# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*
**NDA 21-107/S005**

**APPROVAL LETTER**

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-107/S-005

GlaxoSmithKline
Attention: Olivia Pinkett, Ph.D.
Product Director, Regulatory Affairs
P.O. Box 13398
Five Moore Drive
Research Triangle Park, North Carolina 27709-3398

Dear Dr. Pinkett:

Please refer to your supplemental new drug application dated December 7, 2001, received December 7, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lotronex (alosetron hydrochloride) Tablets, 1 mg. We acknowledge receipt of your submissions dated January 16, 30, and 31; February 1 and 27; March 1 and 22; April 9 and 30, 2002; May 15 and 20, 2002; and June 3, 5, and 6, 2002.

Lotronex was originally approved February 9, 2000, and, subsequently, you voluntarily withdrew the drug from the market after you received reports of ischemic colitis and severe complications of constipation associated with use of the drug. This supplemental application, considered for approval under 21 CFR 314, Subpart H at your request, narrows the original approved indication to use of the drug in a population for whom the benefits of the drug may outweigh the risks and provides for a risk management program.

This supplemental application provides for the use of Lotronex 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

We have completed our review of this supplemental application, as amended, and have concluded that adequate information has been presented to approve a supplemental application for Lotronex (alosetron hydrochloride) Tablets, 1 mg, under 21 CFR 314 Subpart H. You have indicated your agreement with approval under restricted conditions. Accordingly, this supplemental application is approved under 21 CFR 314, Subpart H. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of all FDA regulations and the specific restrictions on distribution and use described below.

*Lotronex Risk Management Program*

We remind you that your Lotronex Risk Management Program is an important part of the postmarketing risk management for Lotronex, and must include each of the following components:

1. Enrollment of qualified physicians in a physician prescribing program.

2. Implementation of a program to educate physicians, pharmacists and patients about the risks and benefits of Lotronex.

3. Implementation of a reporting and collection system for serious adverse events associated with the use of Lotronex that complies with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

4. Implementation of a plan to evaluate the effectiveness of the Lotronex risk management program.

The Lotronex Risk Management Program, as described in the attached documents, adequately addresses each of these requirements. Any changes to the program must be discussed with FDA prior to its institution and is subject to FDA approval. We expect your continued cooperation to resolve any problems regarding the Lotronex Risk Management Program that may be identified following approval of this supplement.

Within the first year of the initiation of the risk management program, and annually thereafter, you must provide FDA with a report under 21 CFR 314.81(b)(2) that describes how each element of the program has been implemented, provides implementation data, and evaluates the success of the program using, among other available data, the studies described in the attached Risk Management Program and post marketing commitments #7 and #8 below.

We remind you of your specific reporting obligations regarding serious adverse events in patients who have received Lotronex. As set forth in the attached document, in addition to the usual postmarketing reporting of adverse drug experiences (21 CFR 314.80 (c)), you will initiate a 15-day report for each of the following:

- All spontaneous reports of ischemic colitis
- All spontaneous reports involving ischemic changes, ischemia, or necrosis of the colon
- All spontaneous reports involving constipation requiring hospitalization or emergency room visit
- All spontaneous reports involving possible complications of constipation such as obstruction, perforation, intestinal ulceration, toxic megacolon, ileus, or impaction resulting in hospitalization or emergency room visit
- All spontaneous reports of death, regardless of causality

*Post Marketing Commitments*

You have committed to conduct postmarketing studies, specified in your submissions dated June 3 and 6, 2002, that are listed below. The commitments listed below replace all previous postmarketing study commitments associated with the original NDA.

1. Conduct a randomized, double-blind, placebo-controlled study in women with severe diarrhea-predominant IBS to determine efficacy and safety of lower doses of Lotronex. The doses to be studied are: 0.5mg QD, 1mg QD, 1mg BID and placebo.

   Protocol Submission: August 2002
   Study Start: First Quarter 2003
   Final Report Submission: Fourth Quarter 2005

2. Conduct a randomized, blinded, dose-titration study in women with severe diarrhea-predominant IBS to determine efficacy and safety "as needed" (prn) dosing of Lotronex. The study arms are: 0.5mg tablets (0-4 tablets) prn vs. placebo prn; and, 1mg BID continuous dosing vs. placebo BID continuous dosing.

   Protocol Submission: August 2002
   Study Start: First Quarter 2003
   Final Report Submission: Fourth Quarter 2005

3. Obtain blood samples prospectively in patients enrolled in at least the studies described under commitments #1 and #2 above, to allow DNA analysis to 1) identify SNPs or haplotypes that predict adverse events in patients who develop ischemic colitis and 2) determine genotype of polymorphic CYP enzymes (CYP 1A2 and 2C9) responsible for Lotronex metabolism.

Protocol Submission: August 2002
Study Start: First Quarter 2003
Final Report Submission: Second Quarter 2006

4. Propose and conduct mechanistic studies to investigate the pathophysiologic etiology of Lotronex-induced ischemic colitis and small bowel ischemia.

   Protocol Submission: September 2002
   Study Start: Fourth Quarter 2002
   Final Report Submission: First Quarter 2004

5. Conduct protocol #S3B10946 entitled, "An open-label, parallel-group, pharmacokinetic and tolerability study of a single 1mg dose of alosetron in hepatically-impaired subjects and in healthy control subjects," as amended on October 25, 2001.

   Protocol Submission: September 2002
   Study Start: Second Quarter 2003
   Final Report Submission: Second Quarter 2005

6. Conduct a pharmacokinetic drug-drug interaction study to evaluate the effect of administration of fluvoxamine, 100mg BID and ketoconazole 200mg BID (7 days of dosing) on the pharmacokinetics of a single dose of 1mg Lotronex in at least 12 healthy females.

   Protocol Submission: September 2002
   Study Start: First Quarter 2003
   Final Report Submission: Third Quarter 2003

7. Conduct a study to periodically (at least quarterly) compare prescribing of physicians enrolled in the prescribing program for Lotronex with all Lotronex prescribing identified in a general prescription data base (e.g., IMS). GlaxoSmithKline and FDA will review the study findings and agree to educational and/or other activities that may be needed to address observations.

   Protocol Submission: September 2002
   Study Start: First Quarter 2003
   Final Report Submission: June 2009

8. Conduct the study as submitted on May 15, 2001, amended June 3, 2002, entitled, "An Epidemiologic Program for the Study of the Safety and Utilization of Lotronex in Medical Practice in the U.S." to 1) evaluate compliance with use of the Patient-Physician Agreement form as a means to ensure patients have severe diarrhea-predominant IBS and been counseled on the risks and benefits of Lotronex, 2) examine appropriate use of Lotronex 3) survey patient knowledge and understanding about the risks of Lotronex, 4) monitor serious gastrointestinal adverse events and deaths associated with Lotronex use, as well as estimate risks associated with long-term use of Lotronex, and 5) evaluate risk factors for serious gastrointestinal adverse events. GlaxoSmithKline and FDA will review study findings and agree to educational and/or other activities that may be needed to address observations.

   Protocol Submission: September 2002
   Study Start: First Quarter 2003
   Final Report Submission: June 2009

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final study reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

Pursuant to 21 CFR Part 208, based on postmarketing information and information provided in this supplemental application, FDA has determined that Lotronex poses a serious and significant public health concern requiring distribution of a Medication Guide. This Medication Guide is necessary for patients' safe and effective use of Lotronex. FDA has determined that Lotronex is a product that has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use Lotronex. In addition, patient labeling could help prevent serious adverse events related to constipation.

The final printed labeling (FPL) must be identical to the enclosed agreed upon labeling text submitted on June 5, 2002, for the Product Information insert, Medication Guide, Patient-Physician Agreement form, and Physician Attestation form; and identical to the immediate container and carton labels submitted on May 20, 2002. Marketing the product with FPL with text that is not identical to the agreed upon approved text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-107**." Approval of this submission by FDA is not required before the labeling is used.

Under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement. Submit all proposed materials in draft or mock up form, not final print. Send one copy to the Division of Gastrointestinal and Coagulation Drug Products and two copies of both the promotional materials and the labeling directly to:

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

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens must contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (21 CFR 314.55).

Based on postmarketing experience and the information submitted in this supplemental application, we do not believe it is appropriate to conduct studies in pediatric patients at this time. Therefore, under 21 CFR 314.55, we are deferring submission of studies for pediatric patients of all ages because such studies should be delayed until additional safety and effectiveness data have been collected and reviewed. If, at a later date, we determine that pediatric studies are necessary or appropriate, we will notify you.

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

Sincerely,

*{See appended electronic signature page}*

Florence Houn, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

LOTRONEX RISK MANAGEMENT PROGRAM

A. Prescribing Program

1. GlaxoSmithKline will enroll in a prescribing program physicians who meet all of the following qualifications:

   i. Ability to diagnose and treat IBS.
   ii. Ability to diagnose and manage ischemic colitis.
   iii. Ability to diagnose and manage constipation and the complications of constipation.
   iv. Understand the risks and benefits of Lotronex treatment for severe diarrhea-predominant IBS, including the information in the package insert, Medication Guide, and Patient-Physician Agreement.

   Physicians may self-attest to meeting these prescribing qualifications. GlaxoSmithKline's receipt of the physician attestation form will precede distribution of Lotronex prescribing materials to the physician.

2. GlaxoSmithKline will enroll in the prescribing program physicians who agree to do each of the following:

   i. Educate patients about the risks and benefits of Lotronex therapy and give each patient a copy of the Medication Guide.

      The Patient-Physician Agreement form will be used to demonstrate that physicians fulfill this responsibility. Physicians who prescribe Lotronex will be asked to agree to obtain the patient's signature on the form, co-sign the form, place the original signed form in the patient's medical record, and give a copy to the patient.

   ii. Report serious adverse events to GlaxoSmithKline or to the Food and Drug Administration's MedWatch Program.

   iii. Participate in a system that will identify for pharmacists the physicians who are enrolled in the GlaxoSmithKline Lotronex prescribing program

3. GlaxoSmithKline will provide a way for patients and pharmacists to identify physicians that are enrolled in the Lotronex prescribing program.

   i. GlaxoSmithKline has proposed to supply stickers to enrolled physicians who will affix them to all their Lotronex prescriptions (i.e., original and all subsequent refill prescriptions) so that pharmacists can identify that prescriptions were written by physicians enrolled in the program.

   ii. GlaxoSmithKline will have a process to facilitate patient access to enrolled physicians.

B. Educational Program

GlaxoSmithKline will implement a program to educate physicians, pharmacists, and patients about the risks and benefits of Lotronex. This program will contain each of the following:

1. Educational opportunities will be provided to physicians to obtain prescribing qualifications and to carry out physician responsibilities under the Lotronex prescribing program as stated in the Physician Attestation form.

2. Pharmacists will be educated about the risks and benefits of Lotronex, information in the approved labeling (including the package insert and the Medication Guide), the program for verifying prescriptions were written by physicians enrolled in the Prescribing Program for Lotronex, recommendations that they not accept telephone, facsimile, or computerized prescriptions for Lotronex, and dispensing of the Medication Guide.

3. Patients will be educated on the risks associated with the use of Lotronex, the signs and symptoms of ischemic colitis and constipation that could lead to serious consequences, and Lotronex's approved indication.

4. The following materials will be submitted to FDA for review and comment by October 30, 2002: educational materials for physicians; educational plan and materials for pharmacists; educational plan and materials for patients.

C. Adverse Event Reporting:

GlaxoSmithKline will implement a reporting and collection system for serious adverse events associated with the use of Lotronex that complies with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81). Under 21 CFR 314.80(c), the following will be submitted to FDA as 15-day reports, and a summary and discussion of the clinical significance of these events will be provided in the periodic report:

- All spontaneous reports of ischemic colitis
- All spontaneous reports involving ischemic changes, ischemia, or necrosis of the colon
- All spontaneous reports involving constipation requiring hospitalization or emergency room visit
- All spontaneous reports involving possible complications of constipation such as obstruction, perforation, intestinal ulceration, toxic megacolon, ileus, or impaction resulting in hospitalization or emergency room visit
- All spontaneous reports of death, regardless of causality

D. Risk Management Evaluation

GlaxoSmithKline will implement a program to evaluate the effectiveness of the overall risk management program in assuring that Lotronex is used safely. This information will allow the Agency to assess, on an ongoing basis, whether Lotronex continues to be safe for use under the conditions of use upon which Lotronex is being approved. The program will include each of the following elements:

1. A study to evaluate whether physicians not enrolled in the Lotronex prescribing program are writing prescriptions and whether pharmacists are filling prescriptions written by physicians not enrolled in the program.

2. A study to evaluate the effect of the Lotronex Risk Management Program on use of Lotronex by patients with severe diarrhea-predominant irritable bowel syndrome, patient knowledge of risks of Lotronex, and frequency of serious gastrointestinal adverse events and death associated with Lotronex.

3. An annual report, submitted in accordance with 21 CFR 314.81(b)(2), beginning with the submission (within the first year of initiation of the risk management program) of the annual report under that regulation, that describes how each element of the program has been implemented, provides implementation data, and evaluates the success of the program using, among other available data, the studies described in paragraphs D1 and 2 above.

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/s/

Florence Houn
6/7/02 09:47:27 AM

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

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# LABELING

# LOTRONEX®

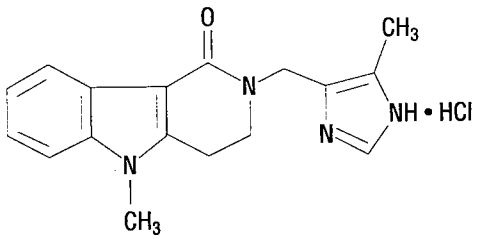
**(alosetron hydrochloride)**
**Tablets**

**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: $C_{17}H_{18}N_4O \cdot HCl$, representing a molecular weight of 330.8. Alosetron is a white to beige solid that has a solubility of 61 mg/mL in water, 42 mg/mL in 0.1M hydrochloric acid, 0.3 mg/mL in pH 6 phosphate buffer, and <0.1 mg/mL in pH 8 phosphate buffer. The chemical structure of alosetron is:

**LOTRONEX® (alosetron hydrochloride) Tablets**




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.

**Pharmacokinetics:** The pharmacokinetics of alosetron have been studied after single oral doses ranging from 0.05 mg to 16 mg in healthy men. The pharmacokinetics of alosetron have also been evaluated in healthy women and men and in patients with IBS after repeated oral doses ranging from 1 mg twice daily to 8 mg twice daily.

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

***Food Effects:*** Alosetron absorption is decreased by approximately 25% by co-administration with food, with a mean delay in time to peak concentration of 15 minutes (see DOSAGE AND ADMINISTRATION).

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

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

Renal elimination of unchanged alosetron accounts for only 6% of the dose. Renal clearance is approximately 94 mL/min.

Alosetron is extensively metabolized in humans. The biological activity of these metabolites is unknown. A mass balance study was performed utilizing an orally administered dose of unlabeled and $^{14}$C-labeled alosetron. This study indicates that on a molar basis, alosetron metabolites reach additive peak plasma concentrations 9-fold greater than alosetron and that the additive metabolite AUCs are 13-fold greater than alosetron's AUC. Plasma radioactivity declined with a half-life 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.

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 Criteria[1] 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

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.

- 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

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 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.

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$^{\pm}$) forward gene mutation test, the human lymphocyte chromosome aberration test, the ex vivo rat hepatocyte unscheduled DNA synthesis (UDS) test, or the in vivo rat micronucleus test for mutagenicity. Alosetron at oral doses up to 40 mg/kg/day (about 160 times the recommended daily human dose based on body surface area) was found to have no effect on fertility 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 needed.

**Nursing Mothers:** Alosetron and/or metabolites of alosetron are excreted in the breast milk of lactating rats. It is not known whether alosetron is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when LOTRONEX is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use:** 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 ($p<0.0001$).

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

| Body System<br>Adverse Event | LOTRONEX<br>1 mg B.I.D.<br>(n = 8,328) | Placebo<br>(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

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.

***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

- 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).

**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
Research Triangle Park, NC 27709

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(Date of issue) RL-

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**NDA 21-107/S005**

# MEDICAL REVIEW

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

| | |
|---|---|
| **NDA:** | **NDA 21-107/S-005** |
| **Applicant:** | **GlaxoSmithKline** |
| **Drug:** | **LOTRONEX (alosetron)** |
| **Pharmacological Category:** | **5HT$_3$ Receptor antagonist** |
| **Material Reviewed:** | **Supplemental NDA 21-107/SE8-05** |
| **Purpose of Review:** | **Labeling Revision** |
| **Reviewer:** | **Scheldon Kress, M.D.** |
| **Date Submitted:** | **May 3, 2002** |

**Labeling Revision**

**Executive Summary**

The goal for possible reintroduction of alosetron remains to design a Risk Management Program-Restricted Distribution Plan (RMP-RDP) under the provisions of 21CFR 314 Subpart H that will optimize benefits and minimize risks. This review provides for several important modifications to the Lotronex labeling approved August 2000.

Several approaches are discussed to optimize the benefit/risk balance. These include:

- Reduced initial dosing.
- Discontinuation of drug in non-responders
- Limitation of use to severely affected diarrhea-predominant IBS patients
- Stopping use of the drug at the onset of constipation (absence of bowel movement, hard, difficult, or painful evacuation)

An attempt is made to elucidate the potential benefit of each component of the proposed modification in the professional labeling, i.e., delineating each component's contribution to minimizing the occurrence of these SAEs of special interest

Significant modifications are also made to the Package Insert and Medication Guide to increase their emphasis on safety issues.

Attestation of the restricted distribution only for female patients with severe diarrhea-type IBS is provided for all three documents: package insert, Medication Guide, and Patient-Physician Agreement,

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## I. Introduction

The purpose of this review is to provide an evaluation of risks and benefits to individual patients and to the public health related to the treatment with alosetron

of women with diarrhea-predominant IBS. GlaxoSmithKline introduced alosetron to the US market on March 13, 2000 following approval of NDA 21-107 on February 9, 2000. As a result of concerns arising from post-marketing reports of serious adverse events and deaths associated with complications of constipation and ischemic colitis, label changes were implemented. However, serious adverse events (SAEs) and deaths continued to occur as shown in Table 1.

**Table 1**
**Lotronex-Associated Serious Adverse Events**

| Selected Outcomes | Ischemic Colitis | Serious Complications of Severe Constipation |
|---|---|---|
| **Pre-Approval** (Nov, 1999) | | |
| **Cases** | **4** | **1** |
| **Hospitalization** | **4** | **1** |
| **Surgery** | **None** | **None** |
| **Death** | **None** | **None** |
| **Randomized Clinical Trial Experience** (December 7, 2001) | | |
| **Cases** | **18** | **11** |
| **Hospitalization** | **7** | **10** |
| **Surgery** | **1** | **1** |
| **Death** | **None** | **None** |
| **ODS Post-Marketing Safety Review** (Data as of December 31, 2001) | | |
| **Cases** | **85** | **107** |
| **Hospitalization** * | **52** | **78** |
| **Surgery** * | **9** | **30** |
| **Death** ‡ * | **2** | **2** |

‡ Three additional deaths (for a total of 7) demonstrated suggestive evidence of alosetron causality, but did not fit in the these categories ( 2 cases of small bowel ischemia and 1 case of necrosis of esophagus, stomach, and small bowel).
* These incidents may be included in multiple categories, therefore, can not be added together to equal the total.

Negotiations continued through November 2000 between the Sponsor and the FDA in an attempt to reduce the risk of SAEs to patients. The FDA assessment of the overall risk-benefit could not justify continued market

availability from a public health perspective without implementation of restricted distribution. This was unacceptable to the Sponsor. As a result, on November 28, 2000, the sponsor made the decision to withdraw alosetron from the US market and did not consider making the drug available to severely affected patients under an IND a viable option.

Subsequent to the withdrawal of alosetron both patients, physicians, and advocacy groups have requested that GlaxoSmithKline and FDA reconsider the withdrawal of alosetron. Discussions between GlaxoWellcome (now GlaxoSmithKline (GSK)) and FDA ensued to re-evaluate the risk-benefit of alosetron, taking into consideration a substantial new body of safety and efficacy data. These data arose from the ongoing clinical and epidemiological studies that were completed post-approval or terminated prematurely at the time of the withdrawal. FDA and GSK agreed to work cooperatively to: (1) further characterize the efficacy and safety profiles, (2) re-assess the benefits versus risks and (3) renew the effort to design an appropriate risk-management restricted-distribution program that could allow the return of alosetron to the market for appropriate and informed patients in a safe and effective manner.

The safety review of the results of Randomized Clinical Trials (RCT) submitted in the sNDA 21-107 of December 7, 2001 evaluated 11,874 patients treated with alosetron. Among the SAEs of special interest that occurred among alosetron-treated patients were 18 cases of ischemic colitis and 11 serious complications of severe constipation. By contrast, the RCT experience revealed one placebo-treated patient who developed ischemic colitis and three placebo-treated patients who developed serious complications of severe constipation.

The objectives of this review are to assess labeling revisions for improving the Benefit/Risk balance for individual patients. As part of the proposed Risk Management Plan for market re-introduction of alosetron, there is a mandate to reduce the incidence and severity of the observed SAEs. The goals of this labeling revision are to: 1.) to minimize risk and severity of serious adverse events, 2.) to optimize benefits, 3.) to optimize the benefit/risk balance.

