRONEX and obtain the patient's signature on the Patient-Physician Agreement form, sign it, place the original signed form in the patient's medical record, and give a copy to the patient
- report serious adverse events to GlaxoSmithKline at 1-888-825-5249 or to the Food and Drug Administration's MedWatch Program at 1-800-FDA-1088
- affix program stickers to all prescriptions for LOTRONEX (i.e., the original and all subsequent refill prescriptions). Stickers will be provided as part of the GlaxoSmithKline Prescribing Program for LOTRONEX. No telephone, facsimile, or computerized prescriptions are permitted with this program.

To enroll in the Prescribing Program for LOTRONEX call 1-888-825-5249 or visit www.LOTRONEX.com.

Usual Dose in Adults: For safety reasons, LOTRONEX should be started at a dosage of 1 mg orally once a day for 4 weeks. This dosage may be less constipating than a regimen of 1 mg twice a day (see WARNINGS). If, after 4 weeks, the 1 mg once-a-day dosage is well tolerated but does not adequately control IBS symptoms, then the dosage can be increased to 1 mg twice a day, the dose used in controlled clinical trials (see CLINICAL TRIALS). Although the efficacy of the 1 mg once-a-day dosage in treating diarrhea-predominant IBS has not been evaluated in clinical trials, for safety reasons consideration should be given to continuing this dosage if well tolerated and IBS symptoms in the individual patient are adequately controlled. **LOTRONEX should be discontinued in patients who have not had adequate control of IBS symptoms after 4 weeks of treatment with 1 mg twice a day.**

LOTRONEX should be discontinued immediately in patients who develop constipation or signs of ischemic colitis. LOTRONEX should not be restarted in patients who develop ischemic colitis.

Clinical trial and postmarketing experience suggest that debilitated patients or patients taking additional medications that decrease gastrointestinal motility may be at greater risk of serious complications of constipation. Therefore, appropriate caution and follow-up should be exercised if LOTRONEX is prescribed for these patients (see also Geriatric Patients).

Pediatric Patients: Safety and effectiveness have not been established in pediatric patients (see PRECAUTIONS: Pediatric Use).

Geriatric Patients: Postmarketing experience suggests that elderly patients may be at greater risk for complications of constipation; therefore, appropriate caution and follow-up should be exercised if LOTRONEX is prescribed for these patients (see WARNINGS).

Patients with Renal Impairment: There are insufficient data available on the biological activity of the metabolites of LOTRONEX. It is unknown if dosage adjustment is needed in patients with renal impairment (see CLINICAL PHARMACOLOGY: Reduced Renal Function).

LOTRONEX® (alosetron hydrochloride) Tablets

Patients with Hepatic Impairment: No studies have been conducted in patients with hepatic impairment. LOTRONEX is extensively metabolized by the liver and increased exposure to LOTRONEX is likely to occur in patients with hepatic impairment. Increased drug exposure may increase the risk of serious adverse events. LOTRONEX should be used with caution in patients with hepatic impairment (see PRECAUTIONS: Hepatic Insufficiency and CLINICAL PHARMACOLOGY: Population Subgroups: Reduced Hepatic Function).

LOTRONEX can be taken with or without food.

HOW SUPPLIED: The physician must attest to meeting the qualifications and accepting the responsibilities in the DOSAGE AND ADMINISTRATION section of this package insert and submit this attestation to GlaxoSmithKline to be enrolled in the Prescribing Program for LOTRONEX, which utilizes special program stickers that the enrolled physician will affix to all prescriptions for LOTRONEX (i.e., the original and all subsequent refill prescriptions). No telephone, facsimile, or computerized prescriptions are permitted with this program.

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

Bottles of 30 (NDC 0173-0690-05) with child-resistant closures.

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

REFERENCE:

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



GlaxoSmithKline

GlaxoSmithKline

Research Triangle Park, NC 27709

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(Date of issue)

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-107/S002

MEDICAL REVIEW



Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and
Coagulation Drug Products
Attention: Division Document Room, Rm 6B2
5600 Fishers Lane
Rockville, Maryland 20857

Memorandum

AUG 11 2000

Date: 08/11/00

From: Lilia Talarico, M.D. *Lilia Talarico*
Director Division of Gastrointestinal and
Coagulation Drug Products, HFD-180

To: NDA 21-107

Re: Labeling Review for Lotronex

This is in reference to the labeling amendments submitted August 10, and 11, 2000, to NDA 21-107/S-002 for Lotronex™ (alosetron hydrochloride) Tablets. These amendments provide for changes to the package insert text, Patient Medication Guide, "Dear HealthCare Practitioner" and "Dear Pharmacist" letters, and container labels. I have reviewed these amendments and find them consistent with the agreements reached between the FDA and GlaxoWellcome. Therefore, I recommend approval.

In accordance with Federal Regulations, The firm should be requested to provide final printed labeling (FPL) identical to the submitted draft labeling (package insert, Patient Medication Guide, immediate container and carton labels), as soon as it is available, in no case more than 30 days after it is printed.

AUG - 8 2000

**DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG
PRODUCTS
MEDICAL OFFICER REVIEW**

NDA: 21-107/S-002 – Labeling

Sponsor: GlaxoWellome

Drug Name: Lotronex (alosetron)

Reviewer: Scheldon Kress, M.D.
Date: July 31, 2000

Objective: Response to request for changes to the
approved labeling,
dated, July 17, 2000

This review consists of side-by-side comparisons of:

- (1) Current Approved Labeling
- (2) Sponsor's Proposed Modifications to Labeling
- (3) Medical Reviewer's Recommendations

Only those pertinent sections where changes have been recommended, are included. Sections of the labeling where neither the sponsor nor the medical reviewer made recommendations for change were omitted from this document.

Medical Reviewer's Summary:

Alosetron, a 5-hydroxytryptamine Type 3 (5-HT₃) receptor antagonist, approved February 9, 2000 for treatment of *women with diarrheal type irritable bowel syndrome*, has been associated with several unique and potentially serious adverse events. Whereas IBS generally does not result in a need for intestinal surgery, these **colonopathies** include constipation with life-threatening sequelae and ischemic colitis.

As of May 31, 2000, there have been approximately — prescriptions dispensed and 12 gastrointestinal serious adverse event (SAE) reports received through AERS (Adverse Event Reporting System). The number of post-marketing gastrointestinal SAE reports approaches 1 SAE per 11,000 prescriptions. In clinical trials, the rate of reported cases of ischemic colitis was 7 among 6800 patients. This translates into a rate of approximately 1/970 with a 95% confidence interval of (1/480, 1/2500) as calculated by the exact binomial method. Complications associated with constipation in clinical trials were reported in one patient.

Constipation is a frequent dose-related side effect of treatment with alosetron, 25 to 30% of approximately 6800 patients receiving this drug in clinical studies experienced constipation. Approximately 9% of patients in the clinical trials had no stool for 4 consecutive days. This constipation was severe enough to cause approximately 10% of patients taking alosetron to withdraw from clinical studies. Post-marketing reports describe patients taking alosetron who developed severe constipation associated with abdominal pain and rectal bleeding. Several known serious complications of constipation requiring hospitalization (6 cases with 3 cases requiring intestinal surgery) have been seen: fecal impaction, intestinal obstruction, ischemic (stercoral - hard feces induced) ulceration, perforation and gangrenous colitis. Some cases have probably been related to the inappropriate use of the drug by constipated patients, e.g., a constipation-prone male IBS patient. Included among the three patients who required intestinal surgery, was a patient with gangrenous colitis that required a total colectomy with ileostomy.

Ischemic colitis has occurred in patients in clinical trials and has been reported after marketing in patients taking alosetron. In patients taking alosetron, this clinical colonopathic syndrome appears to be a new variety of nonthrombotic ischemic colitis. The syndrome consists of abdominal pain (usually crampy and severe), diarrhea, bloody diarrhea and rectal bleeding. Less frequently the syndrome includes nausea, vomiting and bloody constipation. Eight patients with this syndrome required hospitalization and four required out-patient diagnostic endoscopic evaluations. Findings on abdominal computerized tomography scans have included mural thickening of varying degrees of severity occurring in both the small and large bowel.

To date, prompt discontinuation of alosetron in patients with alosetron-associated ischemic colitis has resulted in return of the mucosa to normal upon endoscopic visualization without progression to life-threatening hemorrhage, necrosis, perforation of the colon, or death. However, long term follow up data from these patients to rule out delayed colonic stenosis and stricture formation are not available.

IBS has never been a precise diagnosis, but instead has been a constellation of signs and symptoms meeting a set of diagnostic criteria in the absence of associated laboratory, endoscopic or pathological findings. Prior to the current era of managed care and cost containment, the diagnosis of IBS was one of rigorous and meticulous exclusion. Physicians tested patients extensively to rule out other medical conditions before diagnosing the patient with IBS. Today, physicians and other health care providers may often initiate drug treatment based on a suspected but unproven diagnosis before excluding other more serious disorders. In this setting, patients are more likely to receive inappropriate or delayed treatment of gastrointestinal/colonic lesions unrelated to IBS. As described above, in at least some cases, adverse events occurring in apparent association with alosetron administration turned out to be undetected errors in diagnosis.

Appears This Way On Original

Because the post marketing reporting of serious adverse events associated with LOTRONEX continued to accumulate, an Advisory Committee Meeting was held on June 27, 2000 to make recommendations regarding the Risk Management of the serious adverse events associated with the use of LOTRONEX.

Summarization of their recommendations are:

- The key to risk management of these adverse events is education
- Education of patients and physicians, but especially patients
- Dissemination of the new safety information
- Exclusion of patients with recent constipation
- Need to improve specificity of diagnosis
- Need for studies to identify risk factors

The common goal of FDA and the Sponsor is to lower the future risk of serious adverse events. It was generally felt that the frequency of AEs associated with constipation could and should be reducible to a negligible number of cases. Mandatory distribution of a Medication Guide to every patient taking LOTRONEX seems to be the most effective regulatory tool for disseminating this vital information to all patients planning to take this drug.. It is the consensus at the FDA that this information will help patients, the first line of attack, limit and prevent serious adverse events.

This review has made side-by-side comparisons of:

- Current Approved Labeling
- Sponsor's Proposed Modifications to Labeling

A third column, "Medical Reviewer's Recommendations" has been added. Comments were provided by the reviewer to support his decisions.

The currently approved PPI (patient package insert) is presented in Appendix 1 and the recommended Medication Guide is presented in Appendix 2.

Recommendations for Regulatory Action:

This Medical Reviewer has made the following recommendations for changes in the labeling for LOTRONEX to enhance the safety of this useful and effective drug. These changes are in addition to those recommended by the sponsor that have been noted as acceptable.

The recommended additional changes are :

CONTRAINDICATIONS:

LOTRONEX should not be initiated in patients with a history of severe constipation. (See WARNINGS)

LOTRONEX is contraindicated in patients:

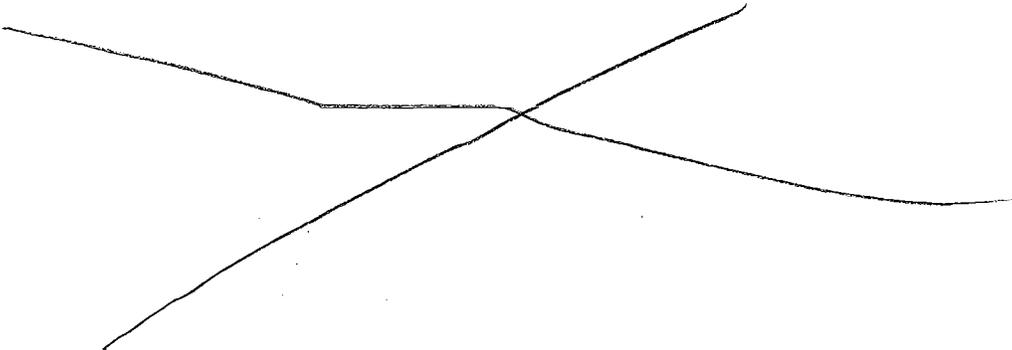
- With a history of chronic or severe constipation or with a history of sequelae from constipation.
- With a history of intestinal obstruction or stricture, toxic megacolon, gastrointestinal perforation, or adhesions.
- With a history of ischemic colitis
- With current or history of
- With
- With known hypersensitivity to any component of the product.

WARNINGS:

Add at the end of this section:

Information for Patients:

See the tear-off leaflet at the end of the labeling for information for the patient.



DOSAGE AND ADMINISTRATION:

Usual Dose In Adults: The recommended adult dosage of LOTRONEX is 1 mg taken orally twice daily with or without food.

LOTRONEX should be discontinued in patients who have not had improvement of IBS symptoms after four weeks of treatment

This Medical Reviewer recommends that the labeling for the patient package insert be modified to accurately reflect the risk/benefit balance, new safety information, patients for which this use of this drug is indicated or excluded, and warnings to potential patients on when to stop taking LOTRONEX and protect themselves from serious life-threatening adverse events. This information can be distributed to patients best be in the format of a Medication Guide. A Medication Guide can prove to be a major step toward enhancing the safe use of this potentially beneficial and effective drug.

Ongoing discussions continue with the sponsor regarding the finalized labeling. Further changes may be introduced in the final approved labeling and Medication Guide.

Scheldon Kress 8-8-00

Scheldon Kress, M.D.

Concur. August 8, 2000

Jugo E. Gallo-Torres, M.D., Ph.D.

CC:

NDA 21-107/S-002-Labeling *W 8-8-00*

HFD-180/Division File

HFD-180/L Talarico

HFD-180/S Aurrecchia

HFD-180/H Gallo-Torres

HFD-180/K Robie-Suh

HFD-180/S Kress

HFD-181/P Levine

HFD-180/JChoudary

HFD-180/LZhou

f/t 8/7/00 jgw

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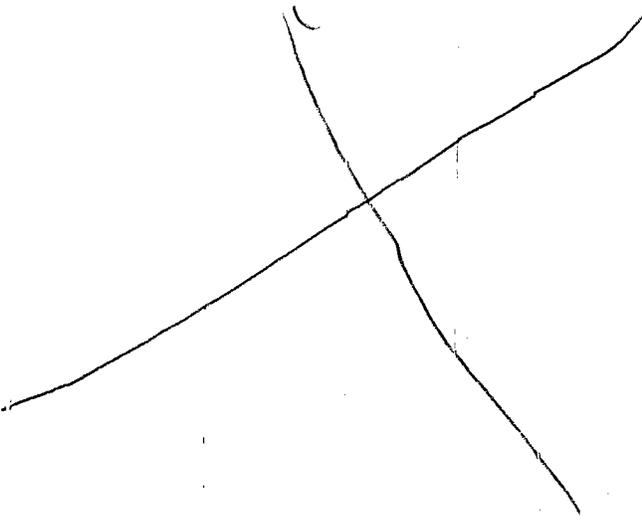
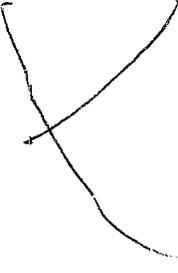
Appendix 1

Currently Approved Patient Package Insert

Current Approved Labeling	Sponsor's Proposed Modification to Labeling	Medical Reviewer's Recommendations
<p>Metabolism and Elimination: Plasma concentrations...</p> <p>80 Plasma radioactivity declined with a half-life two-fold longer than that of alosetron ...</p> <p>CLINICAL TRIALS</p> <p>125 (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, ...</p>	<p>Metabolism and Elimination: Plasma concentrations...</p> <p>72 Plasma radioactivity declined with a half-life two-fold longer than that of alosetron ...</p> <p>CLINICAL TRIALS</p> <p>114 constipated women with IBS meeting the Rome Criteria 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, ...</p>	<p>This change is acceptable</p>
<p>CLINICAL TRIALS</p> <p>125 (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, ...</p>	<p>CLINICAL TRIALS</p> <p>114 constipated women with IBS meeting the Rome Criteria 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, ...</p>	<p>This change is acceptable</p>

Current Approved Labeling	Sponsor's Proposed Modification to Labeling	Medical Reviewer's Recommendations
<p>INDICATIONS AND USAGE:</p> <p>LOTROXEX is indicated for the treatment of irritable bowel syndrome (IBS) in women whose predominant bowel symptom is diarrhea.</p> <p>The safety and effectiveness of LOTROXEX in men have not been established.</p>	<p>INDICATIONS AND USAGE:</p> <p>LOTROXEX is indicated for the treatment</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p>	<p>This change is acceptable</p>

Current Approved Labeling	Sponsor's Proposed Modification to Labeling	Medical Reviewer's Recommendations
<p>CONTRAINDICATIONS:</p> <p>LOTROXEX is contraindicated in patients known to have hypersensitivity to any component of the product.</p>	<p>CONTRAINDICATIONS:</p> <p>LOTROXEX is contraindicated in patients:</p> <ul style="list-style-type: none"> • With a history of chronic or severe constipation or with a history of sequelae from constipation. • With a history of intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforation, or adhesions. • With a history of ischemic colitis. • With known hypersensitivity to any component of the product. <p>LOTROXEX should not be</p>	<p>CONTRAINDICATIONS:</p> <p>LOTROXEX should not be initiated in patients with constipation.</p> <p>LOTROXEX is contraindicated in patients:</p> <ul style="list-style-type: none"> • With chronic or severe constipation or with a history of sequelae from constipation. • With a history of intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforation, or adhesions. • With a history of ischemic colitis. • With known hypersensitivity to any component of the product.
<p>Comments: In an attempt to reduce the risk of constipation-associated serious adverse events, it is prudent to limit this drug's usage to patients with diarrhea-type IBS. Therefore it is reasonable to exclude patients with conditions that place them at greater risk or have already been associated with serious constipation induced adverse events.</p>		

Current Approved Labeling	Sponsor's Proposed Modification to Labeling	Medical Reviewer's Recommendations
<p>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.</p> <p>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</p>		<p>WARNINGS:</p> 

(continued)

(continued)
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.