**Higher SAE Occurrence During First Four Weeks of Therapy**

Based on multiple analyses[1] from the randomized clinical trials, an increased occurrence of the SAEs of special interest was observed during the first 4 weeks of therapy with alosetron:

- 11 of the 18 cases of ischemic colitis
- 5 of the 11 cases of serious complications of severe constipation (SCSC)
- 16 of the 28 cases of these SAEs of special interest

Many study-related factors may have impacted on the timing of the initiation and distribution of these observed SAEs. Included among the more important items are:

- The total number of patients treated for 4 weeks or less was substantially greater than those treated for longer periods of time. Therefore, incidence rates of the event, as a function of time, would need to be corrected by the total number of patients treated at a specified period,
- Nonetheless, the highest number of patients exposed to the drug occurred at the onset of each study (approaching 100%).
- The duration of the studies was variable (6 weeks to 1 year).
- Significant patient withdrawal occurred prior to completion of these studies (as high as 30 percent)
- the premature termination of some of the studies

## II. Labeling Revisions For Improving Benefit/ Risk Balance

### 1. Potential Benefits of A Reduced Starting Dose

The number of patients experiencing these SAEs may be small. However, the marked severity of some of the cases is reason for alarm, when one considers that this drug is for symptomatic treatment of IBS, a condition that does not usually require surgery and is never associated with mortality. Ischemic colitis occured without prodromata in an unpredictable manner. Currently, we have very limited ability to predict those individuals most susceptible to develop ischemic colitis and thus prevent its occurrence. However, it seems reasonable to assume[2] that administration of a reduced dosage over the first four weeks of therapy

[1] Presentations by the sponsor and FDA to the Gastrointestinal Advisory Committee on April 23, 2002.

[2] Concurrence of the members of the Gastrointestinal Advisory Committee with those of the sponsor and FDA (April 23, 2002) on the advisability of initiating therapy with a reduced dose for the initial four weeks.

may diminish the frequency and/or severity of the ischemic colitis and/or severity of serious complications of severe constipation that would occur?

This approach of treating a patient for four weeks at a reduced dosage, i.e. 1 mg QD, re-assessing safety and efficacy at the end of this period of time, and proceeding with an intervention based on these results, offers opportunities for improving the Benefit/Risk balance..

**2. Efficacy After Four Weeks of Therapy As A Predictor of Therapeutic Response**

Efficacy data from the pre-approval studies suggest that the response at 4 weeks is a good predictor of response at the overall 12 weeks of treatment. Therefore, from the efficacy viewpoint, a reasonable approach is that, if no beneficial response is observed at the end of 4 weeks of therapy at the approved dosage of 1 mg BID, the drug should be discontinued. Continuation of the drug past that period may expose the patient to increasing potential risk of SAEs, while at the same time, diminishing the possibility of benefit. Thus, **discontinuation of the drug in non-responders is an important mechanism for minimizing risk.**

A drawback to the four week reduced initial treatment approach is that reducing the dose during the first four week trial may only "delay" the onset of these undesirable SAEs until the time that the full dose is administered 4 weeks later ("move the curve to the right"). Likewise, patients that appear to tolerate half the recommended daily dose well, but in whom the drug is not beneficial, may have to endure a longer trial exposure before determining that the drug will not improve their IBS symptoms.

The available information does not seem to indicate that ischemic colitis is dose related, but for constipation, a definite dose-related response has been repeatedly confirmed. In clinical trials, constipation was reported in approximately 30% of patients taking alosetron 1 mg BID and in 11% of patients taking alosetron 0.5 mg BID. Constipation made up fifty percent of the spontaneous adverse events reported. Therefore, it can be assumed that those **patients who develop constipation [or evidence suggestive of ischemic colitis] during this trial of therapy on the reduced dosage and in whom the drug is stopped, may benefit from developing an adverse event on lesser drug (the AE could be milder) and may be prevented from longer-term exposure to a larger dose of drug (the SAE could be more severe).** Although this strategy may only minimally reduce the overall incidence rates of these AEs and SAEs, reduction in severity may be clinically significant. The impact might be particularly important to those who would have experienced SAEs like those observed

post-marketing, i.e., major lifestyle inconveniences, the requirement for medical attention, hospitalization, surgery, and transfusions, and even life-threatening sequelae.

What could be anticipated from this approach, is that more patients will take the drug for 1 to 2 months; some are expected to withdraw due to constipation and fewer patients might withdraw due to symptoms suggestive of ischemic colitis in those first 1 to 2 months. The expectation based on these assumptions, is that those patients safely withdrawn at this lower dose were being protected from more severe SAEs had they taken the full dosage. Thus, the potential benefits support the proposed approach.

The following schemata has been designed as a "how to manage strategy" for the most likely therapeutic scenarios ( Table 2).

Table 2

**Schemata For Reducing The Incidence And Severity Of Alosetron-Associated SAEs of Special Interest**

| Initiate Trial Therapy During First 4 Weeks | Evaluation During And At End of Initial Trial Period | Dosage Adjustment Intervention After 4 Weeks | Dosage Adjustment Intervention After 8 Weeks |
|---|---|---|---|
| Alosetron 1 mg QD | No Constipation<br>Neither Rectal Bleeding[a] nor Suggestion of Ischemic Colitis | Increase Dosage to 1 mg BID and Re-evaluate during next 4 Weeks | Clinical Benefit Continue |
| | No Clinical Benefit | | No Clinical Benefit, Rectal Bleeding[a] or Suggestion of Ischemic Colitis<br>Discontinue Therapy |
| | No Constipation<br>No Rectal Bleeding[a] or Suggestion of Ischemic Colitis<br>Clinical Benefit | Continue Therapy at 1 mg QD | |
| | Constipation<br>Rectal Bleeding[a] or Suggestion of Ischemic Colitis | Discontinue Therapy | |

[a] Not explained by "specific sources" such as perianal or hemorrhoidal bleeding

This schemata for reducing the severity and perhaps the incidence of the alosetron-associated SAEs of special interest should contribute to reducing the risk of SAEs by promptly **stopping the drug in those patients prone to constipation, more susceptible to 'unexplained" rectal bleeding or ischemic colitis, and for whom the drug has demonstrated no clinical benefit.** GlaxoSmithKline has essentially agreed with this approach.[3]

### 3. Potential Benefits From Only Treating Severely Affected Patients

At the time of withdrawal, the Benefit/Risk balance seemed to be unfavorable; the MedWatch program was receiving SAEs in increasing numbers and severity including the necessity for major abdominal surgery and resultant deaths. Based on the pre-approval 3 month alosetron studies, the risk for alosetron-associated ischemic colitis was estimated at 1/700 (95% CI, 1/100-1/1000). Alosetron was taken for up to 6 months in Protocol S3B30020, and 10 cases of ischemic colitis were reported among 1817 patients (an incidence of approximately 1/200).

In the pre-approval trials, most of the IBS patients manifested only mild to moderate diarrhea. Thus, the question was raised, what benefit could be expected from the more severely affected diarrhea-predominant patients.

As part of the review of the randomized clinical trials, post-hoc analysis of the two so-called "urgency studies," revealed that in Protocols S3B30011 and S3B40031 alosetron 1 mg BID demonstrated significant therapeutic benefit among the more severely symptomatic IBS patients. Patients with 'severe' urgency (urgency present on at least 70% of days) experienced greater therapeutic benefit (satisfactory control of urgency on greater than 75% of days [therapeutic gain 18-19% greater than with placebo]) and possibly lesser likelihood of constipation-associated AEs than less severely symptomatic patients. In Protocol S3B30011, but not in S3B40031, the need for withdrawal of alosetron due to constipation was slightly reduced.

Of course, these suggestive findings were based on small samples of patients and will require replication within a larger study. However, it seems reasonable to speculate that **limiting the use of alosetron to severely affected IBS patients may contribute to optimizing the benefit/risk balance.**

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[3] In their Summary of Benefits and Risks Section (page 34) and in their proposed changes to the labeling (lines 444 to 452) of the December 7, 2001 sNDA. At the Gastrointestinal Advisory Committee Meeting (April 23, 2002) the sponsor proposed dispensing of only 30 day supplies of alosetron initially.

**4. Potential Benefits From Limited Access**

As the possibility of re-introduction of alosetron into the marketplace is under intense review, many unanswered questions and safety concerns remain unanswered, and will require Phase 4 commitment for conducting additional clinical, pathophysiological, and pharmacogenetic studies. The Agency feels strongly about the **need to decrease absolute risk - general exposure must be minimized via restricted distribution and all treated patients and adverse events must be accounted for through institution of a Patient Registry.** In the interim, some of these important questions could be answered. If the initial restricted distribution roll-out is successful, at a predetermined time point a phased-in expansion of distribution could then be implemented.

**5. Stopping Use of The Drug After A Day Without A Bowel Movement**

Constipation is the most frequently observed AE experienced by alosetron users in clinical trials (as high as 37%), and fecal impaction, exaggerated constipation, contributed to 38% of the serious complications of constipation reported post-marketing. Serious complications of constipation reported post-marketing required hospitalizations (66) and included varying degrees of bowel obstruction (12) and colon perforations, (11) resulting in major emergent abdominal surgery (23) with resultant colostomies (9), and one colectomy. Two deaths were associated with colon perforations.[4]

The majority, 86% (66/77), of the patients with SAEs reported to ODS as of August 22, 2001, required hospitalization and 30% (23/77) required surgery. Among patients who experienced serious complications of severe constipation, there was a subgroup of severe "unreported" constipation (14 patients) who required hospitalization in 100% and surgical procedures in 57% (8/14).

Developing constipation on alosetron, both apparent and non-apparent carries a higher risk for hospitalization and surgery. In addition, many drugs potentially have anti-motility or a constipating effect upon the intestinal tract, and many IBS patients require one or even more of these drugs at the same time as alosetron. Diverticulosis and diverticulitis (infected diverticula) occur with increasing frequency as the population ages. These thinned, weakened outpockets of the colonic wall are more susceptible to perforation when subjected to the elevated intra-colonic pressure associated with constipation and fecal impaction. Dilatation of the colon by impacted stool that exceeds 9-12 cm in diameter has

[4] Review of Lotronex-Associated Serious Complications of Severe Constipation Reported Post-Marketing by Dr. S. Kress

been associated with secondary ischemic colitis and perforation, and increased mortality.[5]

**Whereas constipation carries the potential risk of such serious sequelae and should be the easiest risk factor to eliminate, patients taking this drug for diarrhea-predominant IBS who don't have a bowel movement for a day would safely benefit from waiting till the next bowel movement before continuing to take the drug.**

## 6. Attestation of Severity of Patient's IBS

Whereas, LOTRONEX is only indicated for chronic, severe diarrhea-predominant irritable bowel syndrome (IBS), attestation of severity of diarrhea-predominant IBS needs to be incorporated into each document provided to patients and physicians. The recommendations for inclusion in the appropriate documents: Package Insert, Medication Guide , and Patient-Physician Agreement appears in the Summary. Wording for each document is in different format, but the conceptual information is identical. In the Patient-Physician Agreement the information takes the form of a check-list.

### 7. Marketing of Scored 1 mg Alosetron Tablets

The general consensus of the members the Gastrointestinal Advisory Committee Meeting (April 23, 2002) strongly agreed that dosing for patients treated with alosetron needs to be individualized, similar to the treatment of hypertension. **Availability of 1 mg scored tablets would encourage the prescribing of the lowest effective dosage for each patient, thus contributing to a reduced risk of serious adverse events. Modification of the distributed 1 mg alosetron tablet to be scored, i.e., would thereby improve the ability of prescribing physicians to more accurately individualize dosing for each alosetron-treated patient. However, manufacturing of scored tablets will have to wait for a later time.**

## III. Summary

The goal for possible reintroduction of alosetron remains to design a Risk Management Program – Restricted Distribution Plan (RMP-RDP) under the provisions of 21CFR 314 Subpart H that will optimize benefits and minimize risks.

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[5] Dis Colon Rectum 1982;25:157 and 1986,29:203-210

This review has provided scientific justification for several important additional approaches that need to be considered for incorporation into the final RMP-RDP. They include:

1. **REDUCED INITIAL DOSING**
   **Whereas, the risk for ischemic colitis peaks during the first month of therapy, consideration needs to be given to treating patients with a reduced dosage for 30 days, re-assessing safety and efficacy at the end of this period of time, and proceeding with an intervention based on these results. (Details of this schemata has been provided.) This reviewer now believes that 30 days may be the most appropriate time period for the initial reduced dosage to optimize the benefit/risk ratio.**

2. **DISCONTINUATION OF DRUG IN NON-RESPONDERS**
   **Discontinuation of the drug in non-responders is an important mechanism for minimizing risk. Continuation of the drug without a beneficial response after 30 days of treatment at the full recommended dose 1 mg BID may expose the patient to potential risks of SAEs without the possibility of benefit**

3. **LIMITATION OF USE TO SEVERELY AFFECTED DIARRHEA-PREDOMINENT IBS PATIENTS**
   **IBS patients with 'severe' urgency (urgency present on at least 70% of days) may expect greater therapeutic benefit and possibly lesser likelihood of constipation-associated AEs than less severely symptomatic patients. Thus, limiting the use of alosetron to severely affected IBS patients may further optimize the benefit/risk ratio.**

4. **RESTRICTED DISTRIBUTION – LIMITED ACCESS**
   **To decrease absolute risk, provide time to assess the success of the RMP-RDP, to be implemented, and learn how to safely and effectively utilize this drug, general exposure must be minimized. Restricted distribution in conjunction with a Patient Registry and additional clinical and pathophysiological studies should provide the necessary information to select the appropriate 'next phase of use' for this drug.**

5. **STOPPING USE OF THE DRUG AFTER A DAY WITHOUT A BOWEL MOVEMENT**
**Whereas constipation carries the potential risk of such serious sequelae and should be the easiest risk factor to eliminate, patients taking this drug for diarrhea-predominant IBS who don't have a bowel movement for a day, would benefit from waiting till the next bowel movement before continuing to take the drug.**

## 6. Attestation of Severity of Patient's IBS

Whereas, LOTRONEX is only indicated for chronic, severe diarrhea-predominant irritable bowel syndrome (IBS), attestation of severity of diarrhea-predominant IBS needs to be incorporated into each document provided to patients and physicians. The following are recommendations for inclusion in the appropriate documents: Package Insert, Medication Guide , and Patient-Physician Agreement.

### Attestation of Severity of Patient's IBS
### [Package Insert]

- **INDICATIONS AND USAGE:** To justify the risks associated with taking LOTRONEX, it is indicated only for women with chronic, severe diarrhea-predominant irritable bowel syndrome (IBS), who have had other medical conditions ruled out, and have failed to respond to conventional therapy. Severity of symptoms should include frequent abdominal pain/discomfort, severe diarrhea, extreme urgency, or fecal soiling, or disabling and restricting of daily activities. In addition, patients must have signed the Patient-Physician Agreement (see BOXED WARNING, CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

## [Medication Guide]

- **What is the most important information I should know about LOTRONEX?**
- LOTRONEX is only for women who have severe irritable bowel syndrome (IBS) with diarrhea as their main symptom, these symptoms are not due to other medical conditions, and who have not been helped by other treatments. Women who have constipation as their main IBS symptom should **not** use LOTRONEX. LOTRONEX has not been shown to help men with IBS.
- LOTRONEX can have serious unwanted symptoms. Women should not take LOTRONEX unless they have severe diarrhea. The benefits of taking LOTRONEX justify the risk of taking LOTRONEX only if symptoms are severe. Patients with severe IBS often have severe loose bowel movements (diarrhea), extreme urgency (need to quickly have a bowel movement), soiled underwear, and stomach area (abdominal) pain or discomfort. IBS symptoms may make it impossible for women to lead a normal home or work life.

## Attestation of Severity of Patient's IBS
## [Patient-Physician Agreement]

**I know that Lotronex can have serious unwanted symptoms. I know I should not take Lotronex unless I have severe diarrhea. The benefits of taking Lotronex justify the risk of taking Lotronex only if my diarrhea is severe.**

I agree that my IBS symptoms need treatment because

- According to my doctor, my symptoms are not due to other medical conditions; and
- I have had IBS with diarrhea for at least 3 months; and
- Other treatments I have tried do not work.

**My IBS symptoms are severe** as I have at least 1 of the following problems:

- I have severe loose bowel movements (diarrhea) with extreme urgency (need to quickly have a bowel movement), or soiled underwear.
- I have stomach area (abdominal) pain or discomfort.
- My IBS symptoms make it impossible for me to lead a normal home or work life.

# IV. Professional Labeling

**PRODUCT INFORMATION**

# 26 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

__✓__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Medical-* 21-107
5005

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

/s/

Scheldon Kress
5/3/02 12:35:50 PM
MEDICAL OFFICER

Hugo Gallo Torres
5/3/02 01:13:59 PM
MEDICAL OFFICER

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

| | |
|---|---|
| **NDA:** | **NDA 21-107/S-005** |
| **Applicant:** | **GlaxoSmithKline** |
| **Drug:** | **LOTRONEX (alosetron)** |
| **Pharmacological Category:** | **5HT-$_3$ Receptor antagonist** |
| **Material Reviewed:** | **Clinical Study Reports (CSRs) for all studies in NDA 21-107** |
| **Purpose of Review:** | **Clinical Perspectives for Improving the Benefit/ Risk Ratio Among Alosetron-Treated Diarrhea-Type IBS Patients:**<br>**1. Reduce The Risk of Serious Adverse Events of Special Interest**<br>**2. Optimize Benefit**<br>**3. Optimize Benefit/Risk** |
| **Reviewer:** | **Scheldon Kress, M.D.** |
| **Date:** | **April 1, 2002** |

## Clinical Perspectives on Benefit-Risk

### Executive Summary

The goal for possible reintroduction of alosetron remains to design a Risk Management Program-Restricted Distribution Plan (RMP-RDP) under the provisions of 21CFR 314 Subpart H that will optimize benefits and minimize risks. This review has provided justification for several important approaches that need to be considered for incorporation into the final RMP-RDP.

Several approaches discussed to optimize the benefit/risk ratio include:

- Reduced initial dosing.
- Discontinuation of drug in non-responders
- Limitation of use to severely affected diarrhea-predominant IBS patients
- Restricted distribution- limited access
- Stopping use of the drug after a day without a bowel movement

In addition, the reviewer summarizes:

- Lotronex® Benefit-Risk Assessment
- Approaches of the proposed RMP-RDP for reintroduction of alosetron to optimize the Benefit/Risk Ratio.

An attempt is made to elucidate the potential benefit of each component of the proposed RMP-RDP for both SAEs of special interest, i.e., delineating each component's contribution to minimizing the occurrence of these SAEs of special interest.

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## Introduction

The purpose of this review is to provide an evaluation of risks and benefits to individual patients and to the public health related to the treatment with alosetron of women with diarrhea-predominant IBS. GlaxoSmithKline introduced alosetron to the US market on March 13, 2000 following approval of NDA 21-107 on February 9, 2000. As a result of concerns arising from post-marketing reports of serious adverse events and deaths associated with complications of constipation and ischemic colitis, label changes were implemented. However, serious adverse events (SAEs) and deaths continued to occur as shown in Table 1.

**Table 1**
**Lotronex-Associated Serious Adverse Events**

| Selected Outcomes | Ischemic Colitis | Serious Complications of Severe Constipation |
|---|---|---|
| **Pre-Approval** (Nov, 1999) | | |
| Cases | 4 | 1 |
| Hospitalization | 4 | 1 |
| Surgery | None | None |
| Death | None | None |
| **Randomized Clinical Trial Experience** (December 7, 2001) | | |
| Cases | 18 | 11 |
| Hospitalization | 7 | 10 |
| Surgery | 1 | 1 |
| Death | None | None |
| **ODS Post-Marketing Safety Review** (Data as of December 31, 2001) | | |
| Cases | 85 | 107 |
| Hospitalization * | 52 | 78 |
| Surgery * | 9 | 30 |
| Death ‡ * | 2 | 2 |

‡ Three additional deaths (for a total of 7) demonstrated suggestive evidence of alosetron causality, but did not fit in the these categories ( 2 cases of small bowel ischemia and 1 case of necrosis of esophagus, stomach, and small bowel).
* These incidents may be included in multiple categories, therefore, can not be added together to equal the total.

Negotiations continued through November 2000 between the Sponsor and the FDA in an attempt to reduce the risk of SAEs to patients. The FDA assessment of the overall risk-benefit could not justify continued market availability from a public health perspective without implementation of restricted distribution. This was unacceptable to the Sponsor. As a result, on November 28, 2000, the sponsor made the decision to withdraw alosetron from the US market and did not consider making the drug available to severely affected patients under an IND a viable option.

Subsequent to the withdrawal of alosetron both patients, physicians, and advocacy groups have requested that GlaxoSmithKline and FDA reconsider the withdrawal of alosetron. Discussions between GlaxoWellcome (now GlaxoSmithKline (GSK)) and FDA ensued to re-evaluate the risk-benefit of alosetron, taking into consideration a substantial new body of safety and efficacy data. These data arose from the ongoing clinical and epidemiological studies that were terminated prematurely at the time of the withdrawal. FDA and GSK agreed to work cooperatively to (1) further characterize the safety profile, (2) re-assess risks against benefits and (3) renew the effort to design an appropriate program that could allow the return of alosetron to the market in a safe and effective manner to appropriate and informed patients.

The safety review of the results of Randomized Clinical Trials (RCT) submitted in the sNDA 21-107 of December 7, 2001 evaluated 11,874 patients treated with alosetron. Among the SAEs of special interest that occurred among alosetron-treated patients were 18 cases of ischemic colitis and 11 serious complications of severe constipation. By contrast, the RCT experience revealed one placebo-treated patient who developed ischemic colitis and three placebo-treated patients who developed serious complications of severe constipation.