WARNINGS:
Constipation:

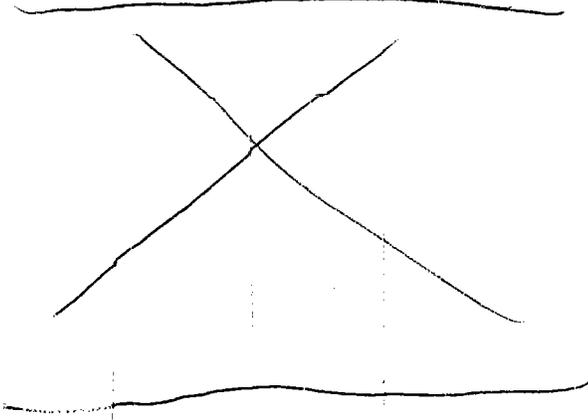
serious complications of constipation, including obstruction, perforation, impaction, toxic megacolon, and secondary. In some cases complications have required intestinal surgery, including colectomy.

Ischemic Colitis:

Ischemic colitis has been reported in patients receiving LOTRONEX in clinical trials as well during marketed use of the drug.

LOTRONEX should be discontinued immediately in patients with signs of ischemic colitis such as of rectal bleeding, bloody diarrhea, or new worsening abdominal pain. Because ischemic colitis can be life-threatening, patients with signs or symptoms of ischemic colitis should be evaluated promptly and have appropriate diagnostic testing performed. Treatment with LOTRONEX should not be resumed in patients with ischemic colitis.

Current Approved Labeling	Sponsor's Proposed Modification to Labeling	Medical Reviewer's Recommendations
<p>Information for Patients: See the tear-off leaflet at the end of the labeling for information for the patient.</p>	<p>Information for Patients: See the tear-off leaflet at the end of the labeling for information for the patient.</p>	<p>Information for Patients: See the tear-off leaflet at the end of the labeling for information for the patient.</p>
<p>Comments: Based on the severity of the serious adverse events observed during the clinical studies and the post-marketing period, physicians and their patients need to evaluate the risk/benefit balance for each patient before starting treatment with this drug. Whereas patients play the most critical role in 1) recognizing the early symptoms of ischemic colitis and more than usual constipation, and 2) taking immediate action to stop taking the drug, patients must be fully informed if we are to reduce the future risk of serious adverse events. Use of a Medication Guide for LOTRONEX seems to be the most effective tool for disseminating this vital information to every patient planning to take this drug for the safe and effective use of LOTRONEX.</p>		

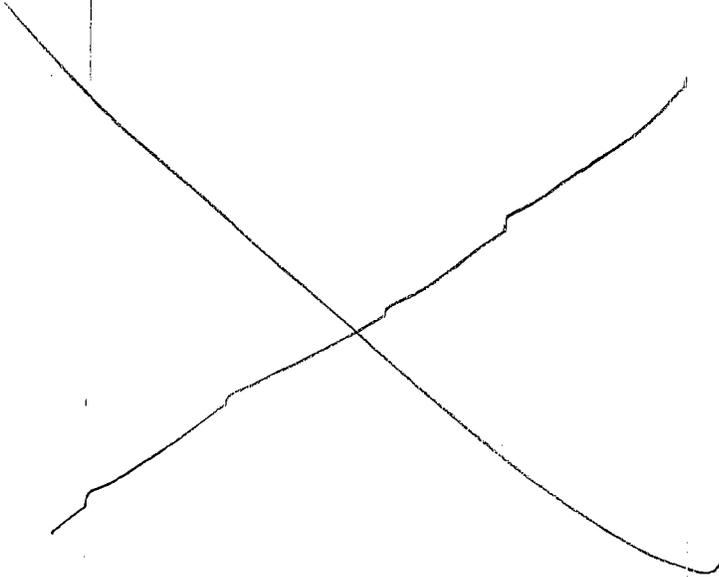
Current Approved Labeling	Sponsor's Proposed Modification to Labeling	Medical Reviewer's Recommendations
<p>Geriatric Use: Of all patients who received at least one dose of alosetron in premarketing studies, 211 were 65 years of age and over and 39 were 75 years of age and over. The safety profile of LOTRONEX was similar in older and younger patients.</p> <p>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).</p>		<p>This change is acceptable</p>

Current Approved Labeling	Sponsor's Proposed Modification to Labeling	Medical Reviewer's Recommendations
<p>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.</p>	<p>Gastrointestinal: (see WARNINGS). In clinical studies, constipation was reported in LOTRONEX 1 mg twice daily. This effect was statistically significant compared to placebo (p<0.0001). of patients treated with withdrew from the studies due to constipation. Occurrences of constipation in clinical trials were generally mild to moderate in intensity, and transient in nature, and most events resolved either spontaneously or with continued treatment or with an interruption of treatment.</p> <p>In studies 1 and 2, 9% of patients treated with LOTRONEX reported constipation and 4 consecutive days with no bowel movement.</p> <p>Following interruption of treatment of the affected patients resumed bowel movements within the day period and were able to re-initiate treatment with LOTRONEX.</p>	<p>This change is acceptable</p>

Current Approved Labeling	Sponsor's Proposed Modification to Labeling	Medical Reviewer's Recommendations
<p>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 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: <i>Infrequent</i> adverse events are those occurring on one or more occasion in 1/100 to 1/1000 patients; <i>Rare</i> adverse events are those occurring on one or more occasion in fewer than 1/1000 patients.</p> <p>Although the events reported occurred during treatment with LOTRONEX, they were not necessarily caused by it.</p>	<p>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 1 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: <i>Infrequent</i> adverse events are those occurring on one or more occasion in 1/100 to 1/1000 patients; <i>Rare</i> adverse events are those occurring on one or more occasion in fewer than 1/1000 patients.</p> <p>Although the events reported occurred during treatment with LOTRONEX, they were not necessarily caused by it.</p>	<p>This change is acceptable</p>

Current Approved Labeling	Sponsor's Proposed Modification to Labeling	Medical Reviewer's Recommendations
<p>Gastrointestinal-Infrequent: Ischemic colitis. Rare: proctitis.</p>	<p>Gastrointestinal-Infrequent: Ischemic colitis. (see WARNINGS). Rare: proctitis</p>	<p>This change is acceptable</p>
<p>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).</p>	<p>Usual Dose In Adults: The recommended adult dosage of LOTRONEX is 1 mg taken orally twice daily with or without food</p> <p>LOTRONEX should be discontinued in patients who have not had improvement of IBS symptoms after four weeks of treatment</p>	<p>Addition of this section is acceptable</p>
<p>Usual Dose in Adults: The recommended adult dosage of LOTRONEX is 1 mg taken orally twice daily with or without food.</p> <p>ADVERSE REACTIONS Gastrointestinal).</p>	<p>Usual Dose In Adults: The recommended adult dosage of LOTRONEX is 1 mg taken orally twice daily with or without food</p> <p>LOTRONEX should be discontinued in patients who have not had improvement of IBS symptoms after four weeks of treatment</p>	<p>DOSAGE AND ADMINISTRATION:</p> <p>Usual Dose In Adults: The recommended adult dosage of LOTRONEX is 1 mg taken orally twice daily with or without food.</p> <p>LOTRONEX should be discontinued in patients who have not had improvement of IBS symptoms after four weeks of treatment</p>
<p>Comments: Since it is near to impossible to grade constipation and clinically constipation cases can be managed with usual care. All others require interruption or cessation of therapy if we are to reduce the incidence of the severe sequelae associated with administration of this drug.</p>		

Current Approved Labeling	Sponsor's Proposed Modification to Labeling	Medical Reviewer's Recommendations
<p>HOW SUPPLIED: LOTRONEX Tablets, 1 mg (1.124 mg alosetron HCl equivalent to 1 mg alosetron), are blue, oval, film-coated tablets debossed with GX CT1 on one face in bottles of 60 tablets (NDC 0173-0690-00) and 120 tablets (NDC 0173-0690-03) with child-resistant closures and Unit Dose Pack of 60 (NDC 0173-0690-04).</p> <p>Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].</p>	<p>HOW SUPPLIED: LOTRONEX Tablets, 1 mg (1.124 mg alosetron HCl equivalent to 1 mg alosetron), are blue, oval, film-coated tablets debossed with GX CT1 on one face of bottles of child-resistant closures.</p> <p>Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].</p>	<p>This change is acceptable</p>

Current Approved Labeling	Sponsor's Proposed Modification to Labeling	Medical Reviewer's Recommendations
<p>APPENDIX</p> <p>Diagnostic Criteria: Irritable Bowel Syndrome (IBS)*</p> <p>At least three months continuous or recurrent symptoms of:</p> <ol style="list-style-type: none">1. abdominal pain or discomfort which is:<ol style="list-style-type: none">(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; and2. two or more of the following, at least a quarter of occasions or days;<ol style="list-style-type: none">(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.	<p>APPENDIX</p> 	<p>This change is acceptable</p>

(continued)

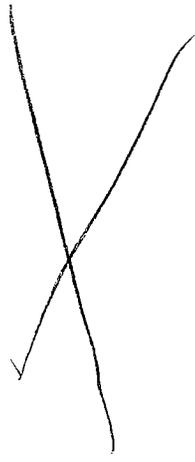
*Thompson WG, Creed F, Drossman DA, et al. Functional bowel disease and functional abdominal pain, *Gastroenterol Int* 1992; 5: 75-91.