The objectives of this review are to assess methods for improving the Benefit/Risk balance for individual patients. As part of the proposed Risk Management Plan for marketing re-introduction of alosetron, there is considerable interest in reducing the incidence and severity of the observed SAEs.[1] The goal is to answer the following questions based on the information currently available:

1. How to minimize risk?
2. How to optimize benefit?
3 How to optimize benefit/risk?
4 Should exposure be minimized to decrease risk?

[1] A more complete time-to-event analysis for ischemic colitis, and an evaluation of hazard ratio is being carried out by Dr. D. Hoberman

**SAEs Occurrence By Study Week**

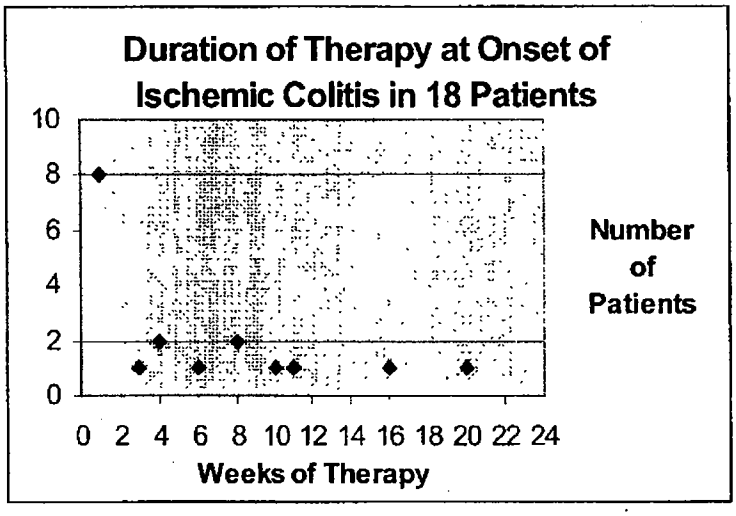
For each of the 29 SAEs of special interest occurring in the RCTs, an initial time to event analysis was undertaken. A determination was made of the duration of alosetron therapy up to the onset of ischemic colitis and serious complications of severe constipation. The information was obtained from the narrative summaries.

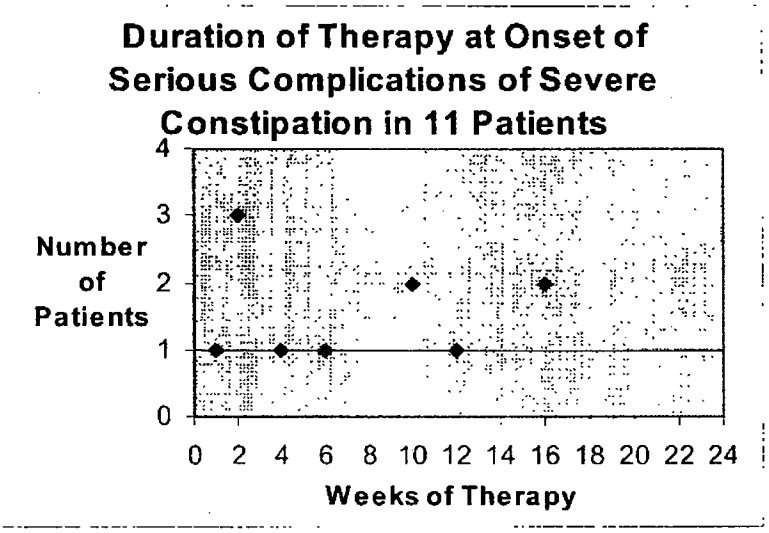
For all patients with ischemic colitis, the therapy was alosetron 1 mg BID except 1 patient with onset during week 1 (alosetron 2 mg BID) and 1 with onset during week 8 (alosetron 0.5 mg BID).

For all patients with serious complications of severe constipation, the therapy was alosetron 1 mg BID.

Figure 1 depicts the duration of therapy in weeks at the onset of the initial symptoms for the 18 patients with ischemic colitis (upper chart) and the 11 with serious complications of severe constipation (lower chart).

**Figure 1**
**Duration of Alosetron Therapy at Onset**
**of the 18 Cases of Ischemic Colitis (Upper Panel)**
**and the 11 Cases of Serious Complications**
**of Severe Constipation (Lower Panel)**
**In The Overall Randomized Clinical Trial experience in NDA 21-107**



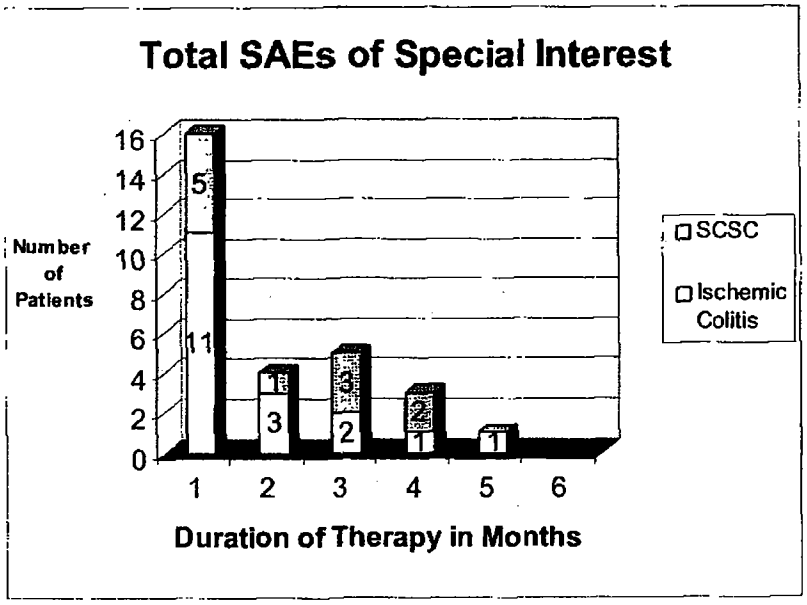
**A most interesting observation made from this analysis, is an increased occurrence of these SAEs during the first 4 weeks of therapy with alosetron:**

- **11 of the 18 cases of ischemic colitis**
- **5 of the 11 cases of serious complications of severe constipation (SCSC)**
- **16 of the 28 cases of these SAEs of special interest**

The total patients with SAEs of special interest from the Randomized Clinical Trial experience are shown in Figure 2.

**Figure 2**

**Onset of The Twenty-eight SAEs of Special Interest From the Randomized Clinical Trial experience**



Many study-related factors may have impacted on the timing of the initiation and distribution of these observed SAEs. Included among the more important items are:

- The total number of patients treated for 4 weeks or less is substantially higher than those treated for longer periods of time. Therefore, incidence rates of the event, as a function of time, would need to be corrected by the total number of patients treated at a specified period,
- Nonetheless, the highest number of patients exposed to the drug occurred at the onset of each study (approaching 100%).
- The duration of the studies was variable (6 weeks to 1 year).
- Significant patient withdrawal occurred prior to completion of these studies (as high as 30 percent)
- the premature termination of some of the studies

Therefore, another approach to evaluate these data is to look at Risk, number of events over time taking into account the number of exposures at each month. Utilizing the same methods as the sponsor supplied at the March 13, 2002 meeting with the FDA and the GI group's data on incidence at onset of SAEs, the following Risks by month were determined (Table 2).

**Table 2**
**Risk of SAEs of Special Interest Over Time**
**In The RCT Studies With Alosetron**

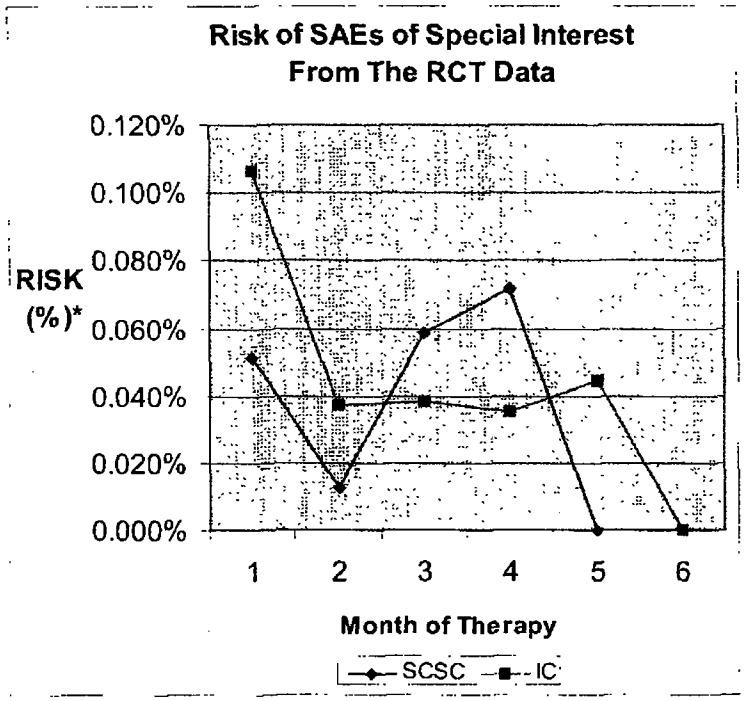
| Month | SCSC Cases | Total # Patients | Total # Censored | SCSC Risk* | IC Cases | Total # Patients | Total # Censored | IC Risk* |
|---|---|---|---|---|---|---|---|---|
| 1 | 5 | 10805 | 2145 | 0.051% | 11 | 11874 | 3062 | 0.106% |
| 2 | 1 | 8657 | 1614 | 0.013% | 3 | 8802 | 1538 | 0.037% |
| 3 | 3 | 7042 | 3890 | 0.059% | 2 | 7263 | 4043 | 0.038% |
| 4 | 2 | 3151 | 728 | 0.072% | 1 | 3218 | 736 | 0.035% |
| 5 | 0 | 2421 | 417 | 0% | 1 | 2480 | 452 | 0.044% |
| 6 | 0 | 2004 | 1279 | 0% | 0 | 2028 | 1298 | 0.0% |

* Life table estimate =
Number of events/(number of subjects-number censored/2) X 100.

These data, based on a small number of cases, are presented graphically in Figure 3. These findings suggest (although they may not prove with certainty) that;

- the risk for **ischemic colitis peaks during the first month of therapy**
- the risk for serious complications of severe constipation does not demonstrate a similar peaked incidence

**Figure 3**




* Life table estimate =
Number of events/(number of subjects-number censored/2) X 100.

**Potential Benefits of A Reduced Starting Dose**

The number of patients experiencing these SAEs may be small. However, the marked severity of some of the cases is reason for alarm, when one considers that this drug is for symptomatic treatment of IBS, a condition that does not usually require surgery and is never associated with mortality. Ischemic colitis occured without prodromata in an unpredictable manner. Currently, we have very limited ability to predict those individuals most susceptible to develop ischemic colitis and thus prevent its occurrence. However, it seems reasonable to assume that patients with coagulopathies, predisposing concomitant medications, and vascular insufficiencies may be at increased risk. Thus, the question arises, what impact would administration of a reduced dosage over the first two to four weeks of therapy have on diminishing the frequency and/or severity of the ischemic colitis and/or severity of serious complications of severe constipation that would occur?

This approach of treating a patient for two to four weeks at a reduced dosage, re-assessing safety and efficacy at the end of this period of time, and proceeding with an intervention based on these results, offers both opportunities and limitations.

Efficacy data from the pre-approval studies suggest that the response at 4 weeks is a good predictor of response at the overall 12 weeks of treatment. Therefore, from the efficacy viewpoint, a reasonable approach is that, if no beneficial response is observed at the end of 4 weeks, the drug should be discontinued. Continuation of the drug past that period may expose the patient to increasing potential risk of SAEs, while at the same time, diminishing the possibility of benefit. Thus, **discontinuation of the drug in non-responders is an important mechanism for minimizing risk.**

A drawback to the two to four week reduced initial treatment approach is that reducing the dose during the first two-to-four week trial may only "delay" the onset of these undesirable SAEs until the time that the full dose is administered 4 weeks later ("move the curve to the right"). Likewise, patients that appear to tolerate half the recommended daily dose well, but in whom the drug is not beneficial, may have to endure a longer trial exposure before determining that the drug will not improve their IBS symptoms.

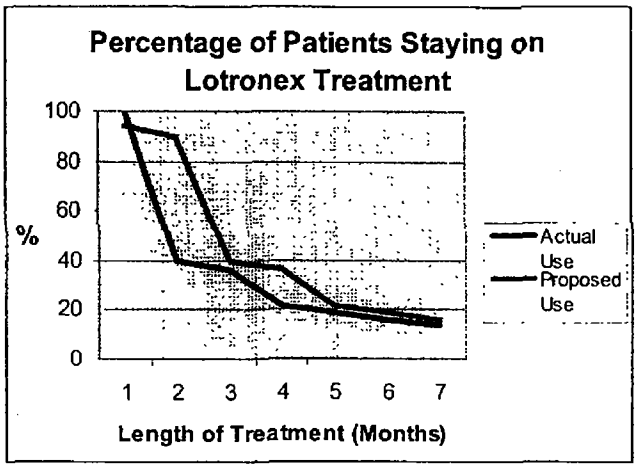
ODS (Office of Drug Safety) evaluated the Lotronex patterns of use during the 9 months of marketing of the drug in the United States. Based on a pharmacy claim database and employing life-table analysis, it was concluded that:

- 64% of patients stopped treatment within the first month
- the median duration of the initial course of treatment was less than 30 days
- only 20% of patients stayed on treatment for more than 3 months, 9% for more than 6 months, 4% for more than 9 months
- patients who claimed dramatic benefits most likely represented only a small fraction of alosetron users

The available information does not seem to indicate that ischemic colitis is dose related, but for constipation, a definite dose-related response has been repeatedly confirmed. In clinical trials, constipation was reported in approximately 30% of patients taking alosetron 1 mg BID and in 11% of patients taking alosetron 0.5 mg BID. Constipation made up fifty percent of the spontaneous adverse events reported. Therefore, it can be assumed that those **patients who develop constipation [or evidence suggestive of ischemic colitis] during this trial of therapy on the reduced dosage and in whom the drug is stopped, may benefit from developing an adverse event on lesser drug (the AE could be milder) and may be prevented from longer-term exposure to a larger dose of drug (the SAE could be more severe).** Although this strategy may only minimally reduce the overall incidence rates of these AEs and SAEs, reduction in severity can be clinically significant. The impact might be particularly important to those who experienced these SAEs, endured major lifestyle inconveniences, and may have required medical attention, hospitalization, surgery, and transfusions, and even suffered life-threatening sequelae.

Figure 4 schematizes these two scenarios: the percentage of patients who stayed on alosetron seen in the actual use data compared to the 'theoretical expected percentage of patients' who may stay on alosetron in the proposed trial lower dose use plan.

**Figure 4**




What could be anticipated from this approach, is that more patients will take the drug for 1 to 2 months; some are expected to withdraw due to constipation and fewer patients might withdraw due to symptoms suggestive of ischemic colitis in those first 1 to 2 months. The expectation based on these assumptions, is that those patients safely withdrawn at this lower dose were being protected from more severe SAEs had they taken the full dosage. Thus, the potential benefits support the proposed approach.

The following schemata has been designed as a "how to manage strategy" for the most likely therapeutic scenarios ( Table 3).

**Table 3**

**Schemata For Reducing The Incidence And Severity Of Alosetron-Associated SAEs of Special Interest**

| Initiate Trial Therapy During First 2-4 Weeks | Evaluation During And At End of Initial Trial Period | Dosage Adjustment Intervention |
|---|---|---|
| Alosetron | Constipation<br>Rectal Bleeding[a] or Suggestion of Ischemic Colitis | Discontinue Therapy |
| | No Constipation<br>No Rectal Bleeding[a] or Suggestion of Ischemic Colitis<br>Clinical Benefit | Continue Therapy at 1 mg QD |
| 1 mg QD | No Constipation<br>Neither Rectal Bleeding[a] nor Suggestion of Ischemic Colitis<br>No Clinical Benefit | Increase Dosage to 1 mg BID and Re-evaluate during next 4 Weeks<br>If:<br>Clinical Benefit-Continue<br>No Clinical Benefit, Rectal Bleeding[a] or Suggestion of Ischemic Colitis Discontinue Therapy |

[a] Not explained by "specific sources" such as perianal or hemorrhoidal bleeding

This schemata for reducing the severity and perhaps the incidence of the alosetron-associated SAEs of special interest should contribute to reducing the risk of SAEs by promptly **stopping the drug in those patients prone to constipation and more susceptible to 'unexplained" rectal bleeding or ischemic colitis.** GlaxoSmithKline has essentially agreed with this approach in their Summary of Benefits and Risks Section (page 34)and in their proposed changes to the labeling (lines 444 to 452) of the December 7, 2001 sNDA.

**Potential Benefits From Only Treating Severely Affected Patients**

Based on the pre-approval 3 month alosetron studies, the risk for alosetron-associated ischemic colitis was estimated at 1/700 (95% CI, 1/100-1/1000). Alosetron was taken for up to 6 months in Protocol S3B30020, and 10 cases of ischemic colitis were reported among 1817 patients (an incidence of approximately 1/200). At the time of withdrawal, the Benefit/Risk balance seemed to be unfavorable; the MedWatch program was receiving SAEs in increasing numbers and severity including the necessity for major abdominal surgery and resultant deaths.

In the pre-approval trials, most of the IBS patients manifested only mild to moderate diarrhea. Thus, the question was raised, what benefit could be expected from the more severely affected diarrhea-predominant patients.

As part of the review of the randomized clinical trials, post-hoc analysis of the two so-called "urgency studies," revealed that in Protocols S3B30011 and S3B40031 alosetron 1 mg BID demonstrated significant therapeutic benefit among the more severely symptomatic IBS patients. In Protocol S3B30011, but not in S3B40031, the need for withdrawal of alosetron due to constipation was slightly reduced.

Thus, patients with 'severe' urgency (urgency present on at least 70% of days) may expect greater therapeutic benefit (satisfactory control of urgency on greater than 75% of days [therapeutic gain 18-19% greater than with placebo]) and possibly lesser likelihood of constipation-associated AEs than less severely symptomatic patients. Of course, these suggestive findings were based on small samples of patients and will require replication within a larger study. However, it seems reasonable to speculate that **limiting the use of alosetron to severely affected IBS patients may contribute to optimizing the benefit/risk balance.**

**Potential Benefits From Limited Access**

As the possibility of re-introduction of alosetron into the marketplace is under intense review, many "questions" related to this drug remain unanswered, such as:

Can a Risk Management Proposal-Restricted Distribution Plan (RMP-RDP) be developed and implemented that will:

1. Improve Benefit/Risk ratio?
2. Effectively reduce the incidence and severity of...
   - Ischemic colitis?
   - Serious complications of severe constipation?
   - "Unreported" constipation complications
   - Vascular enteropathies?

What means can be utilized to effectively

- Assure appropriate and safe prescribing?
- Insure that patients comply with the Medication Guide?
- Constipation management options?
- Limit the potential for off-label use?
  pediatrics, men, alternating symptoms?
- Insure that we gain information from the Patient Registry?
- Utilize pharmacogenetics to prospectively identify responders as well as risk factors of SAEs

What advantages and disadvantages are associated with implementation of dosing regimen optimization schemes (the proposed step-up starting dose, or alternatives such as step-down, intermittent, and p.r.n. usage)?

Should an initial reduced starting dose be given for 2 or 4 weeks?

Should mandatory sigmoidoscopy or colonoscopy be required before initiating therapy?

How does one go about determining what are the risk factors for ischemic colitis and severe constipation?

What will we learn from the Patient Registry?

What is the natural course of "spontaneous ischemic colitis?"

What additional clinical studies should be implemented?

Dose ranging studies
Individual dosing regimens
Randomized withdrawal to placebo or continued therapy
Active comparator studies
Efficacy in men
Epidemiological studies to evaluate risk factors
Influence on Quality of Life (functional improvement)

What pathophysiological studies should be implemented to elucidate mechanisms of disease and drug actions?

Role of drugs that delay intestinal transit
Role of intestinal motility disorders
Role of hyperlipidemia and intestinal atherosclerosis
Activity on vascular endothelium
Role of coagulation factors and hypercoagulable states (most are occult)
Role of drugs reported to induce ischemic colitis such as: birth control pills, estrogens, migraine medications, digitalis, diuretics, cocaine, beta-blockers, NSAIDs, vasoconstrictors, neuroleptics, psychotropics, etc.
Role of prior vasculopathies like thrombophlebitis
Role of diverticulosis and diverticulitis (both very common in general population)

Which should be performed prior to and which after re-introduction?

From the limited data at hand, there seems to be no long-term safety concerns, but additional information is needed. Is there need for studies designed to address the issue of long-term safety?

Can alosetron be safely re-introduced into the marketplace?
Should alosetron be re-introduced into the marketplace at this time?

With so many unanswered questions and safety concerns, the Agency feels strongly about the **need to decrease absolute risk - general exposure must be minimized via restricted distribution and all treated patients and adverse events must be accounted for through institution of a Patient Registry.** In the interim, some of these important questions could be answered. If the initial restricted distribution roll-out is successful, at a predetermined time point a phased-in expansion of distribution could then be implemented.

**Stopping Use of The Drug After A Day Without A Bowel Movement**

Constipation is the most frequently observed AE experienced by alosetron users in clinical trials, and fecal impaction, exaggerated constipation, contributed to 38% of the constipation-related SAEs reported post-marketing. Serious complications of severe constipation reported post-marketing required hospitalizations (66) and included varying degrees of bowel obstruction (12) and colon perforations, (11) resulting in major

emergent abdominal surgery (23) with resultant colostomies (9), and one colectomy. Two deaths were associated with colon perforations.[2]

The majority, 86% (66/77), of the patients with SAEs reported to ODS as of August 22, 2001, required hospitalization and 30% (23/77) required surgery. Among patients who experienced serious complications of severe constipation, was a subgroup of severe "unreported" constipation (14 patients) who required hospitalization in 100% and surgical procedures in 57% (8/14).