(continued)

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

REFERENCES:

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



**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-107/S002

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

MEMORANDUM OF TELECON

DATE: August 18, 2000

APPLICATION NUMBER: NDA 21-107, Lotronex (alosetron) Tablets

BETWEEN:

Name: Mark Baumgartner, Director, Regulatory Affairs
Phone: (919) 483-3073
Representing: Glaxo Wellcome, Inc.

AND

Name: Melodi McNeil, Regulatory Health Project Manager (for
Paul E. Levine, Jr., Project Manager)
Lilia Talarico, Division Director
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: Omission of "Active Diverticulitis" from the Medication Guide

BACKGROUND: NDA 21-107 provides for alosetron tablets and was approved February 9, 2000. The product is indicated for the treatment of women with diarrhea-predominant irritable bowel syndrome (IBS). Following post-marketing reports of ischemic colitis and serious complications of constipation associated with the use of Lotronex, the applicant (at the Center's request) decided to implement a Medication Guide, revise the product labeling, and issue "Dear Doctor" and "Dear Pharmacist" letters to manage the risks associated with alosetron use.

The supplement which provided for the Medication Guide was approved August 11, 2000. Subsequently, Center personnel noticed that the alosetron medication guide contains an omission in that it does not mention that active diverticulitis is a contraindication for alosetron use.

TODAY'S PHONE CALL: Dr. Talarico informed Mr. Baumgartner of the omission and directed the firm to revise the section "Who should not take LOTRONEX?," item 2 ("Do not ever take Lotronex if you...") to include a bullet that reads, "have active diverticulitis."

According to the firm, the "Dear Doctor," "Dear Pharmacist" letters, and associated package insert have the correct information; only the Medication Guide is incorrect. Since printing of the Medication Guide has already begun, Dr. Talarico said that the Medication Guide could remain as is (i.e. "wrong") for now, but that it should be corrected as soon as possible.

Mr. Baumgartner agreed to check with his colleagues at Glaxo and let the Division know 1) whether this plan is acceptable and 2) a reasonable estimate as to when corrected Medication Guides will be available. The call was then concluded.

Melodi McNeil 8/23/00
Melodi McNeil
Regulatory Health Project Manager

NDA 21-107

Page 2

cc:

Archival NDA 21-107

HFD-180/Division File

HFD-180/RPM/Levine

HFD-180/McNeil

HFD-103/Raczkowski

Drafted by: mm/August 22, 2000

Initialed by: PLevine 8/23/00

Final: August 23, 2000

Filename: C:\My Documents\cso\n\21107008-tel.doc

TELECON



NDA 21-107

GlaxoSmithKline
Attention: Mark Baumgartner, R.Ph.
Product Director, Regulatory Affairs
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709-3398

Dear Mr. Baumgartner:

Please refer to your July 17, 2000, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lotronex™ (alosetron hydrochloride) Tablets, 1mg.

We also refer to your submissions dated July 18, 28; and August 09, 10, 11, and 28, 2000.

Your submissions dated August 28, 2000 contained final printed labeling (FPL) for this supplemental application which was approved on August 11, 2000.

We have reviewed the labeling that you submitted and we find it acceptable.

If you have any questions, call Paul E. Levine, Jr., R.Ph., Regulatory Health Project Manager, at 301-827-7310.

Sincerely,

{See appended electronic signature page}

Victor F. C. Raczkowski, M.D., M.Sc.
Acting Director
Division of Gastrointestinal & Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Paul Levine
1/2/02 02:34:30 PM
signed for Div. Dir.

NDA 21-107

Glaxo Wellcome, Inc.
Attention: Mark Baumgartner
Product Director, Regulatory Affairs
Five Moore Drive
Research Triangle Park, NC 27709

Dear Mr. Baumgartner:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lotronex™ (alosetron hydrochloride) Tablets.

Pursuant to 21 C.F.R. Part 208, FDA is notifying GlaxoWellcome that, based on information from post-marketing experience, FDA has determined that Lotronex™ (alosetron hydrochloride) poses a serious and significant public health concern requiring distribution of a Medication Guide.

Distribution of a Medication Guide is necessary for patients' safe and effective use of Lotronex™.

FDA has determined that Lotronex™ is a product for which patient labeling could help prevent serious adverse effects. Lotronex™ also has serious risks relative to its benefits that patients should be made aware of, because this information could affect patients' decision to use, or continue to use, the product. *See* 21 C.F.R. § 208.1(c).

In accordance with 21 C.F.R. 208, GlaxoWellcome is responsible for ensuring that a Medication Guide for Lotronex™ is available for every patient who is dispensed a prescription for Lotronex™. In addition, GlaxoWellcome is responsible for ensuring that the label of each container of Lotronex™ includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided.

If you have any questions, contact Paul E. Levine, Jr., R.Ph., Regulatory Health Project Manager at (301) 443-8347.

Sincerely,

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

NDA 21-107

Page 2

cc:

Archival NDA 21-107

HFD-180/Div. Files

HFD-180/P.Levine

HFD-180/L.Talarico

S.Aurecchia

H.Gallo-Torres

S.Kress

K.Johnson

HF-1/J. Henney

HF-22/B.Hubbard

HFD-001/J.Woodcock

HFD-40/B.Temple

R.Varsaci

HFD-103/F.Houn

V.Rackowski

HF-11/C.Lorraine

HF-2/MedWatch

HFD-002/ORM

HFD-103/ADRA

HFD-102/Post-Marketing PM

HFD-104/Peds/V.Kao

HFD-104/Peds/T.Crescenzi

HFD-42/N.Ostrove

K.Lechter

P.Staub

HFD-440/M.Dempsey

HFI-20/Press Office

HFD-400/OPDRA

HFD-613/OGD

HFD-21/ACS

HFD-095/DDMS-IMT

DISTRICT OFFICE

Drafted by: PEL 08/02/00

Initialed by: MM 08/04/00

final: 08/04/00

filename: Lotronex MedGuide Request ltr 080400.doc

MEDICATION GUIDE - INFORMATION REQUEST

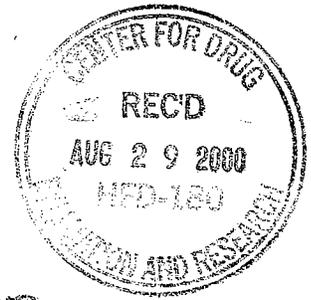
GlaxoWellcome

ARCHIVAL COPY – 1 COPY OF LABELING

August 28, 2000

Lilia Talarico, M.D., Director
Division of Gastrointestinal and Coagulation Drug Products
Center for Drug Evaluation and Research
Attn: Document Control Room
Office of Drug Evaluation III
Food and Drug Administration
HFD-180, PKLN, 6B-45
5600 Fishers Lane
Rockville, MD 20857

ORIGINAL



ORIGINAL
NDA SUPPLEMENT

SLR-002-FA

Re: NDA 21-107/S-002; LOTRONEX® (alosetron hydrochloride) Tablets
General Correspondence: Labeling
Final Printed Labeling (FPL) for approved Supplement NDA 21-107/S-002

Dear Dr. Talarico:

We are submitting 20 copies of final printed labeling (FPL) in response to the August 11, 2000 approval letter for the above supplemental application submitted July 17, 2000 providing for changes to the package insert text and immediate carton and container labels including addition of a new patient Medication Guide. The package insert and Medication Guide copy is identical to that submitted August 11, 2000 and the container labeling to that submitted August 10, 2000.

As discussed in our August 9 teleconference and described in our August 9 and 10 submissions, in order to facilitate implementation and exhaust existing inventory, we will rework existing product stock to remove the old labeling and replace it with the new package insert and medication guide. In addition, a sticker will be affixed to the packaging directing dispensers to provide the Medication Guide. Current inventories of printed sample cartons are being stickered with a non-removable sticker stating "Please read important patient Medication Guide inside". We are providing the stickered sample carton as FPL. The sticker will be an interim measure and will be replaced by printing of the information on the carton at the time future stock is ordered. We will file the actual printed carton in the Annual Report. We are also providing the sticker that will be adhered to the cap of the trade bottle when reworking currently packed stock. As stated above, the old package inserts will be replaced with new package inserts and Medication Guides when reworking the trade bottle and sample packs.

Glaxo Wellcome Inc.

Five Moore Drive
Research Triangle Park
North Carolina 27709

Telephone
919 248 2100

Lilia Talarico, M.D.

August 28, 2000

Page 2

Final printed labeling associated with our submission dated August 21, 2000 is targeted for submission on August 29, 2000.