Developing constipation on alosetron, both apparent and non-apparent carries a higher risk for hospitalization and surgery. In addition, many drugs potentially have anti-motility or a constipating effect upon the intestinal tract, and many IBS patients require one or even more of these drugs at the same time as alosetron. Diverticulosis and diverticulitis (infected diverticula) occur with increasing frequency as the population ages. These thinned, weakened outpockets of the colonic wall are more susceptible to perforation when subjected to the elevated intra-colonic pressure associated with constipation and fecal impaction. Dilatation of the colon by impacted stool that exceeds 9-12 cm in diameter has been associated with ischemic colitis and perforation, and increased mortality.[3]

**Whereas constipation carries the potential risk of such serious sequelae and should be the easiest risk factor to eliminate, patients taking this drug for diarrhea-predominant IBS who don't have a bowel movement for a day would safely benefit from waiting till the next bowel movement before continuing to take the drug.**

**Summary**

For each patient for which alosetron might be prescribed, the prescriber must weigh the potential benefits against the potential risks for that patient. Among the many possible ways to assess the Lotronex® Benefit – Risk, the following **[Benefits – Risks = Net Benefit]** assessment scheme[4] seems appropriate (Table 4).

[2] Review of Lotronex-Associated Serious Complications of Severe Constipation Reported Post-Marketing by Dr. S. Kress
[3] Dis Colon Rectum 1982;25:157 and 1986,29:203-210
[4] suggested by Dr. John Senior of the FDA

**Table 4**
**Lotronex® Benefit – Risk Assessment**
**Benefits – Risks = Net Benefit**

| Beneficial Effects | Magnitude of Effect | Risk of Adverse Effects |
|---|---|---|
| Placebo effect **45 %** *1 | **None, not perceptible** | Negligible- none |
| Adequate relief of IBS pain and discomfort 2 out of 4 weeks for a 3 month period Therapeutic Gain **12-15 %** > placebo *2<br>Improved stool urgency, frequency , and consistency | **Modest** | Constipation **26-30 %** *2 |
| | **Moderate, Considerable** | Constipation resulting in discontinuation of therapy **10 %** *2 |
| Substantial improvement of more severely symptomatic urgency Therapeutic Gain **18-19 %** > placebo *3<br>[Improved satisfactory control of urgency from <30% of days at baseline to >75% of days over 12 weeks of therapy] | **Substantial** | Ischemic colitis, mild, non-transmural *4 **17 / 11,874 in RCT**<br>Constipation with impaction, partial obstruction *4 **10 / 11,874 in RCT** |
| | **Very impressive** | Serious/severe AEs requiring surgery, colon repair or removal *4 **2 /11,874 in RCT** |
| Fully Beneficial Therapy Without Risk of SAEs (Unknown) | **Ultimate** | **5 Possible Deaths** **Post-Marketing** Approximately **5 / 275,000** *5 |

*1 Abstract presented at DDW in Atlanta May 2001, Northcutt, Allison R. et al. Persistent Placebo Response During A Year-Long Controlled Trial of IBS Treatment
*2 Protocol S3BA3001 and Protocol S3BA3002 (pivotal trial studies)
*3 Protocol S3B30011 and Protocol S3B40031 (the "urgency studies")
*4 FDA Perspectives on Safety by Dr. Hugo Gallo-Torres (the 24 Randomized Clinical Trial experience)
*5Review of Post-Marketing Deaths by Dr. S. Kress.
Deaths reported via MedWatch. Approximate number of users of alosetron supplied by sponsor.

The goal for possible reintroduction of alosetron remains to design a Risk Management Program – Restricted Distribution Plan (RMP-RDP) under the provisions of 21CFR 314 Subpart H that will optimize benefits and minimize risks.

Many of the approaches to optimizing the Benefit/Risk Ratio that have been proposed include:

- Mandatory educational programs for prescibers and pharmacists
- Education of patients by physicians, the Medication Guide, and pharmacists
- Enhancement of the professional labeling and mandated to be distributed Medication Guide
- Restricted distribution mechanisms
- Evaluation of outcome of Risk Management Plan

This review has provided scientific justification for several important additional approaches that need to be considered for incorporation into the final RMP-RDP. They include:

- **REDUCED INITIAL DOSING**
  **Whereas, the risk for ischemic colitis peaks during the first month of therapy, consideration needs to be given to treating patients with a reduced dosage for four weeks, re-assessing safety and efficacy at the end of this period of time, and proceeding with an intervention based on these results. (Details of this schemata has been provided.) This reviewer now believes that 4 weeks may be more appropriate than 2 weeks for the initial reduced dosage to optimize the benefit/risk ratio.**

- **DISCONTINUATION OF DRUG IN NON-RESPONDERS**
  **Discontinuation of the drug in non-responders is an important mechanism for minimizing risk. Continuation of the drug without a beneficial response after 4 weeks of treatment at the full recommended dose 1 mg BID may expose the patient to potentai risks of SAEs without the possibility of benefit**

- **LIMITATION OF USE TO SEVERELY AFFECTED DIARRHEA-PREDOMINENT IBS PATIENTS**
  **IBS patients with 'severe' urgency (urgency present on at least 70% of days) may expect greater therapeutic benefit and possibly lesser likelihood of constipation-associated AEs than less severely symptomatic patients. Thus, limiting the use of alosetron to severely affected IBS patients may further optimize the benefit/risk ratio.**

- **RESTRICTED DISTRIBUTION – LIMITED ACCESS**
  **To decrease absolute risk, provide time to assess the success of the RMP-RDP, to be implemented, and learn how to safely and effectively utilize this drug, general exposure must be minimized. Restricted distribution in conjunction with a Patient Registry and additional clinical and pathophysiological studies should provide the necessary information to select the appropriate 'next phase of use' for this drug.**

- **STOPPING USE OF THE DRUG AFTER A DAY WITHOUT A BOWEL MOVEMENT**
  **Whereas constipation carries the potential risk of such serious sequelae and should be the easiest risk factor to eliminate, patients taking this drug for diarrhea-predominant IBS who don't have a bowel movement for a day, would benefit from waiting till the next bowel movement before continuing to take the drug.**

Table 5 summarizes the varied approaches of the proposed RMP-RDP for reintroduction of alosetron and attempts to elucidate the potential benefit of each component for both SAEs of special interest. Each component contributes to minimizing the occurrence of these SAEs of special interest.

**Table 5**
**APPROACHES TO OPTIMIZING THE BENEFIT/RISK RATIO**

| Approaches for Optimizing Benefit/Risk | Approaches Most Beneficial for SAEs of Special Interest | |
|---|---|---|
| | **Ischemic Colitis** | **Serious Complications of Severe Constipation** |
| **Patient selection** | Restrict use to women with diarrhea-predominant IBS who have failed to respond to conventional therapy | |
| | | Severely symptomatic may expect greater benefit/risk |
| **Patient education** | Appropriately informed by physician and Medication Guide, Able to make an informed decision about the use of the drug, recognize the warning signs of potential adverse events, and know when to stop taking medication and seek medical attention | |
| **Physician selection** | Only physicians who are knowledgeable and experienced in the diagnosis and treatment of IBS, able to educate the patient about the potential risks and benefits, diagnose and manage ischemic colitis and complications of constipation, and who have signed a Patient-Physician Agreement for each patient | |
| **Patient exclusion of use** | Prior history:<br>intestinal ischemia<br>ischemic colitis<br>impaired intestinal circulation<br>intestinal surgery<br>diverticulitis or active diverticulitis<br>inflammatory bowel disease<br>Crohn's disease or ulcerative colitis<br>infectious colitis<br>drug-induced ischemic colitis | Prior history:<br>chronic or severe constipation (straining, hard or lumpy stool, absence of bowel movements) or sequelae from constipation<br>inflammatory bowel disease<br>Crohn's disease or ulcerative colitis<br>diverticulitis or active diverticulitis<br>intestinal surgery<br>intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforation, and/or adhesions |
| | Elderly and debilitated patients Hepatic impairment<br>Unable to understand or comply with Patient-Physician Agreement or Medication Guide. | |
| **Relative exclusion** | use of concomitant drugs that have been implicated in causing ischemic colitis | use of concomitant constipating drugs |

**Table 5 (continued)**
**APPROACHES TO OPTIMIZING THE BENEFIT/RISK RATIO**

| Approaches for Optimizing Benefit/Risk | Approaches Most Beneficial for SAEs of Special Interest | |
|---|---|---|
| | **Ischemic Colitis** | **Serious Complications of Severe Constipation** |
| **Supply of drug dispensed limited to 1 month** | Ensures enhanced vigilance during the first month of therapy and monthly review by patient and physician of benefit to risk ratio for each patient | |
| **Early recognition** | New or worsening abdominal pain<br>Bloody diarrhea<br>Blood in stool | New or worsening abdominal pain<br>Signs and symptoms of constipation |
| **Stopping use of drug immediately** | New or worsening abdominal pain<br>Bloody diarrhea<br>Blood in stool | absence of bowel movement for a day |
| | Patients who have not had adequate control of IBS symptoms after 4 weeks of treatment with 1 mg twice daily | |
| **Reduced initial dosage** | ? severity | Decreased frequency and severity of constipation |
| **Restricted distribution** | absolute number of patients at risk decreased by minimizing general exposure | |
| **Subpart H restrictions** | FDA may withdraw approval if it can demonstrate:<br>• Inadequacy of restrictions to assure safe use<br>• Sponsor's failure to adhere to agreed upon restrictions | |

**Scheldon Kress, M.D.**
**April 1, 2002**

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

/s/

Scheldon Kress
4/19/02 05:09:57 PM
MEDICAL OFFICER

Hugo Gallo Torres
4/24/02 02:50:30 PM
MEDICAL OFFICER

**MEMORANDUM** **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: March 26, 2002

FROM: Allen Brinker, M.D., M.S.
Epidemiologist, Team Leader
Division of Drug Risk Evaluation, HFD-430
Office of Drug Safety

THROUGH: Julie Beitz, M.D.
Division Director
Division of Drug Risk Evaluation, HFD-430
Office of Drug Safety

TO: Victor Raczkowski, MD
Acting Division Director
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: **PID# D010598** - Summary comments on 10 epidemiological studies submitted in an efficacy supplement under Lotronex NDA #21-107

**CONTAINS PROPRIETARY INFORMATION FROM IMS HEALTH (BOLDED)**

**NOT TO BE DISTRIBUTED OUTSIDE OF FDA**

EXECUTIVE SUMMARY

Ten epidemiologic studies submitted with the Lotronex (alosetron) sNDA were given expedited review for relevant and novel information pertinent to ischemic colitis and the possible re-introduction of Lotronex to the U.S. marketplace. Although a phase 4, epidemiological study of ischemic colitis in association with Lotronex was planned, these ten studies include NO information on the risk of ischemic colitis in association with Lotronex. Information on Lotronex is limited to general demographic and clinical attributes of patients with a Lotronex prescription claim from one study.

The ten epidemiological studies as submitted do provide insight in the prevalence, diagnosis, and treatment of irritable bowel syndrome (IBS) and selected conditions, including ischemic colitis. In summation, these studies support the following positions:

1. During initial U.S. marketing, the majority of Lotronex prescribers were not gastroenterologists.
2. The diagnosis of irritable bowel syndrome (IBS) is problematic. Clinicians may utilize IBS as an interim diagnosis or as a misdiagnosis of other conditions (e.g., inflammatory bowel disease, ischemic colitis, etc.).
3. Data and analysis based on the Ingenix Research Database support a "background" rate of ischemic colitis among U.S. patients given a diagnosis of IBS in clinical practice. This should be validated by other investigators in other large cohorts of U.S. patients / populations carrying a diagnosis of IBS.
4. Under the hypothesis that there is a "background" rate or risk for misdiagnosed ischemic colitis among patients given the diagnosis of IBS in clinical practice, the best estimate of an association between Lotronex and ischemic colitis will be derived from randomized, double-blind, placebo-controlled trials of Lotronex in IBS patients. If additional placebo-controlled trials are not feasible, further studies of ischemic colitis in association with Lotronex could also include randomized, **double-blind** active control trials in IBS patients.
5. Given the (apparent) heterogeneity of an "IBS" diagnosis and an established concern for ischemic colitis in association with Lotronex, further examination of this association in retrospective, observational settings for regulatory purposes is impractical and not recommended by ODS.
6. A relative risk for ischemic colitis in association with Lotronex of 5.9 (with wide confidence intervals) was seen in the original NDA and represents a compromise summary RR point estimate after consideration of selected, placebo-controlled Lotronex RCTs. This relative risk was used to calculate an expectation that most (83%) spontaneous reports of ischemic colitis reported in association with Lotronex can be attributed to Lotronex and not background disease.

INTRODUCTION

In preparation for the potential re-marketing of alosetron (hereafter referred to as Lotronex), GSK (the sponsor) has submitted 10 epidemiological studies. These 10 studies were submitted with the Dec 7, 2001 sNDA. [Studies 2, 3, and 4 (as enumerated below) were resubmitted as revised on Feb 27, 2002.] These 10 studies are enumerated (for this review) and titled as follows:

1. The occurrence of colonic ischemia, complications of constipation, and non-specific colitis in relation to irritable bowel syndrome (IBS) – phase 1.
2. The occurrence of colonic ischemia complications of constipation, and bowel surgery in relation to irritable bowel syndrome – phase 2.
3. Predictors of colonic ischemia: a case control study.
4. Predictors of complications of constipation requiring hospitalization: a case-control study.
5. Utilization patterns of Lotronex Users, March – November 2000.
6. A descriptive study of ischemic colitis in the General Research Practice Database: a feasibility study.
7. Incidence, outcomes, and risk factors for ischemic colitis in Olmsted County, Minnesota, 1976-1998.
8. Interim report. Retrospective cohort study of vascular insufficiency of the intestine and ischemic colitis and nested case-control study of ischemic colitis.
9. An epidemiological study on the association between drug use, constipation, and various other clinical risk factors and the risk of intestinal obstruction, fecal impaction, intestinal perforation, ileus, or megacolon in the General Practice Research Database (GPRD).
10. A retrospective review of ischemic colitis diagnosed in selected gastroenterology and internal medicine practices.

After review of these 10 studies, three separate areas were identified for emphasis as specifically relevant for the possible re-marketing of Lotronex. This review is organized around these three areas and outlined as follows:

1) Characterization of Lotronex prescribers during initial marketing.

2) IBS diagnosis and the potential for misdiagnosis.
   a. Literature review for IBS diagnosis and prognosis
   b. Ingenix IBS case definition and original Lotronex labeling
   c. inflammatory bowel disease*
   d. bowel surgery*
   e. endoscopic examination*
   f. ischemic colitis*
   *as reported by Ingenix researchers in Studies 1, 2, and 5

3) Estimation of risk for ischemic colitis in Lotronex users.

a. study design issues
b. relative risk estimates for ischemic colitis in association with Lotronex
c. risk attributable to Lotronex use

This review is focused on data from studies conducted by Ingenix Pharmaceutical Services (studies 1-5) and specifically Studies 1, 2, and 5 which provide relevant and novel information pertinent to ischemic colitis and the possible re-introduction of Lotronex to the US marketplace in the opinion of this reviewer. Studies 6, 8, and 9 were not included as they were based on the English General Practice Research Database population. [England has not approved Lotronex and medical practice issues around IBS diagnosis preclude inference on this diagnosis to the U.S.] Study 7 is limited to a study outline / protocol. Study 10 supports current thinking on risk factors for ischemic colitis from a small and potentially selective study population.

SECTION 1 – LOTRONEX PRESCRIBERS – Study #5

Studies 1-5 are based on a subset of the United Health Group database of geographically diverse (but not nationally representative) commercially insured individuals in the U.S. referred to as the "Ingenix Research Database." This database covered approximately 5 million people during the study time interval of Jan 1, 1995 to Dec 31, 1999. Study 5, "Utilization patterns of Lotronex Users, March – November 2000," was further restricted to the time period of initial Lotronex marketing, March – November 2000. Based on an initial eligibility screen of 6 months of enrollment, 2,823 individuals were identified with a claim for Lotronex. First Lotronex prescription by medical specialty for all patients (both male and female) is provided in Table 2, page 8 of the report and summarized below.

| Medical specialty group | Number | % |
|---|---|---|
| Gastroenterologist | 927 | 32.8 |
| Other internist | 586 | 20.8 |
| Family practice | 784 | 27.8 |
| Other doctor | 526 | 18.6 |
| Total | 2,823 | 100.0 |

The 2,823 individuals included 403 males (14.3%) which is also of interest as Lotronex was indicated only for females with diarrhea predominant IBS per the approved label.

The frequency by prescriber is similar after stratification by sex (data not included), to suggest that no medical specialty appeared to prescribe to males more frequently. **Ingenix results on the frequency of Lotronex presciber by specialty were very similar to those seen in an internal analysis of a proprietary physician survey of the IMS Health National Disease and Therapeutic Index (NDTI) that is independent of the Ingenix population and purchased by FDA CDER.**

SECTION 2 - IBS DIAGNOSIS AND THE POTENTIAL FOR MISDIAGNOSIS

Literature Review for IBS Diagnosis and Prognosis: A review of the diagnosis of IBS was conducted, including examination of selected recent (circa 1996) and current (circa 2000 / 2001) textbooks of internal medicine (e.g. Harrison's, Cecil's, Stein) in addition to current textbooks of gastroenterology. In sum, this reviewer concludes that diagnosis of IBS has not changed over the recent past and remains a disease characterized by symptomatology without discrete pathology. Said again, IBS is a diagnosis of exclusion reached after review for "alarm" symptoms and work-up. A recent NEJM review article[1] on IBS recommends a workup to include blood / chemistry profiles and flexible sigmoidoscopy (for those under age 50 yrs) or colonoscopy (for those over age 50 yrs). The same article included a differential diagnosis list to include inflammatory bowel disease, endometriosis, GI malignancy, diverticulitis, ischemia, stricture, and malabsorption / maldigestion. Olden and Schuster, writing in Sleisenger & Fordtran's *Gastroenterology and Liver disease* (1998) outlined prognosis for patients with IBS as follows:

1. IBS does not predispose to other chronic or life threatening conditions (e.g. IBD).
2. IBS does not shorten life.
3. Prognosis for IBS [patients] is good.

Ingenix IBS Case Definition and Original Lotronex Labeling: This review will focus on studies conducted by Ingenix on claims data that rely on use of ICD-9 code ICD-9 564.1 ("irritable colon") with qualifiers as a surrogate for IBS. There is no specific ICD-9 code for "irritable bowel syndrome." In addition to irritable colon, ICD-9 code 564.1 is also listed for adaptive colitis, membranous colitis, mucous colitis, enterospasm, and spastic

colon. Ingenix researchers validate use of ICD-9 code 564.1 for IBS through a review of a sample (n=107) of patient medical records with this diagnosis code. In consultation with a gastroenterologist, 95 (89%) of these patients were deemed to have symptoms "consistent" with IBS [Study 2, page 17]. **Use of ICD-9 code 564.1 as a surrogate for IBS is also supported by an FDA analysis of the IMS Health NDTI physician survey. For the entire period of initial marketing of Lotronex, 83% of Lotronex prescriptions were linked to a diagnosis code of 564.1. Of the remaining diagnostic codes, no other code was used more frequently than 3%.** Furthermore, it should be noted that the original Lotronex label did not restrict Lotronex use by IBS severity or length of IBS symptoms. The original label stated Lotronex was indicated "for the treatment of IBS in women whose predominant bowel symptom is diarrhea" although the discussion under "Clinical Trials" stated that study participants had to meet the Rome IBS criteria for 6 months.

Inflammatory Bowel Disease: In Studies 1 and 2, Ingenix researchers examined patients with at least 6 months of enrollment and a diagnosis of IBS for selected outcomes, including ischemic colitis. Inflammatory Bowel Disease (IBD) was reported in Study 1 as a competing diagnosis and utilized as an exclusion criterion in Study 2 (see below). Thus, both studies highlight the potential for misdiagnosis of IBD (Crohn's disease or ulcerative colitis) as IBS.

Study 1: Study 1 required patients to have a claim for ICD-9 564.1 ("irritable colon") and a diagnostic procedure code for selection as an IBS "case." Ingenix researchers report 1,454 (2.2 %) of 65,063 IBS cases identified in this manner received a diagnosis of Crohn's disease or ulcerative colitis following IBS diagnosis [Study 1, page 59].

Study 2: For inclusion as an IBS "case" in Study 2, individuals were excluded based on the presence of "disqualifying conditions." From a population of 168,990 individuals with a claim/diagnosis of ICD-9 564.1 ("irritable colon"), almost half (81,541, 48.3%) would be excluded from selection as an IBS case due to presence of a disqualifying condition, "principally Crohn's disease and ulcerative colitis." [Study 2, page 5].

Bowel Surgery: After exclusion of patients with a disqualifying condition, Study 2 also reported that 910 (~1%) of patients in the IBS study cohort would undergo bowel surgery (as defined by Ingenix researchers) following the first IBS diagnosis. This is ~5-times the rate expected (in aggregate) [Study 2, page 24]. Ingenix researchers do not explore what conditions / diagnoses these 910 patients were given after surgery. It should be noted that the IBS study cohort created by Ingenix researchers in Study 2 is temporally recent, large (~87,000), and modest in follow-up (1.51 years on average) and offers the potential for further study. Specific questions might include: 1) what conditions could be misdiagnosed as IBS, and 2) what history or tests could isolate IBS patients who will receive a subsequent diagnosis of a discrete, pathophysiologic condition.