This submission is provided in duplicate with a desk copy provided to Mr. Paul Levine, Jr., R.Ph. **Also included with the desk copy to Paul Levine is one market package of the drug product.** The marketed package is provided in response to the request included in your letter of August 11, 2000.

Please contact me at (919) 483-3073 if you have any questions regarding this submission.

Sincerely,

A handwritten signature in black ink, appearing to read 'M. A. Baumgartner', with a large, sweeping flourish extending to the right.

Mark A. Baumgartner, R.Ph.

Director

Regulatory Affairs

FINAL PRINTED LABELING

LOTROX[®] Tablets
(alose tron hydrochloride)

Bottle Label x 60 Tablets

Labeling: Original
NDA No: 21-107 Res'd. 8-28-00
Reviewed by: [Signature]

NDC 0173-0690-00
60 Tablets

Pharmacist:
Provide attached Medication
Guide when dispensing LOTROX.



LOTROX[®]
(alose tron hydrochloride) Tablets

Each film-coated tablet contains alose tron hydrochloride
equivalent to 1 mg alose tron.

Rx only

See package insert for
Dosage and Administration.
Store at 25°C (77°F);
excursions permitted to
15-30°C (59-86°F)
[see USP Controlled Room
Temperature].

Dispense in a tight, light-
resistant container as defined
in the USP.

US Patent No. 5,360,800

Glaxo Wellcome Inc.
Research Triangle Park, NC 27709
4123514 Rev. 8/00

Lot & Exp to be
overprinted in this area

FINAL PRINTED LABELING

LOTRONEX® Tablets
(alosetron hydrochloride)

Sample Carton x 4 Tablets

Labeling: Original
NDA No: 21-107 Rev'd. 8-28
Reviewed by: [Signature]

4114752
LOT107RO
000536

LOTRONEX™
(alosetron hydrochloride) Tablets

GlaxoWellcome

NDC 0173-0690-01

Sample—Not for Sale

LOTRONEX™
(alosetron hydrochloride) Tablets

Each film-coated tablet contains alosetron hydrochloride equivalent to 1 mg alosetron.

Rx only

Please read important patient Medication Guide inside.

4 Tablets (2 blistercards each containing 2 tablets)




Lot & Exp to be overprinted in this area

FINAL PRINTED LABELING

LOTRONEX® Tablets
(alose tron hydrochloride)

Bottle Cap Sticker



Labeling: Original
NDA No: 21-107 Rev'd. 8-28-0
Reviewed by: [Signature]



MEDICATION GUIDE
4126858

MEDICATION GUIDE
4126858

LOTRONEX[®]
(alose-
tron
hydrochloride)
Tablets



MEDICATION GUIDE

LOTRONEX[®] (LOW-trah-nex) Tablets alose- tron hydrochloride

Read this information carefully before you start taking LOTRONEX Tablets. Read the information you get with LOTRONEX each time you refill your prescription. There may be new information. This information does not take the place of talking with your doctor.

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

LOTRONEX is used to help women who have irritable bowel syndrome (IBS) with diarrhea as their main symptom (diarrhea-predominant IBS). **Women who have constipation as their main IBS symptom should not use LOTRONEX.** LOTRONEX has not been shown to help men.

IBS generally does not result in a need for bowel surgery (operation). A few patients taking LOTRONEX can develop intestinal side effects serious enough to need hospitalization and possibly surgery. **Before starting LOTRONEX, discuss with your doctor how troublesome your IBS symptoms are, the possible benefits of LOTRONEX, and its possible side effects to decide if LOTRONEX is right for you.**

Possible serious side effects of LOTRONEX include:

1. Constipation

LOTRONEX may result in constipation that infrequently may be serious enough to block movement of stools through the intestines. In a few women, this may lead to hospitalization and possibly surgery.

• **Do not start taking LOTRONEX if you**

- new or worsening abdominal (lower stomach area) pain
- bloody diarrhea or blood in the stool (bowel movements)

What is LOTRONEX?

LOTRONEX is a prescription medicine used to treat IBS in women who have diarrhea as their main symptom (diarrhea-predominant). LOTRONEX has not been shown to help men with IBS.

IBS is also called irritable colon and spastic colon. IBS causes lower abdominal (stomach) pain and discomfort, urgency (a sudden need to have a bowel movement), and irregular bowel habits, such as diarrhea or constipation. It is not clear why people develop IBS. Some scientists think IBS is caused by an overreaction to a body chemical called serotonin. This may cause patients' intestines to be overactive. IBS can be constipation-predominant, diarrhea-predominant, or can involve constipation and diarrhea. LOTRONEX is only for women with diarrhea-predominant IBS.

6858

LOTRONEX does not help everyone. For those who get relief, LOTRONEX helps reduce IBS-related lower abdominal pain, abdominal discomfort, urgency and diarrhea. You may get relief of some or all of your symptoms after 1 to 4 weeks of use. If LOTRONEX does not reduce your symptoms after 4 weeks, stop using it and tell your doctor.

LOTRONEX does not cure IBS. When you stop taking LOTRONEX, your IBS symptoms will probably return within 1 week.

Who should not take LOTRONEX?

LOTRONEX is not right for everyone. It is only for women with troublesome diarrhea-predominant IBS.

1. Do not **start** taking LOTRONEX if you are constipated
2. Do not **ever** take LOTRONEX if you
 - are constipated most of the time
 - have ever had severe constipation or a serious problem from constipation
 - have ever had Crohn's Disease or ulcerative colitis
 - have ever had ischemic colitis
 - are allergic to LOTRONEX or any of its ingredients (see list of ingredients at the end of this Medication Guide).

Possible serious side effects of LOTRONEX include:

1. Constipation

LOTRONEX may result in constipation that infrequently may be serious enough to block movement of stools through the intestines. In a few women, this may lead to hospitalization and possibly surgery.

- **Do not start taking LOTRONEX if you are constipated.**
 - **If you get constipated while taking LOTRONEX call your doctor right away. If you develop any of the following symptoms while waiting to talk to your doctor, stop taking LOTRONEX:**
 - severe constipation
 - worsening or bothersome constipation with increased abdominal discomfort
- Do not start taking LOTRONEX again until you talk to your doctor.**

2. Ischemic colitis

Some patients (about 1 in 700) developed ischemic colitis while using LOTRONEX. Ischemic colitis is a serious condition caused by reduced blood flow to the intestines. This condition may need hospitalization and possibly surgery. **Stop using LOTRONEX and call your doctor right away** if you have any of these signs of ischemic colitis:

- new or worsening abdominal (lower stomach area) pain
- bloody diarrhea or blood in the stool (bowel movements)

What is LOTRONEX?

LOTRONEX is a prescription medicine used to treat IBS in women who have diarrhea as their main symptom (diarrhea-predominant). LOTRONEX has not been shown to help men with IBS.

IBS is also called irritable colon and spastic colon. IBS causes lower abdominal (stomach) pain and discomfort, urgency (a sudden need to have a bowel movement), and irregular bowel habits, such as diarrhea or constipation. It is not clear why people develop IBS. Some scientists think IBS is caused by an overreaction to a body chemical called serotonin. This may cause patients' intestines to be overactive. IBS can be constipation-predominant, diarrhea-predominant, or can involve constipation and diarrhea. LOTRONEX is only for women with diarrhea-predominant IBS.

LOTRONEX does not help everyone. For those who get relief, LOTRONEX helps reduce IBS-related lower abdominal pain, abdominal discomfort, urgency and diarrhea. You may get relief of some or all of your symptoms after 1 to 4 weeks of use. If LOTRONEX does not reduce your symptoms after 4 weeks, stop using it and tell your doctor.

LOTRONEX does not cure IBS. When you

LOTRONEX® (alosetron hydrochloride) Tablets

If you take LOTRONEX under these conditions, you increase your risk of getting serious side effects.

Tell your doctor if you are pregnant, planning to get pregnant, breast feeding, or taking or planning to take other prescription or non-prescription medicines.

How should I take LOTRONEX?

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. Wait until the next scheduled dosing time and take your normal dose.

What are the possible side effects of LOTRONEX?

Constipation is the most common side effect of LOTRONEX. A few patients may develop serious intestinal side effects. A description of these side effects, how to identify them, and what action to take if you get them, is in the first section of this Medication Guide, "What is the most important information I should know about LOTRONEX?" Refer to the information about constipation and ischemic colitis in that section.

These are not all the side effects of LOTRONEX. Your doctor or pharmacist can give you a more complete list.

General advice about prescription medicines

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you have any concerns about LOTRONEX, ask your doctor. Your doctor or pharmacist can give you information about LOTRONEX that was written for health care professionals. Do not use LOTRONEX for a condition for which it was not prescribed. Do not share LOTRONEX with other people.

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

This Medication Guide has been approved by the US Food and Drug Administration.

GlaxoWellcome

Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

US Patent No. 5,360,800
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August 2000 MG-008 4126858



GlaxoWellcome

August 25, 2000

ORIGINAL

08/31/00
HG-T



Lilia Talarico, M.D., Director
Division of Gastrointestinal and Coagulation Drug Products
Center for Drug Evaluation and Research
Attn: Document Control Room
Office of Drug Evaluation III
Food and Drug Administration
HFD-180, PKLN, 6B-45
5600 Fishers Lane
Rockville, MD 20857

SUPPL NEW CORRESP

SLR-002-C

Re: NDA 21-107/S-002; LOTRONEX® (alosetron hydrochloride) Tablets
General Correspondence: Labeling

Dear Dr. Talarico:

Please refer to our supplemental New Drug Application (S-002) that provided revised labeling including a Medication Guide. Please also refer to your approval letter for 21-107/S-002 dated August 11, 2000 in which you requested that Glaxo Wellcome submit a copy of the "Dear Health Care Practitioner" letter to this application. The purpose of this submission is to provide the requested letters to health care providers.

Appended to this submission are copies of the "Dear Health Care Professional (Attachment 1) and "Dear Pharmacist" (Attachment 2) letters that Glaxo Wellcome began mailing on June 23, 2000. The letters inform prescribers and pharmacists of labeling changes regarding updated safety information for Lotronex. The Dear Pharmacist letter also informs Pharmacists of their obligation to provide a Medication Guide with each Lotronex prescription filled.

This submission is provided in duplicate with a desk copy provided to Mr. Paul Levine, Jr., R.Ph. We have also submitted a copy of this letter and copies of the letters to health care professionals to the address below:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Glaxo Wellcome Research and Development

Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709-3398

Telephone
919 483 2100

A Division of
Glaxo Wellcome Inc.

Lilia Talarico, M.D.

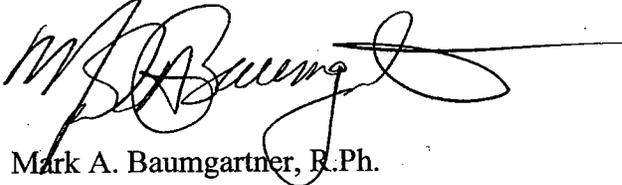
August 25, 2000

Page 2

We are targeting submission of Final Printed Labeling (FPL) applicable to the supplemental application and the requested market package of the drug product by August 28, 2000.

If you have any questions regarding this submission, please do not hesitate to contact me at (919) 483-3073.

Sincerely,

A handwritten signature in black ink, appearing to read 'Mark A. Baumgartner', with a long horizontal line extending to the right.

Mark A. Baumgartner, R.Ph.

Director

Regulatory Affairs

IMPORTANT DRUG WARNING

**RE: Important New Dispensing Information; Issuance of a Patient Medication Guide
Safety-related Revisions to Labeling for LOTRONEX® (alosetron hydrochloride) Tablets**

Dear Pharmacist:

Glaxo Wellcome Inc. is writing to inform you of important new safety information reflected in recent changes to the labeling for Lotronex (alosetron hydrochloride), a serotonin 5-HT₃ antagonist indicated for the treatment of women with diarrhea-predominant irritable bowel syndrome (IBS). This new safety information pertains to reports of constipation, that in a few cases have resulted in serious sequelae, and infrequent reports of ischemic colitis occurring in association with the use of Lotronex. To help ensure that patients are informed of this important and significant safety information, the "Information for Patients" that was previously provided as a tear-off section of the prescribing information has been changed to a Medication Guide. This Medication Guide has been approved by the Food and Drug Administration. Each authorized dispenser of Lotronex is required to provide a Medication Guide directly to the patient (or to the patient's agent) when Lotronex is dispensed. This applies to new prescriptions and refills.

At the time of approval of Lotronex in February 2000, the labeling included warnings of occurrences of ischemic colitis and dose-related occurrences of constipation that had been reported in clinical trials. Subsequently, we have received post-marketing reports of a few cases of serious complications of constipation, including obstruction, perforation, impaction, toxic megacolon, and secondary ischemia, in patients treated with Lotronex. In some cases these complications have required intestinal surgery, including colectomy. Since approval, a few additional cases of ischemic colitis have also been reported. These cases of ischemic colitis are comparable in frequency and severity to those reported prior to approval.

To communicate this important information to health care professionals, the **CONTRAINDICATIONS**, **WARNINGS**, **PRECAUTIONS**, and **DOSAGE AND ADMINISTRATION** sections of the package insert for Lotronex have been revised to highlight information about constipation and ischemic colitis. Important safety-related changes include the following:

- **CONTRAINDICATIONS**

Lotronex should not be initiated in patients experiencing constipation.

Lotronex is contraindicated in patients:

- With a history of chronic or severe constipation or with a history of sequelae from constipation.
- With a history of intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforation, and/or adhesions.
- With a history of ischemic colitis.
- With current or a history of Crohn's Disease or ulcerative colitis.
- With active diverticulitis.
- With known hypersensitivity to any component of the product.
- The **WARNINGS** section has been revised to include information about infrequent reports of serious complications of constipation, including obstruction, perforation, impaction, toxic megacolon, and secondary ischemia, in association with alosetron administration. In some cases these complications have required intestinal surgery, including colectomy.

Lotronex should be discontinued immediately and not restarted in patients who experience severe constipation while receiving the drug. Patients with non-severe constipation should be closely monitored. Cases of non-severe constipation can be managed with an interruption of therapy or usual

care including laxatives. However, if constipation does not resolve within four days with these measures, treatment should be discontinued and not resumed.

- The **WARNINGS** section of the labeling also describes the incidence of ischemic colitis in female subjects in clinical trials as approximately 1 in 700 patients. Lotronex should be discontinued immediately in patients with signs of ischemic colitis. These patients should be evaluated promptly and have appropriate diagnostic testing performed. Treatment with Lotronex should not be resumed in patients who have developed ischemic colitis.
- The Information for Patients subsection of the **PRECAUTIONS** section of the labeling has been revised to provide direction to the healthcare provider concerning discussions with the patient about Lotronex.
- The **DOSAGE AND ADMINISTRATION** section has been revised to include recommendations regarding situations where treatment with Lotronex should be interrupted or discontinued because of constipation.

Copies of the revised prescribing information and the patient medication guide are enclosed.

Glaxo Wellcome is committed to providing you with the most current product information for Lotronex. You can assist us in monitoring the safety of Lotronex by reporting adverse reactions to Glaxo Wellcome at 1-888-825-5249 to the FDA MedWatch program by telephone at 1-800-332-1088, by FAX at 1-800-332-0178, via www.FDA.gov/medwatch, or by mail to MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20857.

Please refer to the enclosed complete prescribing information for Lotronex. Additional copies of the Patient Medication Guide are enclosed for you to distribute to patients. If you have any questions about the new information or want additional information about Lotronex, or if you want additional copies of the enclosed information for patients, please contact the Glaxo Wellcome Customer Response Center at 1-888-825-5249.

Sincerely,

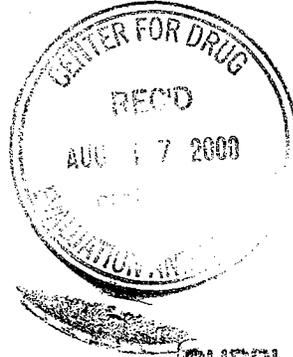
Richard S. Kent, MD
Vice President and Chief Medical Officer

GlaxoWellcome

August 16, 2000

ORIGINAL

Lilia Talarico, M.D., Director
Division of Gastrointestinal and Coagulation Drug Products
Center for Drug Evaluation and Research
Attn: Document Control Room
Office of Drug Evaluation III
Food and Drug Administration
HFD-180, PKLN, 6B-45
5600 Fishers Lane
Rockville, MD 20857



SUPPL NEW CORRESP

**Re: NDA 21-107/S-002; LOTRONEX® (alosetron hydrochloride) Tablets
Response to FDA Request: Labeling**

SLR-002-C

Dear Dr. Talarico:

Please refer to the above New Drug Application (NDA) for LOTRONEX and our labeling supplement (S-002) approved on August 11, 2000. Please also refer to our submissions dated August 11, 2000 providing copies of the final agreed package insert, Medication Guide, Dear Health Care Professional letter, and Dear Pharmacist letter.

During our telephone conversation, earlier today, Mr. Paul Levine of your Division requested that Glaxo Wellcome provide electronic files for the documents provided in the August 11, 2000 submissions. Accordingly, included with this submission we are providing word-processing files (MS WORD 97) for the following documents:

- Final agreed Package Insert.
- Final agreed Medication Guide.
- Final agreed Dear Health Care Professional letter.
- Final agreed Dear Pharmacist letter.

Glaxo Wellcome Research and Development

Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709-3398

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919 483 2100

A Division of
Glaxo Wellcome Inc.

Lilia Talarico, M.D.

August 16, 2000

Page 2

During a review of our records we identified two typographical errors in the Dear Pharmacist Letter provided as Attachment 3 (pages 21 and 22) of our submission of August 11, 2000. The following errors have been corrected:

- Paragraph 1, line 5: The word ~~✓~~ has been replaced with infrequent.
- Paragraph 2, line 1: ~~_____~~ has been replaced with "At the time of approval of..."