Endoscopic Examination: With regard to diagnostic specificity, some information on the work-up of patients with a prescription claim for IBS is provided in Study 5. [page 15]. Under the best case scenario, in which each female Lotronex patient is linked to one endoscopic procedure, it appears that around one-third of the 2,420 **females** with a Lotronex prescription claim had evidence of an endoscopic exam in the 6 months prior to their first prescription. [Ingenix researchers do not attempt to collapse procedures or estimate what fraction of patients with a prescription claim for Lotronex had ANY diagnostic GI procedure in the 6 months prior to their initial prescription.]

Ischemic colitis: In Study 2, cases of colonic ischemia (this review will use the terms "colonic ischemia" and "ischemic colitis" interchangeably) were identified using a two-stage process. First, putative cases were collected using a diagnosis claim for "vascular insufficiency of the intestine" (ICD-9 code 557) within 3 months of a colonoscopy or colectomy. However, as ischemic colitis is one of many discrete but similar medical conditions listed under ICD-9 code 557, these cases were then subjected to an internally validated "case algorithm" before classification as an ischemic colitis "case." Ingenix researchers report 76 cases in the IBS cohort of 87,449 created for Study 2. [page 24]. The aggregate absolute incidence of colonic ischemia in the Ingenix IBS study cohort is thus (8.7 / 10,000) and is similar for females (8.9 / 10,000) and males (8.2 / 10,000).

Further data on incidence (as incidence density) with interest in age as a potential risk factor is presented in the table below for females aged 30-59 years.

| Age range (years) | CI* cases (#) | Person-years | Rate as incidence density (cases per 10,000 person-years) |
|---|---|---|---|
| 30 – 39 | 5 | 29,606 | 1.7 |
| 40 – 49 | 20 | 26,684 | 7.5 |
| 50 – 59 | 23 | 20,354 | 11.3 |
| Total | 48 | 76,644 | 6.3 |

*colonic ischemia

These data support the current, clinical concept that age is an important risk factor for ischemic colitis.

Ingenix researchers also stratify colonic ischemia in relation to time since first IBS claim. These data, restricted (as above) to the 48 cases in females aged 30-59 years, are presented in the following table (adapted from Study 2, page 30).

| | CI* dx ≤ 3 wks following first IBS claim | CI dx > 3 wks & ≤ 6 mo following first IBS claim | CI dx > 6 mo & ≤ 12 mo following first IBS claim | CI dx > 12 mo following first IBS claim |
|---|---|---|---|---|
| Count | 10 | 10 | 9 | 19 |
| Rate** | 56 | 4.2 | 5.1 | 5.3 |

*CI = colonic ischemia

**Rate as cases per 10,000 person-years

As shown, the rate of ischemic colitis is high (56 per 10,000 p-yrs) in the 3 weeks immediately following an initial IBS diagnosis and then falls to a rate that appears constant through 12 months (~5 per 10,000 p-yrs). Thus, even after adjustment for acute (< 3 wks) or semi-acute (<6 mo) illness, these data suggest that there is a background rate for ischemic colitis in this population. It can be hypothesized that these cases represent: 1) use of IBS as an interim diagnosis; or 2) apparent misdiagnosis of ischemic colitis as "IBS." As shown in the Ingenix analysis, the association declines but remains upon

stratification for time from IBS diagnosis. This supports this reviewer's opinion that some patients with discrete GI pathology are receiving the diagnosis of IBS in error ("misdiagnosis") and this misdiagnosis appears to persist over time. Ingenix researchers described this concept as follows:

> "Although we have eliminated IBS [patients] with alternative diagnoses that declared themselves and were diagnosed, there may remain substantial heterogeneity among IBS patients. The label "IBS" in mainstream US medical care includes symptomatic patients who have not been fully evaluated for alternative sources of their symptoms, and it is possible, even likely, that the high rates of colonic ischemia [and other conditions] that we have identified stem in part from conditions that are not truly IBS, but instead have symptomatic presentations that can be mistaken for IBS." [Study 2, page 23, Conclusions].

SECTION 3 -

ESTIMATION OF RISK FOR ISCHEMIC COLITIS IN LOTRONEX USERS

Study Design Issues: The data presented above support the hypothesis that a "background" rate of ischemic colitis (and other conditions) exists "misdiagnosed" as IBS in a subpopulation of U.S. IBS patients. Pending validation by other investigators in other US settings, this hypothesis is not unrealistic and could affect assessment of the risk for IC in association with Lotronex. Thus, under the hypothesis that there is a non-insignificant "background" rate of ischemic colitis misdiagnosed as IBS, and as Lotronex has been associated with ischemic colitis, any investigation of ischemic colitis in association with Lotronex must be derived from randomized, double blind studies – preferably placebo controlled. Restriction to these studies will mitigate (actually equalize through randomization) the potential for misdiagnosis between arms. In addition, given the (apparent) heterogeneity of an "IBS" diagnosis (including misdiagnoses), an established concern for ischemic colitis in association with Lotronex (which may prompt screening), and a desire to prospectively adjudicate putative cases of ischemic colitis, further examination of this association in retrospective, observational studies for regulatory purposes is not practical and not recommended by ODS.

Relative risk estimates for ischemic colitis in association with Lotronex: In a final assessment of case counts of ischemic colitis in clinical trials of Lotronex, reviewers from HFD-580 report 19 cases in the RCTs of Lotronex. Ten of these cases come from one, open label study (30020). Six cases (5 on Lotronex and one on placebo) come from 8 US randomized, double-blind, placebo-controlled studies of Lotronex restricted to females with IBS. [Three remaining cases include one male patient, one female patient from a Canadian RCT, and one female patient from another open-label study.] The following table outlines study characteristics and ischemic colitis cases in association with Lotronex from the 8 randomized, double-blind, placebo-controlled studies of females with IBS conducted in the US. The table is based on data contained in the review by Hugo Gallo-Torres dated March 7, 2001 (e.g. number of cases, case descriptions) and other data provided by Dr. Gallo-Torres directly to this reviewer (e.g. number of FEMALE participants per treatment arm).

| Study ID # | Length (weeks) | Lotronex # IC† cases / # in arm | Placebo # IC† cases / # in arm |
|---|---|---|---|
| A2001 | 12 | 1 / 196 | 0 / 56 |
| A3001 | 12 | 1 / 309 | 0 / 317 |
| A3002 | 12 | 1 / 324 | 0 / 323 |
| 30011 | 12 | 1 / 532 | 0 / 269 |
| 30006 | 48 | 0 / 351 | 0 / 363 |
| 40031 | 12 | 0 / 246 | 0 / 246 |
| 30013 | 12 | 1 / 280 | 0 / 281 |
| A3003 | 52 | 0 / 480 | 1* / 155 |
| Sum | | 5 / 2718 | 1* / 2010 |

†IC = ischemic colitis

*The authors of the article (Am J Gastro 2001;96:803-11) describing this study concluded that endoscopic colonic biopsy did not support the clinical diagnosis of ischemic colitis in this 27 year old.

The following table outlines relative risk estimates for ischemic colitis with exposure to Lotronex based on the original NDA studies followed by the sum of the studies shown above, with and without the case assigned to a placebo arm:

| Setting (# of IC† cases, Lotronex vs placebo) | RR | 95% CI (logit) | P-value (Fisher's exact, 2 tail) |
|---|---|---|---|
| Original NDA (3 vs 0) | 5.9* | 0.3 - 114 | 0.26 |
| sNDA (5 vs 1) | 3.7 | 0.5 - 31 | 0.25 |
| sNDA (5 vs 0) | 8.1* | 0.4 – 147 | 0.08 |

†IC = ischemic colitis
*based on addition of 0.5 to every cell

Risk Attributable to Lotronex Use: Attributable risk is an epidemiological concept that permits attribution of disease to a selective factor when there is a background rate for the disease. It is calculated by the differences in rates (exposed – unexposed) divided by the rate in the exposed. Thus, given that FDA CDER has and will receive reports of ischemic colitis in association with Lotronex, and the hypothesis that there is a "background" rate of ischemic colitis in IBS patients, calculation of attributable risk permits attribution of the percent of spontaneous reports expected to be due to Lotronex. While described as a difference in rates, the relative risk for the disease given exposure is the primary factor in the calculation of attributable risk. Thus, observation (or selection) of an absolute rate and a rate with exposure is not necessary. Based on a choice of 5.9 as the best estimate for the relative risk for ischemic colitis in association with Lotronex use, we expect that 83% of reports of ischemic colitis reported in association with Lotronex will be attributable to Lotronex – the remaining 17% of reports will be attributable to background disease.

## DISCUSSION

This review has included a summary relative risk estimate based on studies submitted in the Lotronex NDA and sNDA. It is very important to note that generation of this summary risk estimate is analogous to a meta-analysis and the trials may have substantial differences. I restrict my summary estimate to 8 US randomized, double-blind, placebo-

controlled studies of Lotronex that enrolled females with IBS. There are other studies, specifically randomized but open label studies that can be used to examine rates and risks for ischemic colitis in association with Lotronex. In a separate review, ODS MO Zili Li presents a strong case against pooling studies and suggests a substantially higher relative risk estimate. Different relative risk point estimates and/or rates have also been generated in other reviews by different members of the Biometrics review team and HFD-180 review team. The relative risk point estimate I used for calculation of attributable risk was 5.9. This was the point estimate calculated from the initial NDA and a compromise given point estimates of 3.7 and 8.1 (shown in the table above) from the sNDA. While none of these point estimates reach the statistical test of 0.05, it is important to note that one of the open-label trials (30020) included 10 cases of ischemic colitis on the Lotronex arm versus 0 for patients randomized to conventional treatment. Further details on this trial are available in the reviews by Dr. Sheldon Kress (dated Feb 8, 2002) and Zili Li, MD.

CONCLUSIONS

Ten epidemiological studies submitted with the Lotronex (alosetron) sNDA were given expedited review for relevant and novel information pertinent to ischemic colitis and the possible re-introduction of Lotronex to the US marketplace. In summation, these studies support the following positions:

1. During initial U.S. marketing, the majority of Lotronex prescribers were not gastroenterologists.
2. The diagnosis of irritable bowel syndrome (IBS) is problematic. Clinicians may utilize IBS as an interim diagnosis or as a misdiagnosis of other conditions (e.g., inflammatory bowel disease, ischemic colitis, etc.).
3. Data and analysis based on the Ingenix Research Database support a "background" rate of ischemic colitis among U.S. patients given a diagnosis of IBS in clinical practice. This should be validated by other investigators in other large cohorts of U.S. patients / populations carrying a diagnosis of IBS.

4. Under the hypothesis that there is a "background" rate or risk for misdiagnosed ischemic colitis among patients given the diagnosis of IBS in clinical practice, the best estimate of an association between Lotronex and ischemic colitis will be derived from randomized, double-blind, placebo-controlled trials of Lotronex in IBS patients. If additional placebo-controlled trials are not feasible, further studies of ischemic colitis in association with Lotronex could also include randomized, **double-blind** active control trials in IBS patients.

5. Given the (apparent) heterogeneity of an "IBS" diagnosis and an established concern for ischemic colitis in association with Lotronex, further examination of this association in retrospective, observational settings for regulatory purposes is impractical and not recommended by ODS.

6. A relative risk for ischemic colitis in association with Lotronex of 5.9 (with wide confidence intervals) was seen in the original NDA and represents a compromise summary RR point estimate after consideration of selected, placebo-controlled Lotronex RCTs. This relative risk was used to calculate an expectation that most (83%) spontaneous reports of ischemic colitis reported in association with Lotronex can be attributed to Lotronex and not background disease.

REFERENCES

1. Horwitz BJ, Fisher RS. The irritable bowel syndrome. N Engl J Med 2001;344(24):1846-50.

Allen Brinker, MD, MS

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

**MEDICAL OFFICER'S REVIEW**

**POSSIBLE MECHANISMS (PHYSIOPATHOLOGY) BY WHICH ALOSETRON-INDUCED ISCHEMIC BOWEL DISEASE/ISCHEMIC COLITIS OCCURS**

NDA: 21-107 S-005
SPONSOR: GlaxoSmithkline (formerly Glaxo Wellcome, Inc)
DRUG: Alosetron Hydrochloride (LOTRONEX™) Tablets
DATE OF ORIGINAL SUBMISSION: 29 June, 1999
DATE OF ORIGINAL APPROVAL: 9 February, 2000
VOLUNTARY WITHDRAWAL FROM THE MARKET: 28 November, 2000
DATE OF sNDA SUBMISSION: 7 December, 2001
MEDICAL OFFICER: Marcelo A. Barreiro, MD, MSc
MATERIAL REVIEWED: 1) Alosetron Investigator's Brochures, 2) References cited

## I - BACKGROUND

Serotonin receptors are highly heterogeneous and have been regrouped within seven different families (5-HT 1 to 5-HT 7). With the exception of the 5 HT-3 which is a **ligand-gated ion channel**, all others are **G-protein coupled receptors** with each family sharing structural, pharmacological and transductional characteristics.
**Channel proteins** form water filled pores across membranes. Channel proteins in the plasma membrane of animal and plant cells have small, highly selective pores. All these channel proteins are concerned specifically with ion transport and so are referred to as **ion channels**. These ion channels differ from simple pores in that they are not continually open, but they have **"gates",** which open and close in response to perturbations of the membrane. The binding of a single molecule (**ligand-gated channels**) can be a factor triggering the opening of the ion channel. **The signaling ligand can be either an extracellular mediator, called a neurotransmitter (transmitter-gated channels), or an intracellular mediator, such as an ion, a nucleotide, or a GTP-binding regulatory protein (G-protein-gated channels).** Approximately 50 types of ion channels have been described and they are responsible for the electrical excitability of nerve and muscle cells and mediate most forms of electrical signaling in the nervous system. A single nerve cell contains more than five kinds of ion channels.

## II - POSSIBLE MECHANISMS

**A - Summary of Pertinent Literature Data.** The intimate mechanism of drug-induced IC hasn't been elucidated. Possible mechanisms may be proposed in what is known with other drugs, including those that are known to induce ischemic bowel disease/ischemic colitis. Necrosis of the gastrointestinal mucosa has been reported with **paclitaxel**, which also inhibits angiogenesis, and is used as chemotherapy in cancer [J Clin Gast 2001;33(2) 159-160]. Transient colonic ischemia (ischemic colitis) before the age of 50 is found almost exclusively in women and is associate with the use **of exogenous estrogenic agents** [Am J Surg Pathol 1995; 19(4):454-462]. **Pseudoepinephrine** present

in nasal decongestants, because of its vasoconstrictive action may predispose peri-menopausal women to develop IC. The irregular ovulation may result in relative **vasoconstriction when estrogen levels are low or a hypercoagulable state when estrogen levels are excessive** [Am J Gastroenterol 1999; 94(9):2430-2434]. **Premarin** (equine conjugated estrogen) has also been associated with IC [J Clin Gastroent. 1994; 19(2):108-111]. Eight cases of serious **sumatriptan**-induced IC in patients with migraine have been reported. Vasopressor responses distinct from the cranial circulation have occurred with this 5-HT 1 receptor agonist.[Arch Intern Med 1998; 158(17):1946-1948]

**B - Information Applicable to Alosetron.**

All forms of Ischemic Bowel Disease have been observed associated with alosetron, from the transient IC to severe gangrene of the small and/or large bowel due to mesenteric vein thromboses or mesenteric artery thromboses.

Alosetron is a 5-HT 3 receptor antagonist. The following points are relevant to our understanding of alosetron-associated ischemic bowel disease (AAIscBD):

- Agonists of 5-HT 3 receptor sites increase motility, increase secretion from the colonic crypt (diarrhea) and increase the micro-circulation to support the additional energy expenditure (demand).
- Alosetron inhibits colonic motility, increases colonic compliance, decreases colonic sensitivity and decreases colonic secretion from the glandular crypt (constipation).
- The vascular and hemodynamic effects of Alosetron have not been studied with the same degree of interest than its motility effects. There is a large gap of knowledge in this respect, that precludes a detailed understanding of AAIscBD.
- Alosetron-induced IC has been reported in man [Gastroenterology 2001;120(2):557-560]
- Five cases reported by this reviewer[1] had frank diagnosis or strong suspicion of a[1] hypercoagulable state (#s 7195, 68, 157, 152 and 25). Whether these were cases of congenital thrombophilia (5-8 % of the population) or were secondary to estrogen use, is not known.
- We now know that each vascular bed is qualitatively unique in maintaining its hemostatic balance. The molecular mechanisms that underlie these vascular-bed-specific differences are found in complex signaling networks that have evolved in the endothelial-cell lining of the vascular tree. The endothelium integrates and transduces multiple signals that vary in both time and space. In patients with congenital or acquired thrombophilia, signaling pathways are differentially affected in different segments of the vascular tree, leading to characteristic thrombotic phenotypes.
- Alosetron is metabolized in the liver by CYP 1A2, 2C9, and 3A4, sharing these metabolic pathways with other drugs, such as exogenous sex hormones, antidepressants, etc. Drug-drug interactions might be possible.
- Drug-drug interactions involving Alosetron have been studied in healthy volunteers or small groups of patients with IBS, but not in patients that may be susceptible to

[1] M. A. Barreiro, MD, MSc Medical Officer's Review. Ischemic Bowel complications associated with alosetron (Lotronex™) intake

develop ischemic changes of the gastrointestinal mucosa, such as those affected with a hyper-coagulable state.

**III - HYPOTHESIS: A small but significant percentage of the population is genetically different in one of possible ways:**

- They metabolize alosetron differently when in presence of other drugs metabolized by same CYP 450 enzyme systems. This interaction may result in either unusually high blood levels of alosetron, or biologically active metabolites. These metabolites may trigger signals in the endothelium of the splachnic vascular bed.
- In patients with a congenital (and undiagnosed) thrombophilia, alosetron or one of its (active) metabolites trigger a cascade of events leading to AAIscBD that may range in severity from the usually seen mild, acute, self-limited IC to more serious thrombotic events. These are patients with a history of deep vein thromboses associated with birth control pills, complicated pregnancies, myeloproliferative disorders, malignancies, etc.

**IV - RECOMMENDATIONS FOR REGULATORY ACTION:**

- As part of the RMP, patients who are prescribed Alosetron, should receive a card with instructions for the ER physician: in case of abdominal pain and/or rectal bleeding, on arrival to the ER or immediately after triage, obtain two blood samples (eg: two red-tops, or one lavender and one red-top, etc) for genetic studies and coagulation studies.
- Perform a retrospective study of genetic and coagulation factors in patients who have had any form of AAIscBD, during the RCTs or, if possible, during the post-marketing period up to 28 November 2000.

Marcelo A. Barreiro, MD, MSc

I concur,

H. Gallo-Torres, MD, PhD

cc: Hugo Gallo-Torres, MD, PhD
Joyce Korvick, MD, MPH
Victor Raczkowsky, MD
S. Kress, MD
Zili Li, MD, PhD
Julie B Meitz, MD
M. A. Barreiro, MD, MSc

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

/s/
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Marcelo Barreiro
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Hugo Gallo Torres
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**M E M O R A N D U M** **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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**DATE:** March 15, 2002

**TO:** Victor Raczkowski, M.D., Acting Director
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

**THROUGH:** Julie Beitz, M.D. Director
Division of Drug Risk Evaluation, HFD-430
Office of Drug Safety

**FROM:** Zili Li, M.D., M.P.H., Medical Epidemiologist
Division of Drug Risk Evaluation, HFD-430
Office of Drug Safety

**SUBJECT:** **Reevaluating the risk of ischemic colitis and its association with alosetron among female IBS patients in the United States**

**PID#:** D#020115 **NDA #:** 21-107

## I. Executive Summary

This memorandum is in response to a request from Dr. Victor Raczkowski, Acting Director of Division of Gastrointestinal and Coagulation Drug Products (HFD-180), to summarize the analysis that this reviewer had conducted on the risk of ischemic colitis (IC) and its association with alosetron among female irritable bowel syndrome IBS patients in the United States. The analysis was designed to establish a statistical association, to quantify the magnitude of the risk, and to search for the factors that may play a role in reducing the risk of IC.

This analysis focused on 11 of 86 clinical studies that GlaxoSmithKline (GSK) submitted on December 7, 2001. These 11 clinical efficacy or outcomes studies were conducted on female IBS patients in the US, a population similar to the target population under regulatory consideration. These 11 studies, ranging from 12 to 52 weeks, enrolled a total of 5,525 women in alosetron groups, and 2,905 in either placebo or traditional therapy groups. The strongest evidence that supports a causal relationship for alosetron and IC comes from clinical trial S3B30020 where 1,819 alosetron-treated patients and 899 control patients were treated and followed for up to 24 weeks. Ten IC cases were observed in the alosetron group and none in the control group. The incidence rate of IC was 16.9 cases per 1,000 person years and 0 respectively for the two groups ($p<0.001$). In addition, 6 more IC cases occurred in the alosetron-treated groups of the remaining 10 studies, while only one case was reported in the control groups of those same studies.

Pooling data from these 11 studies or any other studies included in the December 7, 2001 submission is problematic given the differences in trial designs, patient host factors and potential case ascertainment bias. After examining the distribution of patient characteristics and the study-specific incidence rates among these 11 studies, this reviewer concluded that the incidence rate from study S3B30020 represents the most reasonable and reliable estimate for the risk of IC among female IBS patients in the United States. The rate of 16.9 cases per 1,000 person years, while being consistent with our previous estimate of 18.3 per 1,000 person years, is approximately three times higher than that calculated by GSK (5.6 per 1,000 person years) in their submission. As discussed in this consult, the lower estimate from GSK was the result of data pooling from 86 studies and is limited by case ascertainment bias and inclusion of heterogeneous patient populations.