Please find attached a copy of the corrected Dear Pharmacist Letter. The electronic file for the corrected letter is provided with the enclosed diskettes.

This submission is provided in duplicate with a desk copy provided to Mr. Paul Levine. A diskette with the word-processing files described above is provided with the archival copy and one desk copy.

If you have any questions regarding this submission, please do not hesitate to contact me (919) 483-3073.

Sincerely,

A handwritten signature in black ink, appearing to read "Mark A. Baumgartner". The signature is fluid and cursive, with a long horizontal stroke extending to the right.

Mark A. Baumgartner, R.Ph.

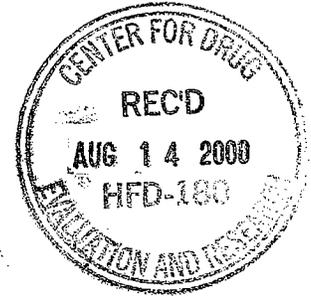
Director

Regulatory Affairs

GlaxoWellcome

August 11, 2000

Lilia Talarico, M.D., Director
Division of Gastrointestinal and Coagulation Drug Products
Center for Drug Evaluation and Research
Attn: Document Control Room
Office of Drug Evaluation III
Food and Drug Administration
HFD-180, PKLN, 6B-45
5600 Fishers Lane
Rockville, MD 20857



Re: NDA 21-107; LOTRONEX® (alosetron hydrochloride) Tablets **SUPPL NEW CORRESP**
Amendment to Pending Supplemental Application: Labeling

Dear Dr. Talarico:

SUR-002-C

Please refer to the above New Drug Application (NDA) for LOTRONEX and our pending supplemental NDA, originally submitted on July 17, 2000, requesting changes to the product labeling. Please also refer to our August 9 and August 10, 2000 amendments to this supplement.

In follow up to the August 11, 2000 teleconference between Glaxo Wellcome and Agency representatives, we are further amending the supplemental application to reflect final changes to the Package Insert (Attachment 1) agreed to during this teleconference.

We are also providing final copies of the Dear Health Care Professional (Attachment 2) and Dear Pharmacist (Attachment 3) letters revised in accordance with the agreements reached at the aforementioned teleconference.

This submission is provided in duplicate with one additional desk copy provided to Mr. Levine. A copy of this information has also been provided to Mr. Levine by fax. Please contact me at (919) 483-3640 if you have questions regarding this submission. Thank you.

Sincerely,

Craig A. Metz
Craig A. Metz, Ph.D.
Director, Regulatory Affairs

Glaxo Wellcome Research and Development

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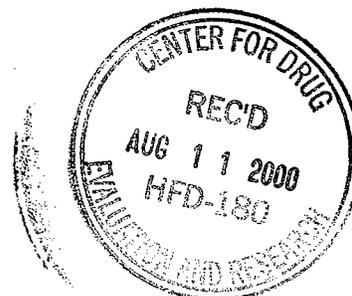
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GlaxoWellcome

August 10, 2000

Lilia Talarico, M.D., Director
Division of Gastrointestinal and Coagulation Drug Products
Center for Drug Evaluation and Research
Attn: Document Control Room
Office of Drug Evaluation III
Food and Drug Administration
HFD-180, PKLN, 6B-45
5600 Fishers Lane
Rockville, MD 20857

SUPL NEW CORRESP



**Re: NDA 21-107; LOTRONEX® (alosetron hydrochloride) Tablets
Amendment to Pending Supplemental Application: Labeling**

~~XXXXXXXXXXXXXXXXXXXX~~
NDA SUPP AMEND

Dear Dr. Talarico:

~~STR-002-BL~~

Please refer to the above New Drug Application (NDA) for LOTRONEX and our pending supplemental NDA, originally submitted on July 17, 2000, requesting changes to the product labeling. Please also refer to our Amendment dated August 9, 2000 and the teleconference between representatives of FDA and Glaxo Wellcome of August 9, 2000. During that teleconference final agreement was reached on the changes to the LOTRONEX package insert and the content of the Medication Guide.

This submission is intended to provide revised labeling that reflects changes agreed during the teleconference of August 9, 2000. From the discussion yesterday, we understand that these changes require final approval by the Agency prior to implementation. It our intention to commence implementation within 30 days of receipt of FDA approval.

We have provided as Attachment 1 the currently approved labeling for LOTRONEX (submitted as FPL on March 14, 2000) with the agreed changes indicated. Attachment 2 provides labeling with our proposed changes incorporated. Attachment 3 provides a copy of the text for the Medication Guide that will appear at the end of the package insert and will also be distributed, in accordance with requirements described under 21 CFR Part 208, as a separate document. The labeling presented in Attachments 2 and 3 is also being provided as word processing files (MS WORD 97).

A description of the approved labeling changes, including replacement of the patient package insert with a FDA approved Medication Guide, will be announced in Dear

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Lilia Talarico, M.D.

August 10, 2000

Page 2

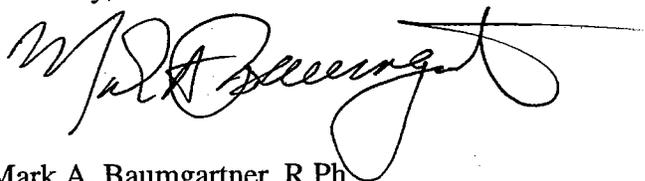
Healthcare Professional and Dear Pharmacist letters. We have previously provided to the Agency copies of the proposed Dear Health Care Professional and Dear Pharmacist letters for review. As agreed yesterday, a teleconference to reach final agreement on the content of the letters is to be scheduled as soon as possible. As previously discussed with you, Glaxo Wellcome intends to begin mailings within 10 working days of FDA approval of the labeling changes.

In our submission of August 9, 2000, Glaxo Wellcome had submitted artwork for packaging changes necessary to reflect the use of a Medication Guide. These packaging changes were discussed and agreed during the teleconference on August 9, 2000. Artwork reflecting the final agreement is provided as Attachment 4. Please note that in order to facilitate implementation and exhaust existing inventory, the following statement regarding the Medication guide will initially be affixed to the sample carton as a non-removable sticker: "Please read important patient Medication Guide inside." Printing of this statement on the carton stock (same color and text) will commence as soon as practicable.

This submission is provided in duplicate with 8 desk copies provided to Mr. Paul Levine. A diskette with the word processing files of labeling, described above, is provided with the archival copy and one desk copy.

If you have any questions regarding this submission please do not hesitate to contact me at (919) 483-3073.

Sincerely,

A handwritten signature in black ink, appearing to read "Mark A. Baumgartner". The signature is fluid and cursive, with a long horizontal stroke extending to the right.

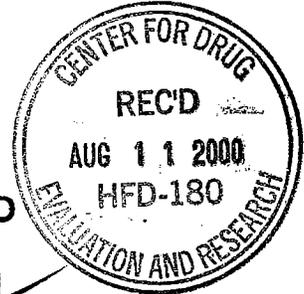
Mark A. Baumgartner, R.Ph.

Director

Regulatory Affairs

August 10, 2000

Lilia Talarico, M.D., Director
Division of Gastrointestinal and Coagulation Drug Products
Center for Drug Evaluation and Research
Attn: Document Control Room
Office of Drug Evaluation III
Food and Drug Administration
HFD-180, PKLN, 6B-45
5600 Fishers Lane
Rockville, MD 20857



NDA SUPP AMEND

SLR 002-BL

**Re: NDA 21-107; LOTRONEX® (alosetron hydrochloride) Tablets
Amendment to Pending Supplemental Application: Labeling**

Dear Dr. Talarico:

Please refer to the above New Drug Application (NDA) for LOTRONEX and our pending supplemental NDA, originally submitted on July 17, 2000, requesting changes to the product labeling. Please also refer to our Amendment to this supplement dated August 9, 2000.

In follow-up to the 10 August 2000 teleconference between Glaxo Wellcome representatives, Dr. Raczowski, Mr. Paul Levine and yourself, we are further amending the supplemental application to reflect final changes to the Package Insert (Attachment 1) and Medication Guide (Attachment 2) agreed to during the aforementioned teleconference.

This submission is provided in duplicate. A fax of this information was also provided to Mr. Levine on 10 August 2000. A diskette containing word processing files of both documents is enclosed.

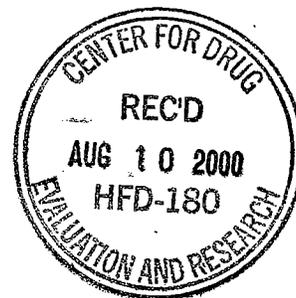
Sincerely,

Craig A. Metz, Ph.D.
Director

GlaxoWellcome

August 9, 2000

Lilia Talarico, M.D., Director
Division of Gastrointestinal and Coagulation Drug Products
Center for Drug Evaluation and Research
Attn: Document Control Room
Office of Drug Evaluation III
Food and Drug Administration
HFD-180, PKLN, 6B-45
5600 Fishers Lane
Rockville, MD 20857



NDA SUPP AMEND

SR-002-BL

**Re: NDA 21-107; LOTRONEX® (alosetron hydrochloride) Tablets
Amendment to Pending Supplemental Application: Labeling**

Dear Dr. Talarico:

Please refer to the above New Drug Application (NDA) for LOTRONEX and our pending supplemental NDA dated July 17, 2000 requesting changes to the product labeling. Please also refer to your letter dated August 4 and your telefacsimile (fax) transmissions of July 26, 27, 28, and August 2, 2000. In response to these communications we have submitted to you our letter dated July 28, 2000 and provided information in our fax of August 4, 2000.