The risk of IC appeared to be at the highest during the first month of treatment, with a rate of 3.6 cases per 1,000 persons. Due to small numbers of IC cases in the remaining monthly intervals, however, no statistically meaningful conclusion can be made about the risk of IC over time. Age, weight and estrogen use were not associated with the development of IC among alosetron-treated patients. At this point, we are lacking strategies to reduce the risk of IC, though the number of IC cases may be reduced by limiting the number of patients exposed to the drug and shortening the duration of the treatment.

This reviewer suggests that the risk of IC may be three times higher than that presented in GSK's current submission.

## II. Background

Alosetron, a 5-$HT_3$ antagonist, approved for the treatment of diarrhea-predominant irritable bowel syndrome (IBS) among women in the United States, is associated with the risk of ischemic colitis (IC). While GlaxoSmithKline (GSK) suspended the sale of the drug on November 28, 2008, the magnitude of the risk has not yet been fully determined.

In his original NDA review in June 1999, Dr. John Senior pointed out that the risk of IC was 1 per 307 persons for a 12-week treatment based on two pivotal studies submitted by GSK[1] (Sponsor). In a letter to the GI review division[2], however, the sponsor argued that, as of November 16, 1999, only 4 out of 3,000 subjects treated with Alosetron were reported as having IC. As of June 1, 2000, the number was 7 out of 6,500 treated subjects. The risk, therefore, should be 1 in 700 or 1000 persons. The official estimate in Product Labeling was 1/700 persons.

In March 2000, Dr. Houn, director of the Office of Drug Evaluation III (ODE III), asked this reviewer to reevaluate the methods used by the sponsor in the calculation of the risk of IC as stated in the Product Labeling. That review found that the risk of IC was underestimated because, among many other reasons, the sponsor had failed to adjust for duration of treatment while pooling data from the different studies[3]. Based on all relevant data that was available to this reviewer, the incidence of IC was estimated at 1 in 656 persons for a one-month treatment, or 1 in 218 persons for a three-month treatment. That rate is equivalent to 18.3 per 1,000 person years.

On December 7, 2001, the sponsor submitted a sNDA requesting reintroduction of alosetron in the US market under a restricted program. As part of the submission, the sponsor included an analytical database, including all recognized adverse events for all subjects from their clinical development program. This consult summarizes the analyses that this reviewer has conducted to address several issues, including evidence of a statistical association, magnitude of the risk, and risk factors for IC. A summary of these analyses were presented at Office of Drug Safety (ODS)'s Epi Forum on January 28, to the GI division on March 7, and to GSK on March 13, 2002.

**III. Risk Assessment: GKS Analysis**

The sponsor's risk assessment was based on data pooled from 86 clinical studies, ranging from single dose PK/PD studies to 52-week randomized, placebo controlled clinical trials. In addition to differences in the study design and duration, the patient populations also differed in many ways. The study population included:

(1) Study subjects: healthy volunteers, patients with IBS (all three subtypes), and patients with functional dyspepsia or other conditions;
(2) Gender: female and male patients
(3) Genetic/Geographic Variation: US, Canada, Europe, South America and Asia sites enrolled patients.

The submission stated that 11,874 subjects had received one or more doses of alosetron, representing a total of 2881 person years of drug exposure. Among them, 16 developed an episode of IC. The sponsor, therefore, concluded that the incidence rate of IC was 5.6 cases per 1,000 person years of alosetron therapy. The sponsor did not provide an analysis of the statistical association and the role of potential risk factors. A detailed analysis and conclusion from the sponsor is listed under Appendix A.

**Reviewer's Comments:** *Pooling data from different studies (data pooling) is a commonly used strategy to achieve a more stable estimate for a low frequency adverse event, such as IC. Before data pooling is conducted, however, the following principles should be considered:*

*(1) Principle of Relevancy: Alosetron is only approved for diarrhea-predominant IBS women in the US (target population). By including male, non-IBS and non-US populations in the rate calculation, the sponsor produced an estimate that may not be relevant to the target population under regulatory consideration. At a minimum, the estimates for the target and non-target populations should be calculated separately.*

*(2) Principle of Homogeneity: The purpose of data pooling is to establish a stable estimate for a population that is relatively homogenous. Data pooling over a heterogeneous population, as was done in this case, may conceal the risk differences among each subset of the population.*

*(3) Principle of Study-Specific Assessment: Even if the patient populations from the various studies appear to be homogenous, the study-specific incidence rates should be calculated and compared before those studies are pooled. Since none of the 86 studies submitted were safety trials, an ACTIVE surveillance process was not used to identify or report IC cases. Safety reporting depended on a patient's motivation to report the symptoms of IC to their physicians, the physician's ability to recognize those symptoms, and to conduct an*

*appropriate work-up. If poor case ascertainment occurred in some of the studies, the risk could be underestimated when all studies are combined.*

## IV. Risk Assessment: ODS Analysis

**Data Source and Quality:**
The sponsor submitted an analytical database (SAS format) on November 19, 2001, which is the source of the data for this analysis. Appendix B lists the original database structure, and the computer programming and procedures that this reviewer used to convert the original event-level database into a patient-level database. 11,601 subjects from 86 studies were identified as having received at least one dose of alosetron, representing a total of 2874 years of drug exposure. Although these numbers differed from those provided by the sponsor (11,874 subjects and 2881 person years of alosetron use), the difference was minor, and should have little impact on the analyses and study conclusions.

**Analytical Strategy:**
The analytical approach consists of the following three steps:

1. Limit the primary analysis to the target population that is relevant to the regulatory decision;
2. Assess the appropriateness of data pooling within the target population (if data pooling is not appropriate, go to next step)
3. Review the totality of the evidence and select a "representative" study.

The risk of IC was calculated and expressed in person years. The statistical significance for the rate difference was based on Poisson distribution. A Cox model was used to assess the roles of age, weight and estrogen use in the development of IC among alosetron-treated patients. All analyses were conducted using Stata 7.0.

**Step 1: Selecting the Studies of the Target Population:**
As stated earlier, the primary analysis focused on the target population that was relevant to the regulatory decision. Appendix C shows a flow chart on the selection process used to choose the studies in the target population. Since the database did not provide indicators for IBS subtype, the target population in this analysis included all IBS patients regardless of subtype. The chart provides a step-by-step illustration of the number of studies, the number of subjects, the cumulative length of alosetron use (in person years), the number of IC cases reported, and incidence rates calculated for each subset of the original patient population.

The chart clearly demonstrated not only that the 11,601 alosetron-treated patients from the original 86 clinical studies were heterogeneous in terms IBS status, gender and geographic variation, but also the incidence rates among the sub-groups of this heterogeneous population varied widely, ranging from 0 to 9.3 per 1,000 person years. This finding strongly supports the conclusion that the data pooling strategy employed by the sponsor was problematic.

Of 14 studies in the target population listed under Appendix C, three were excluded from further analysis because they had less than 50 study subjects in the alosetron group (S3B30004, S3B30015, and S3B30019). Of the remaining 11 studies, 5,525 female IBS patients accumulated a total of 1745.3 years of alosetron use, where 16 cases of IC were discovered, resulting in an average incidence rate of 9.2 cases per 1,000 person years.

**Step 2: Assessing the appropriateness of data pooling from the studies of the target population:**

It could be argued that 9.2 cases per 1,000 person years represents a reasonable estimate for the risk of IC among alosetron-treated female IBS patients in the United States. All 11 studies come from a relatively homogenous population - female IBS in the US and patient characteristics appeared to be similar among these studies (Table 1).

Table 1. Mean age and weight and percentages with estrogen use among 11 clinical studies of the target population

| Study ID | Length of the Study (weeks) | Number of Female Patients Enrolled | Age (Mean) | Weight (Mean) | % with Estrogen |
|---|---|---|---|---|---|
| S3B30020 | 26 | 1819 | 48.7 | 167 | 47.0% |
| S3BA2001 | 12 | 196 | 43.9 | 163 | 51.5% |
| S3BA3001 | 12 | 309 | 46.5 | 166 | 53.1% |
| S3BA3002 | 12 | 323 | 46.6 | 164 | 49.5% |
| S3B30011 | 12 | 532 | 47.5 | 167 | 49.8% |
| S3B30006 | 48 | 348 | 46.0 | 169 | 49.1% |
| S3B30012 | 8+16 | 422 | 40.3 | 173 | 47.6% |
| S3B30013 | 12 | 280 | 47.1 | 171 | 51.4% |
| S3B40031 | 12 | 246 | 48.5 | 169 | 48.4% |
| S3B40032 | 12 | 577 | 47.2 | --- | 6.9% |
| S3BA3003 | 52 | 473 | 47.5 | 162 | 59.4% |

If we look at the study-specific incidence rates of IC among those studies, however, they varied widely from 0 to 26.7 per 1,000 person years (Table 2), which makes data pooling problematic. Of special concern was that the trials with the largest person time (S3B30020) had 10 IC cases, but two long-term clinical trials with the 2nd and 3rd largest person time (S3B30006 and S3BA3003) had none. Therefore, the pooled estimate (9.2 cases per 1,000 person years) from these 11 studies may under-estimate the real risk of IC in this population because of the inclusion of long-term trials with no IC cases.

One of the arguments, of course, could be that trials with no IC cases may just represent random variation, i.e. they could happen just by chance alone. This reviewer conducted a test of statistical significance of the results of S3BA3003 and S3B30020, which generated a p-value of 0.005 based on Poisson distribution (Appendix D). Assuming that patient characteristics from these two studies were similar, this result indicates that the chance that ten cases occurred in one study but none in the other is approximately 5 per 1,000. The chance that two long-term trials

had no IC cases could only be smaller. The more probable explanation for the absence of IC cases in long-term studies is poor case ascertainment, as explained earlier.

Table 2. Study-specific incidence rates of ischemic colitis among 11 studies conducted in the target population (female IBS in the United States)

| Study ID | Length of the Study (weeks) | Number of Female Patients Enrolled | Person Years of Exposure | Number of Ischemic Colitis | Incidence Rate (in 1,000 PY) |
|---|---|---|---|---|---|
| S3BA2001 | 12 | 196 | 37.5 | 1 | 26.7 |
| S3B30013 | 12 | 280 | 53.7 | 1 | 18.6 |
| **S3B30020** | **24** | **1819** | **592.4** | **10** | **16.9** |
| S3BA3001 | 12 | 309 | 60.9 | 1 | 16.4 |
| S3BA3002 | 12 | 323 | 63.5 | 1 | 15.7 |
| S3B30011 | 12 | 532 | 110.3 | 1 | 9.1 |
| S3B30012 | 8+16 | 422 | 124.1 | 1 | 8.1 |
| S3B30006 | 48 | 348 | 232.5 | 0 | 0 |
| S3B40031 | 12 | 246 | 45.2 | 0 | 0 |
| S3B40032 | 12 | 577 | 104.2 | 0 | 0 |
| S3BA3003 | 52 | 473 | 321.0 | 0 | 0 |
| Total | | 5,525 | 1745.3 | 16 | 9.2 |

**Step 3: Reviewing the totality of the evidence and selecting a "representative" study**
The reluctance of this reviewer to pool data from these 11 studies, however, does not suggest that we should not look at the totality of evidence presented by all studies. On the contrary, if we look carefully at all the evidence presented by these 11 studies, it is not difficult to conclude that the best estimate for the risk of IC is the rate calculated from study S3B30020. This trial is selected because it has the greatest potential to produce a stable estimate since it has the longest person years of patient follow-up. In addition, patient characteristics, such as IBS status, age, weight and estrogen use were similar between S3B30020 and the remaining ten studies as demonstrated under Table 2 except for estrogen use in S3B40032.

Since S3B30020 has also had the largest number of IC cases in the alosetron group, one possible argument against this choice could be that this open-label study produced a biased estimate against alosetron because investigators were specifically instructed to look for IC. As a result, more IC cases were reported.

Again, there was no evidence that the result of study S3B30020 was biased against alosetron because the incidence rate from S3B30020 was right in the middle of all estimates generated by these 11 studies as shown in Table 2. The fact that more cases were reported in this study may mean that there might be less under-reporting in this study.

**What can we learn from Study S3B30020 ?**

Study S3B30020 was a randomized, US multi-center, open label study among women with diarrhea predominant IBS. The study was initiated on March 21, 1999 and was terminated on November 28, 2000 after the sponsor suspended sales of alosetron in the United States. 1,819 patients received at least one dose of alosetron (alosetron group), and 889 patients were treated with traditional therapy (control group). This study was used by this reviewer to explore the following four questions that are relevant and important to future regulatory decisions on alosetron:

(1) Is there a statistical association between alosetron and IC?
(2) What is the magnitude of the risk?
(3) Is the risk constant over time?
(4) What are potential risk factors for alosetron-induced IC?

*Magnitude of the risk and statistical association:* The patients in the alosetron group were comparable to those in the control group with regard to age, weight, and percentage of patients using estrogen and beta-blocker (Table 3). Ten IC cases occurred in the alosetron group but none in the control group. The incidence rates in the alosetron and control group were 16.9 cases per 1,000 person years and 0 cases per 1,000 person years respectively. The rate difference was statistically significant at $p = 0.001$ level (Table 4). This is so far the strongest evidence that links alosetron to IC.

Table 3: Patient characteristics of the alosetron and control group in S3B30020

| Study ID | Alosetron Group (n=1819) | Control Group (n=889) | p-value |
|---|---|---|---|
| Age (mean) | 48.7 yrs | 48.1 yrs | 0.364 |
| Weight (mean) | 167 lbs | 169 lbs | 0.253 |
| % with estrogen use | 47.0% | 46.1% | 0.665 |
| % with beta-blocker use | 8.5% | 10.1% | 0.172 |
| Length of Treatment (mean) | 119 days | 143 days | <0.001 |

Table 4: Rate difference between the alosetron and control group in S3B30020

| | Alosetron (n=1819) | Control (n=889) |
|---|---|---|
| Number of Ischemic Colitis Cases | 10 | 0 |
| Cumulative Drug Exposure (in person years) | 592.4 | 348.0 |
| Incidence Rate (per 1,000 person years) | 16.9 | 0 |
| Rate difference (95% CI) | 16.9 (6.4, 27.4) ($p < 0.001$) | |

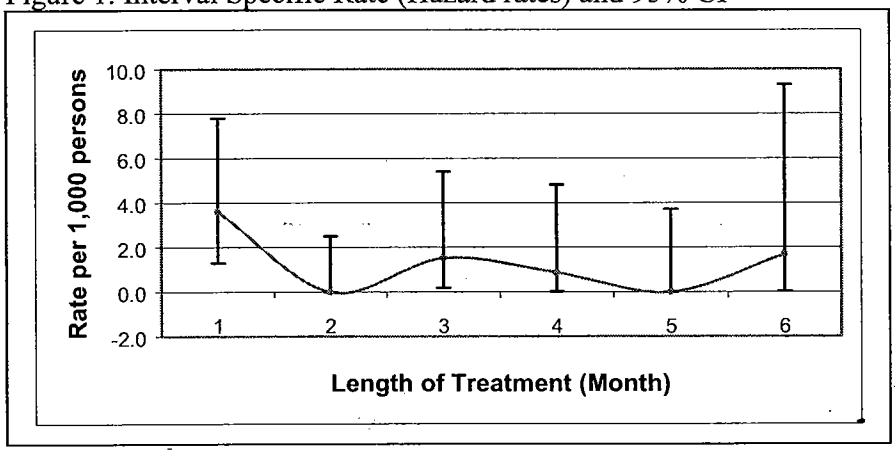
*Risk constancy:* Of the 10 IC cases in the study, 6 occurred within the first 30 days of alosetron treatment. The interval specific rate (hazard rate) during the first month of therapy was 3.6 per 1,000 persons, which appeared to be higher than rates observed during the ensuing five months

(Table 5). However, there is insufficient statistical power to confirm changes in rates over time due to the wide range of 95% confidence intervals (CI) around these estimates (Figure 1).

Table 5: Life-table analysis on the hazard rates

| Interval (Days) | Number of Patients Remaining on Study at the Beginning of the Interval | Number of Ischemic Colitis Cases | Number of Patients Lost to Follow-up | Interval Specific Rate (per 1,000) | Cumulative Rate (per 1,000) |
|---|---|---|---|---|---|
| 0 - 30 | 1819 | 6 | 279 | 3.6 | 3.6 |
| 31-60 | 1534 | 0 | 120 | 0 | 3.6 |
| 61-90 | 1414 | 2 | 175 | 1.51 | 5.1 |
| 91-120 | 1237 | 1 | 167 | 0.87 | 5.9 |
| 121-150 | 1069 | 0 | 157 | 0 | 5.9 |
| 151-180 | 912 | 1 | 822 | 1.68 | 7.9 |
| 181-210 | 89 | 0 | 77 | -- | -- |

Figure 1. Interval Specific Rate (Hazard rates) and 95% CI




*Risk factors:* By employing a Cox model, this reviewer explored the role of age, weight and estrogen use in the development of IC among alosetron-treated patients. The results showed that there was no statistical evidence that any of these variables played a role in the development of alosetron-associated IC (Table 6).

Table 6: The relative risk (expressed as hazard ratio) of age, weight and estrogen use in the development of ischemic colitis among 1819 alosetron-treated female IBS patients*

| Variables | Hazard Ratio | P value |
|---|---|---|
| Age (in years) | 1.0 | 0.454 |
| Weight (in lb.) | 1.0 | 0.901 |
| Estrogen use (yes or no) | 1.6 | 0.471 |

* 20 of 1819 patients had a missing value in weight and were replaced with 167 lb. (the mean for the remaining population)

The following should be considered when interpreting the study findings from S3B30020:

(1) The reason to express the risk in person years instead of other units, such as person months, or person days, was to provide a comparable unit of measurement to the results that were presented by GSK. Since the clinical trial lasted only 6 months, the incidence rate is strictly only applicable to the first 6 months of therapy. There are little data to either support or reject any prediction beyond the first 6 months of treatment. Given the totality of the evidence demonstrated here, however, this reviewer believes that the risk should be assumed to be continuous beyond the first 6 months unless proven otherwise.

(2) To express risk in person time assumes that the risk is constant over the period during which the rate is calculated. Even if the risk is not constant, it is difficult to prove it in most cases, because we are dealing with rare adverse events and insufficient sample size.

(3) When predicting the number of patients who may develop IC during alosetron treatment, it is important to remember that not all patients in the real world will stay on the drug for the same period of time.

**VI. Conclusion:**

Data pooling may produce an estimate ranging from 5.6 to 9.2 per 1,000 person years. Given the heterogeneity of the patient population enrolled on clinical studies and the potential for case ascertainment bias, it was problematic to use data pooling to quantify the risk of IC among female IBS patients in the United States. By employing a study-specific approach, this reviewer concluded that the best estimate of the risk is 16.9 cases per 1,000 person years among female IBS patient in the US. This conclusion is supported by the totality of the evidence from 11 clinical studies in the target population. The risk of IC appeared to be at the highest during the first month of alosetron treatment. In the absence of statistical confirmation, however, constant risk over time seems to be a reasonable assumption. A strong statistical association between alosetron and IC was demonstrated. Age, weight and estrogen use were not associated with the development of IC. At this point, we are lacking strategies to reduce the risk or rate of IC among alosetron-treated patients, though the numbers of IC cases may be reduced by limiting the number of patients exposed to the drug and by reducing the duration of treatment.

Zili Li, MD, MPH
Medical Officer (Epidemiology)

Concur:

Mary E. Willy, PhD, MPH
Team Leader

**Reference:**


1. John R. Senior. Medical officer's new drug application (NDA) review, October 15, 1999, FDA's Division Files System
2. NDA 21-107; Lotronex (alosetron hydrochloride) Tablets General Correspondence: labeling, Glaxo Wellcome Inc, June 12, 2000
3. Zili Li. Recalculation of the incidence rate of alosetron-associated ischemic colitis among women in the United States. Memorandum to HFD-103, April 2, 2001.

cc:
NDA 21-107
Division Files
HFD-103 Director, Deputy
HFD-180 Deputy, Medical TL, MO, CPMS
HFD-440 Director, Deputy, Epi, SETL, SE, PM, Chron, Drug

Appendix A
Analysis and Conclusion of GSK on the Risk of Ischemic Colitis

The following three pages are copied from GSK's December 7th, 2001 submission.

## The GlaxoSmithKline group of companies

# Integrated Summary of Safety of Alosetron (GR68755) for the Treatment of Irritable Bowel Syndrome

**Document Number: RM2001/00175/00**

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Integrated Summary of Safety of Alosetron (GR68755) for the Treatment of Irritable Bowel Syndrome

Date of Report: November 2001

---

**Sponsor Signatory:**
(and Medical Officer)
Vanessa Z. Ameen, MD
Director, Clinical Development, North American Medical Affairs

All clinical studies were performed in compliance with Good Clinical Practices and GlaxoSmithKline Standard Operating Procedures for all processes involved, including the archiving of essential documents.

### 5.9.2.2. Onset, risk, and incidence rate of ischemic colitis in all studies evaluating alosetron

Tables 5.9.4.1, 5.9.4.2, and 5.9.4.3 summarize the incidence of ischemic colitis (event term "colitis") and all other AEs reported by the subjects considered to have had ischemic colitis. These tables summarize data by month for Months 1-4, Months 5-9, and Months 10-12, respectively, for all 85 studies in the integrated safety database plus one study in patients with Functional dsypepsia (S3B20015). In these tables, all doses of alosetron have been combined into a single "dose" labeled "Alosetron," and a summary of other AEs that were also reported by the same patients/subjects who reported colitis have been included.

Most of these cases (10/16) occurred during the first month of treatment, as shown in the following table which summarizes the risk (incidence) and rate (incidence per unit of time) of ischemic colitis for each month and cumulatively over 12 months:

- The simple cumulative risk of ischemic colitis among alosetron-treated patients is 1.35 events per 1000 patients (1 event in 742 patients) compared with 0.29 events per 1000 placebo-treated patients (1 event in 3500 patients).
- Because the extent of exposure varies over time, a life table method is also used to calculate the risk. In alosetron-treated patients, the risk varies over time and is highest during the first month. The cumulative life table risk increases over time to 0.29% (~3 in 1000 patients) at 12 months compared with a cumulative risk of 0.28% in placebo-treated patients at 12 months. The cumulative life table risk by month (i.e., Hazard plot) is depicted in Figure 5.9.4.2 for both treatment groups. In addition, a Kaplan-Meier plot is presented in Figure 5.9.4.1.
- During the first month of alosetron treatment the incidence rate of ischemic colitis was 11.7 cases /1000 person-years, and by 12 months the incidence rate was ~5.6 cases/1000 person-years. In placebo-treated patients, the incidence rate during the first month and at 12 months was 0 and 1.1 cases/1000 person-years, respectively.

**Ischemic Colitis Events over Time in All Studies with Alosetron**
**(Excludes 7 studies with 95 subjects)**

| | Alosetron (N=11874) | | | | | | |
|---|---|---|---|---|---|---|---|
| | No. of events | No. of subjects | No. subj. censored | Risk (%)[a] | Cumulative Risk (%) | Person-years (cumulative) | Incidence Rate (per 1000 person-years) |
| Month 1 | 10 | 11874 | 3062 | 0.0967 | 0.0967 | 854.751 | 11.699 |
| Month 2 | 1 | 8802 | 1538 | 0.0124 | 0.1092 | 1549.110 | 7.101 |
| Month 3 | 2 | 7263 | 4043 | 0.0382 | 0.1473 | 2053.494 | 6.331 |
| Month 4 | 2 | 3218 | 736 | 0.0702 | 0.2175 | 2288.976 | 6.553 |
| Month 5 | 0 | 2480 | 452 | 0 | 0.2175 | 2481.201 | 6.045 |
| Month 6 | 1 | 2028 | 1298 | 0.0725 | 0.2900 | 2597.201 | 6.160 |
| Month 7 | 0 | 729 | 91 | 0 | 0.2900 | 2654.554 | 6.027 |
| Month 8 | 0 | 638 | 15 | 0 | 0.2900 | 2708.127 | 5.908 |
| Month 9 | 0 | 623 | 13 | 0 | 0.2900 | 2760.456 | 5.796 |
| Month 10 | 0 | 610 | 10 | 0 | 0.2900 | 2811.725 | 5.690 |
| Month 11 | 0 | 600 | 179 | 0 | 0.2900 | 2859.640 | 5.595 |
| Month 12 | 0 | 421 | 421 | 0 | 0.2900 | 2881.465 | 5.553 |
| | **Placebo (N=3500)** | | | | | | |
| | No. of events | No. of subjects | No. subj. censored | Risk (%)[a] | Cumulative Risk (%) | Person-years (cumulative) | Incidence Rate (per 1000 person-years) |
| Month 1 | 0 | 3500 | 899 | 0 | 0 | 248.236 | 0 |
| Month 2 | 0 | 2601 | 277 | 0 | 0 | 458.231 | 0 |
| Month 3 | 0 | 2324 | 1526 | 0 | 0 | 618.823 | 0 |
| Month 4 | 0 | 798 | 185 | 0 | 0 | 677.152 | 0 |
| Month 5 | 0 | 613 | 93 | 0 | 0 | 725.719 | 0 |
| Month 6 | 0 | 520 | 130 | 0 | 0 | 763.464 | 0 |
| Month 7 | 0 | 390 | 10 | 0 | 0 | 796.026 | 0 |
| Month 8 | 0 | 380 | 14 | 0 | 0 | 827.787 | 0 |
| Month 9 | 0 | 366 | 6 | 0 | 0 | 858.527 | 0 |
| Month 10 | 1 | 360 | 7 | 0.2805 | 0.2805 | 888.801 | 1.125 |
| Month 11 | 0 | 352 | 192 | 0 | 0.2805 | 915.686 | 1.092 |
| Month 12 | 0 | 160 | 160 | 0 | 0.2805 | 923.245 | 1.083 |

[a] Life table estimate = No. of events / (No. of subjects - No. censored/2) x 100.
Source: Tables 5.9.4.1, 5.9.4..2, 5.9.4.3

# Appendix B
## Data Conversion Procedures

1. Convert the database submitted by the sponsor from SAS format to Stata format by using Stat Transfer 5.0;

2. Convert the event level database to patient level database by using Stata 7.0 procedures (please see next two pages for the original data structure)

```
****Making a patient level by treatment group & does dataset
*** Date: 1/17/02
*** By: Zili Li

clear
set mem 128m
set more off
use "C:\My Documents\Lotronex\Cininal Trial Information\GSK 2001-11-19 Data\lotronex.dta", clear
sort ptid
egen tmtgrp = group(tmtname)
recode tmtgrp 1=3 2=1 3/16=2 17/25=3 26=4 27/31=3
label define tmtgrpM 1 "Alosetron Only" 2 "Alosetron w/active control drugs" 3 "Active controls" 4 "Placebo"
label value tmtgrp tmtgrpM
label variable tmtgrp "treatment groups"
gen temp = 0
replace temp = 1 if medcode == "EDA001"
replace temp = 1 if medcode == "EDX001"
egen estrogen = max(temp), by (uspatno)
drop temp
gen temp = 0
replace temp = 1 if medcode == "NLA001"
replace temp = 1 if medcode == "CGX001"
egen blocker = max(temp), by (uspatno)
drop temp
merge ptid using "C:\My Documents\Lotronex\Cininal Trial Information\GSK 2001-11-19 Data\ref_std.dta"
drop _merge
save "C:\My Documents\Lotronex\Cininal Trial Information\GSK 2001-11-19 Data\gsk master file.dta", replace
contract uspatno ibs
tab ibs
use "C:\My Documents\Lotronex\Cininal Trial Information\GSK 2001-11-19 Data\gsk master file.dta", clear
contract uspatno age sex wtlb ptid us_site us_site1 tmtgrp tmtstdt tmt_exp tmtdose estrogen blocker ibs
drop _freq
egen order = rank(tmtstdt), by(uspatno)
recode tmt_exp .=0
egen days_exp = sum(tmt_exp) if tmtgrp == 1 | tmtgrp==2, by(uspatno)
replace days_exp = tmt_exp if tmtgrp > 2
label variable days_exp "days exposure - combined for all treatment episodes"
label variable order "order of treatment episode"
sort uspatno
merge uspatno using "C:\My Documents\Lotronex\Cininal Trial Information\GSK 2001-11-19 Data\ref_ic.dta"
drop _merge
sort uspatno
merge uspatno using "C:\My Documents\Lotronex\Cininal Trial Information\GSK 2001-11-19 Data\ref_gi.dta"
drop _merge
*** define ic cases by GI review
gen gsk_ic = 1
replace gsk_ic = 0 if tm_ic == .
gen gi_ic = gsk_ic
replace gi_ic = 1 if substr(uspatno,11,5) == "65443"
replace gi_ic = 1 if substr(uspatno,11,5) == "32451"
replace gi_ic = 1 if substr(uspatno,11,5) == "49203"
replace gi_ic = 0 if gsk_ic == 1 & ptid == "S3B30017"
replace gi = 0 if gi==.
replace gi = 0 if gi_ic==1
label variable us_site "based on pag 23 of main table"
label variable us_site1 "Based on detailed table - more accurate"
label variable ibs "ibs patients"
label define ibsm 0 "Healthy Volunteers" 1 "IBS patients" 2 "FD"
label value ibs ibsm
label variable estrogen "Taking estrogen"
label variable blocker "taking b-blocker"
save "C:\My Documents\Lotronex\Cininal Trial Information\GSK 2001-11-19 Data\gsk master file.dta", replace
```

FDA Lotronex dataset

CONTENTS PROCEDURE

| | | | |
|---|---|---|---|
| Data Set Name: | ISS.LOTRONEX | Observations: | 78629 |
| Member Type: | DATA | Variables: | 37 |
| Engine: | V612 | Indexes: | 0 |
| Created: | Tue, Nov 13, 01 | Observation Length: | 492 |
| Last Modified: | Tue, Nov 13, 01 | Deleted Observations: | 0 |
| Protection: | | Compressed: | NO |
| Data Set Type: | | Sorted: | YES |
| Label: | | | |

-----Engine/Host Dependent Information-----

| | |
|---|---|
| Data Set Page Size: | 40960 |
| Number of Data Set Pages: | 948 |
| File Format: | 607 |
| First Data Page: | 1 |
| Max Obs per Page: | 83 |
| Obs in First Data Page: | 73 |
| File Name: | /data/usmedstat/s3b2/safety/iss/update /datasets/lotronex.ssd01 |
| Inode Number: | 100412 |
| Access Permission: | rw-rw-r-- |
| Owner Name: | djms1933 |
| File Size (bytes): | 38838272 |

-----Alphabetic List of Variables and Attributes-----

| # | Variable | Type | Len | Pos | Format | Informat | Label |
|---|---|---|---|---|---|---|---|
| 32 | AECODE | Char | 10 | 409 | | | AE group term code |
| 27 | AEONDT | Num | 8 | 390 | DATE9. | | AE onset date |
| 28 | AEOUT | Char | 1 | 398 | $1. | $1. | AE outcome R=Resolved U=Unresolved,F=Fatal, ?=unknown,N=No change, S=Resolved w/ sequelae |
| 29 | AERESDT | Num | 8 | 399 | DATE9. | | AE date of resolution or death |
| 30 | AESER | Char | 1 | 407 | $1. | $1. | Serious AE (N=No,Y=Yes) |
| 33 | AETEXT | Char | 51 | 419 | | | Adverse Event Text |
| 31 | AEWDRN | Char | 1 | 408 | $1. | $1. | Withdrawn due to AE (N=No, Y=Yes) |
| 14 | AGE | Num | 8 | 212 | 3. | 3. | Age calculated in years |
| 34 | CNST | Num | 3 | 470 | | | Serious Constipation Indicator (0=No,1=Yes) |
| 21 | DGINDTX | Char | 66 | 245 | | | Condition for which con. med. is taken |
| 17 | DGPRTMT | Char | 1 | 229 | | | Con. med. started pre-trial (Y=Yes) |
| 20 | DGPSTMT | Char | 1 | 244 | | | Con. med. continued post-trial (Y=Yes) |
| 19 | DGSPDT | Char | 7 | 237 | | | Con. med. stop date |
| 18 | DGSTDT | Char | 7 | 230 | | | Con. med. start date |

FDA Lotronex dataset

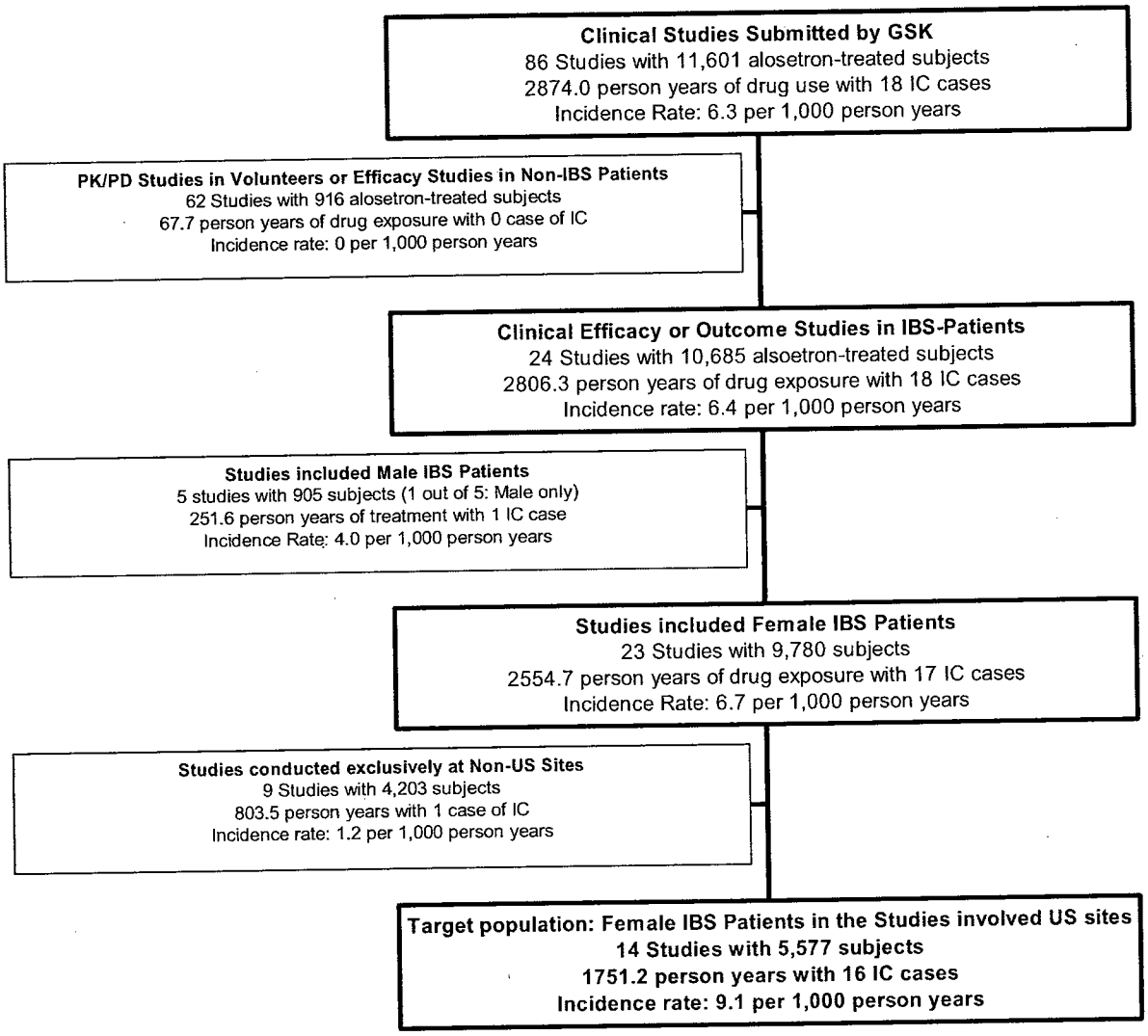
CONTENTS PROCEDURE

| # | Variable | Type | Len | Pos | Format | Informat | Label |
|---|---|---|---|---|---|---|---|
| 35 | IC | Num | 3 | 473 | | | Ischemic Colitis Event Indicator (0=No,1=Yes) |
| 22 | MEDCODE | Char | 6 | 311 | | | Con. med. code variable |
| 23 | MEDTEXT | Char | 59 | 317 | | | Con. med. text variable |
| 24 | OCCUR | Num | 8 | 376 | | | No. of occurrences of AEs and con. meds. |
| 2 | PTID | Char | 9 | 18 | | | Protocol ID |
| 15 | SEX | Char | 1 | 220 | $1. | $1. | Sex |
| 3 | TMTDOSE | Num | 8 | 27 | | | Treatment dosage |
| 5 | TMTFREQ | Char | 3 | 41 | | | Treatment frequency (eg, 1, 2, 3, 4) |
| 10 | TMTNAME | Char | 66 | 64 | | | Treatment Name (Alosetron,Placebo,etc. ) |
| 11 | TMTNAMED | Char | 71 | 130 | | | Treatment Name + Dose (Alosetron 1) |
| 12 | TMTPER | Num | 3 | 201 | | | Treatment Period |
| 6 | TMTROUTE | Char | 3 | 44 | | | Treatment route (eg, PO, IV) |
| 8 | TMTSPDT | Num | 8 | 55 | DATE9. | DATE7. | Treatment stop date run |
| 7 | TMTSTDT | Num | 8 | 47 | DATE9. | DATE7. | Treatment start date |
| 4 | TMTUNITS | Char | 6 | 35 | | | Treatment drug units |
| 13 | TMT_EXP | Num | 8 | 204 | | | Exposure to Treatment (days) |
| 37 | TM_CNST | Num | 8 | 484 | | | Time to Serious Constipation (days) |
| 36 | TM_IC | Num | 8 | 476 | | | Time to Ischemic Colitis (days) |
| 25 | USPATCNS | Num | 3 | 384 | | | Patient w/ Constipation (1=Yes,0=No) |
| 26 | USPATIC | Num | 3 | 387 | | | Patient w/ Ischemic Colitis (1=Yes,0=No) |
| 1 | USPATNO | Char | 18 | 0 | | | Unique Sequential Patient Number |
| 9 | US_STUDY | Char | 1 | 63 | | | US study? (0=no,1=yes) |
| 16 | WTLB | Num | 8 | 221 | 3. | 3. | Weight in Pounds |

-----Sort Information-----

Sortedby: PTID USPATNO TMTSTDT OCCUR
Validated: YES
Character Set: ASCII

## Appendix C
Flow Chart on Study Selection



## Appendix D

How likely this rate difference will happen by the chance alone ?

**Table D1: Difference of Incidence Rates between Study S3B30020 and S3BA3003**

| Study Protocol Number | S3B30020 | S3BA3003 |
|---|---|---|
| Number of Patients | 1819 | 473 |
| Number of Ischemic Colitis | 10 | 0 |
| Cumulative Drug Exposure (in person years) | 592.4 | 321.0 |
| Incidence Rate (per 1,000 person years) | 16.9 | 0 |
| Rate difference (95% CI) | 16.9 (4.8, 29) (p = 0.005) Based on Poisson Distribution | |

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

/s/
---
Zili Li
3/25/02 03:43:35 PM
MEDICAL OFFICER

Julie Beitz
3/26/02 07:27:10 AM
DIRECTOR

**M E M O R A N D U M** **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

---

**DATE:** March 15, 2002

**TO:** Victor Raczkowski, M.D., Acting Director
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

**THROUGH:** Julie Beitz, M.D. Director
Division of Drug Risk Evaluation, HFD-430
Office of Drug Safety

**FROM:** Zili Li, M.D., M.P.H., Medical Epidemiologist
Division of Drug Risk Evaluation, HFD-430
Office of Drug Safety

**SUBJECT:** Causality assessment between alosetron use and constipation, ischemic colitis and their complications

**PID#:** D020114 **NDA #:** 21-107

## I. Background

This memorandum is in response to a consult request from Dr. Hugo Gallo-Torres of HFD-180 to provide a brief statement on the causality assessment for alosetron (trade name: Lotronex) use and constipation, ischemic colitis and their complications. This document is prepared with the understanding that the GI Division is interested in a summary statement rather than a detailed discussion on causality. This information will be used as part of a briefing document for the upcoming Advisory Committee Meeting on April 23, 2002.

The content of this consult was preliminarily communicated to HFD-180 via e-mail on March 1, 2002.

## II. Summary of Causality Assessment

When we use the word "causality" in this document, it is not our intention to determine whether a particular adverse event, such as ischemic colitis, experienced by an individual patient is the result, or likely to be the result of alosetron use. Instead we use the word "causality" to address the issue on a population basis – how likely is alosetron associated with a particular adverse event? Since causality can never be proven with 100% certainty, causality assessment represents, in essence, a judgement formulated on the strength of evidence that links alosetron with a particular adverse event.

**Constipation:** There is little debate that alosetron can cause constipation or cause a patient to discontinue alosetron due to constipation. Constipation is expected based on the mechanism of action of alosetron. In two pivotal clinical trials submitted before the drug's original approval, the percentages of patients who had developed constipation or had to discontinue treatment due to constipation were higher in alosetron-treated patients than in placebo-treated patients. The differences were statistically significant at $p < 0.001$ level[1]. This statistical association is consistently observed in additional studies submitted by GSK in its December 7, 2001 submission. In addition, the percentage of patients who experience constipation is related to the dose of alosetron. Such a dose-response is further evidence of a causal association.[1]

**Ischemic Colitis:** Compared to constipation, ischemic colitis occurs with a lower frequency among alosetron users. Among women with irritable bowel syndrome who were enrolled in 11 US clinical trials with greater than 50 patients, 5,525 received alosetron and 2,905 placebo or traditional therapies. The strongest evidence that supports a causal relationship is from study S3B30020, a randomized and open labeled clinical trial where 1819 alosetron-treated patients and 889 control patients were treated and followed for up to 24 weeks. As shown in Table 1, ten cases of ischemic colitis were observed in alosetron-treated patients and none in the control group. The incidence rates of ischemic colitis were 16.9 per 1,000 person years and 0 respectively for the two groups ($p < 0.001$)[2,3]. In addition, 6 other cases of ischemic colitis occurred in alosetron-treated females enrolled on the remaining ten clinical trials whereas only one case was reported in a patient on placebo[4]. The pooled analysis of these 11 studies also demonstrated a statistically significant difference in the incidence rates of ischemic colitis between alosetron and control groups (9.2 vs. 1.0 per 1,000 person years, $p = 0.0012$ ). Note that incidence rates from these pooled studies may not represent the true risk of alosetron-associated ischemic colitis among female IBS patient in the US given potential differences in trial designs, patient host factors and case ascertaiment[3].

Table 1. Rate difference between alosetron group and control group in S3B30020

| | Alosetron (n=1,819) | Control (n=889) |
|---|---|---|
| Number of Ischemic Colitis Cases | 10 | 0 |
| Cumulative Drug Exposure (in person years) | 592.4 | 348.0 |
| Incidence Rate (per 1,000 person years) | 16.9 | 0 |
| Rate difference (95% CI) | 16.9 (6.4, 27.4) $p < 0.001$ | |

Ischemic colitis cases reported during the post-marketing period also provided some supporting evidence. Between November 1997 and October 2000, alosetron alone accounted for 27% of the total cases of ischemic colitis reported to FDA, followed by Imitrex (7%) and Premarin (4%). The remaining 62% of reported cases were from 78 different drugs and no ischemic colitis reports were ever received for other $5HT_3$ drugs[5].