We note that in your letter dated August 4, 2000 FDA has notified Glaxo Wellcome that a Medication Guide will be required for LOTRONEX. During teleconferences held between representatives of FDA and Glaxo Wellcome on August 4 and 7, 2000, representatives of FDA and Glaxo Wellcome discussed and reached substantive agreement on changes to be made to the LOTRONEX package insert as well as the content of the Medication Guide. This submission is intended to reflect these changes which require final agreement by the Agency. In addition, we are providing for your review, copies of the current draft Dear Health Care Provider letters and artwork for packaging changes necessary to reflect the use of a Medication Guide.

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Lilia Talarico, M.D.

August 9, 2000

Page 2

Labeling: Package Insert and Medication Guide

In the Package Insert (PI) provided as Attachment 1:

- We understand that we have agreement on the text of the CONTRAINDICATIONS section.
- We understand that we have agreement on the WARNINGS section.
- Under PRECAUTIONS: Information for Patients: We understand that we need to reach agreement on the text for lines 210 through 215. As discussed on August 7, we have proposed text that is consistent with the corresponding language mutually agreed for the Medication Guide.
- We understand that we have reached agreement on the ADVERSE REACTIONS section.
- We understand that we have reached agreement on the DOSAGE AND ADMINISTRATION section. As discussed on August 7, this section was changed to reflect the language mutually agreed for the WARNINGS section.

We need to reach final agreement on the text of the Medication Guide. The draft Medication Guide provided as Attachment 2 has been modified in accordance with our discussions on August 7, 2000:

- Lines 16 through 21 reflect Glaxo Wellcome acceptance of FDA's proposed statement regarding IBS and surgery and agreement on text regarding the need for an assessment of benefits and risks prior to prescribing.
- We need to confirm agreement on the language on lines 25 through 27. We have taken the agreed language _____ We believe this reads more clearly and retains agreed language regarding frequency.
- As suggested by FDA, we have attempted to improve the flow of the text on lines 31 through 38. We have intended to retain the language mutually agreed _____ Accordingly, we need to reach agreement on the acceptability of the proposed order and text.
- Lines 47 and 48 reflect agreed changes.
- Lines 55 through 59: After reviewing other Medication Guides, _____ In view of the concerns expressed by FDA, _____ We believe this information is helpful and informative to patients.

- Lines 63 through 65 provide the language mutually agreed. After further internal discussion, we would like to offer and obtain your agreement on the / _____ /

- The bullets on lines 89 through 91 need agreement. We have modified these statements to reflect our discussion on August 7. / _____ /
/ _____ /
/ _____ /
/ _____ /

_____ should be deleted.

- We need to reach agreement on lines 107 through 130. In accordance with your suggestion. / _____ /
/ _____ /
/ _____ /
/ _____ /

“What are the possible side effects of LOTRONEX?”

“Constipation is the most common side effect of LOTRONEX. A few patients may develop serious intestinal side effects. A description of these side effects, how to identify them, and what action to take if you experience them, is provided above in / _____ /

_____ refer to the information regarding constipation and ischemic colitis in that section.”

- We plan to print the Medication Guide in accordance with the requirements for text size and prominence described under 21 CFR Part 208. Our current plan is to print the Medication Guide in _____ to add to prominence and set apart as distinct from the PPI. The Medication Guide text will appear at the end of the Package Insert but will also be provided as a separate document affixed or enclosed with the product packaging. Additional copies will also be provided to health care providers/dispensers. Our intention is to implement changes to the labeling (including distribution of a Medication Guide) within 30 days of FDA approval of our pending supplement. As we have previously proposed, in order to expedite availability of the revised labeling, with FDA agreement, we would be willing to pursue / _____ /

Lilia Talarico, M.D.

August 9, 2000

Page 4

Labeling: Packaging Changes

In Attachment 3 we have provided the artwork for proposed package labeling changes that reflect the Medication Guide. We intend to exhaust inventory in stock by reworking it to remove the old PI and add the new PI with a separate Medication Guide. A sticker will be affixed to the cap directing the dispenser to provide the Medication Guide.

Dear Health Care Professional Letters

We have revised the previously provided Dear Health Care Professional Letters to be consistent with the proposed labeling changes described above. These documents can be found as Attachments 4 and 5. As discussed, we intend to initiate mailing within 10 working days of approval of the labeling changes by FDA.

This submission is provided in duplicate with 8 desk copies provided to Mr. Paul Levine. If you have any questions regarding this submission please contact me at (919) 483-3073.

Sincerely,

A handwritten signature in black ink, appearing to read "Mark A. Baumgartner", with a long horizontal line extending to the right.

Mark A. Baumgartner, R.Ph.

Director

Regulatory Affairs

SLR.

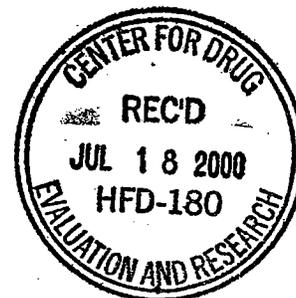
GlaxoWellcome

NDA NO. 21-107 REF. NO. 002

NDA SUPPL FOR SLR Labeling

July 17, 2000

Lilia Talarico, M.D., Director
Division of Gastrointestinal and Coagulation Drug Products
Center for Drug Evaluation and Research
Attn: Document Control Room
Office of Drug Evaluation III
Food and Drug Administration
HFD-180, PKLN, 6B-45
5600 Fishers Lane
Rockville, MD 20857



ORIGINAL

**Re: NDA 21-107; LOTRONEX® (alosetron hydrochloride) Tablets
Supplemental Application: Labeling**

Dear Dr. Talarico:

Please refer to the above New Drug Application (NDA) for LOTRONEX® Tablets that was approved on February 9, 2000. Please also refer to the telephone facsimile transmission (fax) of July 14, 2000 (dated July 13, 2000) from Mr. Paul Levine containing a request by your Division that Glaxo Wellcome submit an official labeling supplement to include the proposed labeling changes previously submitted by Glaxo Wellcome in correspondence dated June 21, 2000.

In response to the Agency's request, Glaxo Wellcome is submitting this supplemental NDA requesting changes to the approved labeling for LOTRONEX. The proposed changes to the approved labeling provided in this submission reflect previous interactions between the Agency and Glaxo Wellcome. The specific changes proposed are identical to those proposed in our correspondence dated June 21, 2000. In addition, we have also accepted changes to the **INDICATIONS AND USAGE** and the **WARNINGS** sections of the labeling, suggested in your fax of July 14, 2000. Accordingly, we have incorporated the most recent FDA suggested changes in the enclosed proposed labeling for which we are seeking approval.

For convenience of review, we have provided a copy of your July 14, 2000 fax as Attachment 1. We have provided as Attachment 2 the approved labeling (submitted as FPL on March 14, 2000) with our changes indicated. Attachment 3 provides labeling with our proposed changes incorporated. Both versions of the Glaxo Wellcome proposed labeling are also provided as a word processing files (MS WORD 97).

Glaxo Wellcome Research and Development

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Glaxo Wellcome Inc.

Lilia Talarico, M.D.

July 17, 2000

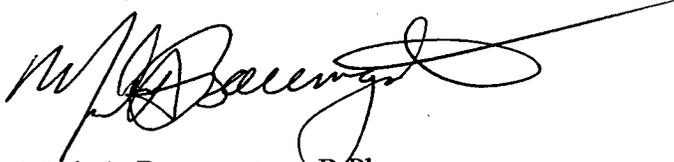
Page 2

We note that your fax of July 14, 2000 also included a request for Glaxo Wellcome to submit a current risk management plan. We are presently updating the risk management plan submitted on June 14, 2000 to reflect discussion at the June 27, 2000 FDA Gastrointestinal Drugs Advisory Committee Meeting. Included with the updated risk management plan will be estimated targets for completion of activities. We will also provide estimates for the availability of draft protocols for which FDA input will be requested. Our goal is to submit the updated risk management plan to NDA 20-107 and IND () Friday July 21, 2000.

This submission is provided in duplicate with 8 additional desk copies to Mr. Paul Levine, Jr. Also provided with the archival copy as well as one desk copy, is a diskette containing word processing files for the proposed labeling presented in Attachments 2 and 3.

If you have any questions regarding the contents of this submission, please do not hesitate to contact me at (919) 483-3073.

Sincerely,

A handwritten signature in black ink, appearing to read 'Mark A. Baumgartner', with a long horizontal flourish extending to the right.

Mark A. Baumgartner, R.Ph.

Director

Regulatory Affairs