**Necrosis or perforation of colon requiring surgical intervention:** One case of toxic

megacolon and one case of colon perforation occurred in trial S3B30020 and both required a surgical intervention[2]. More than 30 cases of constipation-related or ischemic colitis-related complications requiring a surgical intervention among alosetron users in the US have been reported to FDA during the post-marketing period[6]. Although there are not enough cases from the clinical trials to establish a statistical association between alosetron and necrosis/perforation, such evidence should not be necessary given that an association between the drug and constipation and ischemic colitis has been shown. Since necrosis and perforation are known sequelae of constipation and ischemic colitis, it is reasonable to expect that these serious events will be less common than constipation and ischemic colitis, but important adverse outcomes of alosetron users.

**Conclusion:** The totality of evidence supports the hypothesis that alosetron can cause constipation and ischemic colitis, which may lead to rare but serious complications. It should be emphasized again, however, that causality here only implies that alosetron is capable of either directly or indirectly leading to constipation, ischemic colitis and the complications of these two events on a population basis. It does not mean, however, that all reported cases of constipation, ischemic colitis and their complications among alosetron users are necessarily the result of alosetron use. The causality assessment for an individual patient is beyond the scope of this document.

Date: March 15, 2002

Zili Li, MD, MPH
Medical Officer (Epidemiology)

Concur:

Date: March 15, 2002

Mary E. Willy, PhD, MPH
Team Leader

**REFERENCES**


1. John R. Senior. Medical officer's new drug application (NDA) review, October 15, 1999, FDA's Division Files System
2. Scheldon Kress. Medical officer's review – Safety review of clinical reports for protocol S3B30020, March 2002
3. Zili Li. Reevaluating the risk of ischemic colitis among female alosetron users with IBS in the US, March 15, 2002
4. Hugo Gallo-Torres. Medical team leader's review, March 2002
5. Kathleen Uhl, Zili Li, Ann Corken and Paul Stolley. NDA 21-107: Lotronex (alosetron) safety & risk management summary. Memorandum to HFD-180, November 16, 2000.
6. Ann Corken Mackey and Zili Li. Monthly Update: Ischemic colitis and complications of serious constipation events as of December 31, 2001. Memorandum to HFD-180, February 1, 2002.

cc:
NDA 21-107
Division Files
HFD-103 Director, Deputy
HFD-180 Deputy, Medical TL, MO, CPMS
HFD-440 Director, Deputy, Epi, SETL, SE, PM, Chron, Drug

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/s/
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3/27/02 09:19:31 AM
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**DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS**
**MEDICAL OFFICER'S REVIEW**

| | |
|---|---|
| **NDA:** | **21-107** |
| **Applicant:** | **GlaxoSmithKline (formerly GlaxoWellcome)** |
| **Drug:** | **LOTRONEX (alosetron)** |
| **Pharmacological Category:** | **5HT-3 Receptor antagonist** |
| **Drug Study:** | **A Twelve Week Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Tolerability of Alosetron Hydrochloride 1 mg Tablets Twice Daily for Control of Bowel Urgency in Females with Non-constipated Irritable Bowel Syndrome in an Independent Practitioner Association (IPA) Model** |
| **Study Initiation Date:** | **10 March 2000** |
| **Completion Date:** | **08 January 2001** |
| **Early Termination Date:** | **28 November 2000** |
| **Study Administration:** | / |
| **Material Reviewed:** | **(Phase IV) Clinical Study Report for Protocol S3B40031** |
| **Reviewer:** | **Scheldon Kress, M.D.** |


**Executive Summary**

Protocol S3B40031 was designed to evaluate the efficacy and safety of alosetron 1 mg BID in a 12 week randomized, double-blind, placebo-controlled, parallel group, multicenter study for control of bowel urgency in females with lack of satisfactory control of urgency on less than 50% of days with non-constipated irritable bowel syndrome (IBS). A total of 492 female patients were studied, 246 treated with alosetron and 246 treated with placebo.).

**Executive Summary (continued)**

The criteria for evaluation were: 1) Primary Efficacy compared the two treatment groups for satisfactory control of bowel urgency over the 12-week Treatment Phase. 2) Secondary Efficacy measures included the proportion of patients who were IBS Global Improvement Responders, daily analysis of satisfactory control of bowel urgency, and lower gastrointestinal symptoms (stool consistency, stool frequency, and sense of incomplete evacuation). Exploratory efficacy measures included the proportion of patients who were Bowel Urgency Improvement Responders and correlation between control of bowel urgency and other endpoints. Health outcome measures included satisfaction with treatment, Lost Workplace Productivity, and Lost Activity Time. Safety measures assessed AEs and laboratory abnormalities.

Based on the primary endpoints after 12 weeks of study, alosetron-treated patients experienced satisfactory control of urgency for a median of 69% of days compared to 56% for the placebo-treated patients (therapeutic gain 13%; $p=\leq 0.001$). In addition, alosetron-treated patients demonstrated significant statistical therapeutic advantage over placebo throughout the treatment phase as measured by the following secondary supportive efficacy measurements: global improvement and lower gastrointestinal functions of stool frequency, stool consistency, and incomplete stool evacuation.

Health outcomes findings indicated that for the PE Population a statistically significantly greater percentage of alosetron-treated patients (117/200, 59%) compared with placebo-treated patients (94/192, 49%) were satisfied or very satisfied with their IBS therapy following 12 weeks of treatment ($p\leq 0.001$). In addition, alosetron was associated with greater satisfaction than placebo for 9 of 11 medication attributes assessed ($p\leq 0.05$) and favorable satisfaction ratings for alosetron were assigned to the five medication attributes that the majority of the patients considered to be most important.

Due to an 11% loss of sample size in the PE Population from the ITT Population, Lost Workplace Productivity and Lost Activity time results were not statistically significantly different in the PE population. The ITT population alosetron-treated patients experienced 40% less Lost Workplace Productivity ($p=0.112$) and 12% less Lost Activity Time ($p=0.173$) compared with placebo-treated patients over the 12-week Treatment Phase.

**Executive Summary (continued)**

The incidence of all AEs was 52% (127/246) and 59% (145/246) in the placebo and alosetron groups, respectively. Gastrointestinal AEs were more common among alosetron-treated patients than among placebo-treated patients , a result that was driven primarily by the incidence of constipation (9% with placebo versus 28% with alosetron) and gastrointestinal discomfort and pain in the alosetron group (6% with placebo versus 15% with alosetron). Similarly, the incidence of drug-related AEs, especially constipation and gastrointestinal discomfort and pain, was higher among alosetron-treated patients than placebo-treated patients . Serious adverse events (SAEs) occurred at a similar frequency between treatments. The incidence of study drug discontinuation and the rate of withdrawal from the study were consistent with that of prior clinical trials. Three pregnancies (one in the placebo group and two in the alosetron group) occurred; the outcomes for each was unknown at the time of reporting. Clinical laboratory value profiles were comparable between treatment groups.

In summary, the results of this study demonstrated the clinical benefit of alosetron 1 mg BID in the treatment of women with nonconstipated IBS. Alosetron provided statistically significant, control of bowel urgency and improvement of other bothersome clinical symptoms. Additionally, alosetron was associated with a higher degree of patient satisfaction and a convenient dosing regimen. Apart from constipation and gastrointestinal discomfort and pain, in this study, alosetron was associated with minimal side effects. Rates for other AEs and laboratory abnormalities were similar for alosetron and placebo-treated patients.

No SAEs of special interest, sequelae of constipation, ischemic colitis, or death occurred within the alosetron-treated or placebo-treated groups within this study population. No constipated patient experienced any of the SAEs that were observed post marketing, suggesting that complications of constipation should be preventable with proper physician and patient vigilance.

A customized mutually acceptable Restricted Distribution Program-Restricted Management Plan should be able to improve the Risk-Benefit ratio and achieve measurable reductions in the incidence of serious complications of severe constipation including hospitalizations, hemorrhages, operations and deaths associated with the use of alosetron. On the other hand, we still know very little about risk factors responsible for ischemic colitis associated with alosetron and therefore can not offer patients advice for prevention of ischemic colitis and its serious sequelae.

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## I. Introduction - Background

Irritable Bowel Syndrome (IBS) is a functional disorder of the gastrointestinal tract characterized by abdominal pain or discomfort accompanied by alterations in bowel function. IBS has been estimated to be diagnosed in 4.7 million subjects in the United States, and symptoms of IBS are responsible for between 2.5 and 3.5 million visits to physicians yearly. Other data suggest that IBS may be present in as many as 11-14% of adults. The exact mechanisms leading to IBS are unclear, however abnormal visceral perception, abnormal secretory and motor function, psychologic distress, and irritating intestinal luminal factors have all been implicated in the pathogenesis.

No specific diagnostic marker has been associated with IBS. Therefore, the diagnosis remains primarily one of exclusion. Once anatomical and biochemical abnormalities are eliminated, a diagnosis of IBS may be considered to explain symptoms. Diagnostic criteria for IBS were developed by Manning, and more recently, a consensus meeting in Rome further refined these criteria. The criteria focus on the primary symptoms of IBS, namely pain and change in bowel function. To date, the treatment of IBS has been suboptimal because of ineffective therapeutic options. Given that IBS represents a significant unmet medical need, drugs are needed to treat the manifestations of this disease.

IBS is a costly disease in terms of use of health care services. Annual physician visits related to IBS symptoms are estimated at [illegible] million with over [illegible] million prescriptions dispensed. The use of specialty care is particularly high as 20-40% of all visits to gastroenterologists are for treatment of IBS. Less widely known are the indirect costs associated with this disease, such as time lost from work and decreased productivity due to IBS. IBS sufferers frequently miss workdays or often experience job loss. However, lack of data confounds attempts to quantify the indirect costs (such as time lost from work or time lost due to reduced effectiveness) associated with IBS symptoms.

Alosetron hydrochloride was evaluated as a treatment for IBS on the basis of its clinical activity and preclinical pharmacology. Based on the results of four large trials, two Phase II and two Phase III studies, alosetron was approved February 8, 2000 to treat female subjects with diarrhea-predominant IBS at a 1.0 mg BID dosage. Heightened safety concerns, resulted in voluntary withdrawal by the Sponsor November 28, 2000. The current study, identical to Protocol S3B30011, evaluated the efficacy of alosetron in controlling bowel urgency, one of the most bothersome symptoms associated with IBS in a female population significantly impacted by a lack of control of urgency.

Since patients with IBS are characterized by a constellation of symptoms, including abdominal pain and discomfort, and changes in stool frequency or stool form, it is important to include an outcome measure which assesses overall changes in IBS symptoms. Therefore, patients' self-evaluation of their overall improvement from IBS was also measured in this study.

Additionally, since IBS results in lost time from work and work-related changes such as job loss, the current study performed analyses evaluating the impact of alosetron on overall workplace productivity and activity time.

Prior to alosetron, no available treatment option has demonstrated consistent benefit for the multiple symptoms of IBS. Other IBS treatments include lifestyle modification, anticholinergic agents, fiber supplements, anti-depressants, and/or antidiarrheal agents.

The current study assessed patient satisfaction over previous regimens and bowel urgency improvement in a model managed care IPA. Constipation is a class effect of 5-$HT_3$ receptor antagonists by slowing of gut transit and increasing salt-water reabsorption. Phase II and III trials of alosetron reported constipation as the most common side effect related to study drug treatment (28% alosetron versus 5% placebo). Unlike Protocol S3B30011, this current study did not evaluate interventions directed at managing constipation and enabling subjects to continue on therapy.

## II. Study Objectives and Endpoints

### Primary Objective

Compare treatment with alosetron 1 mg twice daily to matching placebo twice daily with respect to the proportion of days patients reported satisfactory control of bowel urgency. This study is designed to replicate Protocol S3B30011 to study efficacy in control of bowel urgency.

### Secondary Objectives

Compare the two treatment groups with respect to:

1. Self-ratings of IBS global improvement
2. Lost workplace productivity and activity time due to IBS-associated symptoms
3. Self-reports of gastrointestinal functions: stool frequency, stool consistency, and sense of incomplete evacuation
4. Proportion of subjects who report satisfactory control of urgency by day over the first 14 days of treatment
5. Overall satisfaction with treatment

### Safety Objectives

The safety objectives of the study were to:

Compare the alosetron and placebo groups with respect to the incidence of adverse events (AEs) and abnormalities in laboratory tests

### Study Endpoints

#### Primary Endpoint

Proportion of days patients reported satisfactory control of bowel urgency.

#### Secondary Endpoints

1. Difference between the two treatment groups in the IBS Global Improvement
2. Difference between the two treatment groups in Lost Workplace Productivity and Activity Time due to IBS symptoms.
3. Difference between the two treatment groups with respect to changes in gastrointestinal symptoms over the 12-week Treatment Phase.
4. Difference between the two treatment groups with respect to the proportion of patients who report satisfactory control of urgency by day over the first 14 days of treatment.
5. Difference between the two treatment groups in the overall satisfaction with treatment

#### Safety Endpoints

1. Adverse events grouped by body system and preferred term.

2. Shifts in laboratory values.

## III. Study Design – Investigational Plan

This randomized, double-blind, placebo-controlled, parallel group, multicenter trial in ambulatory female outpatients with non-constipated IBS was conducted by / ~~[redacted]~~ / under contract for Glaxo Wellcome Inc. Patients were at least 18 years of age, without satisfactory control of bowel urgency on at least 50% of the days in the 2-week Screening Phase. They also must have recorded at least 12 daily entries in the touch-tone telephone data entry system

during the 2-week Screening Phase and met all other inclusion/exclusion criteria. Patients participated in a 2-week Screening Phase followed by a 5-day randomization window, if needed for colon procedure. Once randomized, patients received either oral alosetron 1 mg BID or oral placebo BID over a 12-week Treatment Phase. Upon completion of the Treatment Phase, patients underwent a 2-week Follow-up Phase. Total study duration was 16 weeks.

### Control Group

An inactive (placebo) control group was included in the study for comparison with the alosetron treatment group.

### Study Design Issues

Because constipation is a common side effect among patients receiving alosetron, this study intended to utilize non-constipated patients for participation. Patients reporting constipation during the study followed these outlined procedures:

1. Reported constipation at a scheduled clinic visit
2. Reported constipation by contacting the site between scheduled visits
3. Reported absence of stool for 4 consecutive days by means of the daily phone calls in the interactive voice response system (IVRS)
4. Discussed the constipation event with the patient or confirmed the absence of stool for 4 consecutive days and discussed the use of a laxative. Constipation was recorded as an AE.
5. Confirmed absence of stool for 8 consecutive days, even with the use of the laxative, led to the patient's withdrawal from study and discontinuation of the study drug.

## Protocol Amendments

There were no Protocol Amendments.

## Study Population

### Inclusion Criteria

A patient was eligible for inclusion in this study only if all of the following criteria applied:

1. signed written informed consent
2. at least 18 years of age
3. female gender
   A female was eligible to enter and participate in this study if she was of:

a) non-childbearing potential (i.e., physiologically incapable of becoming pregnant) including any female who was post-menopausal; or
b) childbearing potential, had a negative serum pregnancy test at screen, and agreed to an acceptable contraceptive methods, when used consistently and correctly (i.e., in accordance with both the approved product label and the instructions of a physician).

4. an ambulatory outpatient.
5. diagnosed with non-constipated IBS meeting the following criteria:
consistent or recurrent symptoms ≥12 weeks in the previous 12 months

**abdominal pain/discomfort associated with two or more:**

- **relief with defecation**
- **change in stool frequency**
- **change in stool consistency**

These symptoms may have been supported further by difficult passage of stools, mucous present in stools and/or bloating.

**AND**

during the Screening Phase

- **documented lack of satisfactory control of bowel urgency on at least 50% of days (75% of days for antidiarrheal medication dependent patients)**

6. normal results from a flexible sigmoidoscopy or colonoscopy, or a barium enema plus flexible sigmoidoscopy according to the patient 's age within 5 years of the Randomization Visit:

- for patients less than 50 years of age, flexible sigmoidoscopy or colonoscopy after the onset of their IBS symptoms and within 5 years prior to the Randomization Visit using a flexible sigmoidoscope to ≥40cm. Symptoms must have remained stable since the subject's last flexible sigmoidoscopy or the procedure must have been repeated.

- for patients 50 years of age and older, a full colonoscopy (using a scope of ≥180cm, visualizing the cecum) or an air contrast (double contrast) barium enema plus flexible sigmoidoscopy, after the onset of IBS symptoms and within 5 years of the Randomization Visit. Symptoms must have remained stable since the last colonoscopy, or last flexible sigmoidoscopy and barium enema, or the procedure(s) must have been repeated.

7. recorded at least 12 out of 14 days (4 out of 5 days for antidiarrheal-dependent subjects) of daily self-assessments in the touch-tone telephone data entry system for the Screening Phase.

**Exclusion Criteria**

A patient was not eligible for inclusion in this study if any of the following criteria applied:

1. diagnosis of IBS with subtype constipation
2. evidence of a biochemical or structural abnormality of the digestive tract.
3. presence of any unstable cardiovascular, renal, hepatic, pulmonary, endocrine, metabolic, hematologic, neurologic, or gastrointestinal conditions (other than IBS)
4. documented endometriosis determined by laparoscopy
5. renal impairment (serum creatinine >2.0mg/dL)
6. hepatic dysfunction (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >2.5 times the upper limit of normal [ULN].)
7. abnormal thyroid stimulating hormone (TSH). (If not assessed within the previous 3 years testing must have been completed prior to starting study drug.)
8. any evidence or treatment of malignancy (other than localized basal cell, squamous cell skin cancer or cancer *in situ* that had been resected) within the previous 5 years.
9. current use of ondansetron, tropisetron, granisetron, dolasetron, or mirtazapine.
10. use of concurrent prohibited medications. (patients must not have taken prohibited medication for at least 7 days prior to screening and must have abstained from taking these medications for the duration of this study. Patients using any of these medications must have been on a stable dose for at least 30 days prior to randomization.)
11. major psychiatric disorder within the past 2 years not controlled by a stable dose of medication for the last 6 months.
12. alcohol or substance abuse within the past 2 years.

13. unwilling or unable to follow directions or use the touch-tone telephone data entry system.
14. refusal or inability to complete the self-rating questionnaires.
15. use of an investigational drug within 30 days.
16. pregnant or breastfeeding.
17. previous use of alosetron.

**Criteria for Premature Study Drug and/or Study Discontinuation**

**Premature Discontinuation from the Study**

A completed patient was one who completed the 2-week Screening Phase, 12-week Treatment Phase, and 2-week Follow-up Phase. A randomized patient who did not complete these study periods was considered prematurely discontinued from the study and was not replaced.

Patients experiencing no stool for 8 consecutive days with or without laxative use were contacted by the investigator, discontinued from the study, and were considered prematurely discontinued. The constipation event was recorded as an AE.

A patient may have been withdrawn from the study at any time at the investigator's or patient's discretion. Acceptable reasons for discontinuing participation in the study during the Treatment or Follow-up Phase were recorded on the End of Study Record page in the case report form (CRF) and may have included one or more of the following:

- adverse event necessitating discontinuation of therapy
- protocol violation
- pregnancy
- lack of efficacy
- any condition or circumstance that jeopardized the welfare of the patient if he/she continued in the trial
- patient did not wish to continue participating in the study.

If a patient was prematurely discontinued from participation in the study for any reason, the investigator made every effort to perform the following evaluations prior to discharging the patient from the study:

- assess concurrent medications
- assess AEs
- perform physical examination
- obtain blood for hematology testing
- obtain blood for serum chemistry testing
- obtain blood for serum pregnancy test
- administer Satisfaction with IBS Treatment questionnaire
- administer IBS Global Improvement and Bowel Urgency improvement questions

- access touch-tone telephone data entry system to record the subject's premature discontinuation and the date of premature discontinuation
- re-instruct the patient on the touch-tone telephone data entry system
- assess drug accountability
- schedule the 14-day Follow-up Phone Contact
- complete the patient CRF.

### Treatment Assignment

Patients were assigned to study treatment in accordance with a blocked randomization schedule. A blocked randomization schedule for treatment allocation was generated using GlaxoWellcome Inc.'s Random Codes System. Treatments were randomly assigned to consecutive patients using an allocation ratio of 1:1 for the two treatment groups (alosetron 1mg BID and placebo BID, respectively). Patients who did not complete the 12-week Treatment Phase were considered prematurely discontinued from study drug. Patients who were prematurely discontinued from study drug were not replaced but could continue to participate in the Follow-up Phase of the study and had a Follow-up Phone Contact scheduled at the premature discontinuation visit. If a patient prematurely discontinued from study drug and entered the Follow-up Phase, the date of the Follow-up Phone Contact was entered in the CRF, once completed.

### Study Treatments

#### Study Drugs

Study drug was manufactured in the United Kingdom at Glaxo Wellcome, plc. Double-blind study drug was packaged for individual patients and shipped to the site in treatment cartons. Beginning with the Randomization Visit and at the next two scheduled visits (Weeks 4 and 8), each patient received one individual zipper pouch (i.e., a 5-week supply or 70 tablets) of double-blind study drug.

### Treatment Administration

Patients were randomized to receive either oral alosetron 1 mg BID or placebo BID for the 12-week Treatment Phase of the study. Patients were instructed to take one study drug tablet before breakfast and one tablet before the evening meal during the Treatment Phase. If the patient skipped his/her breakfast, the dose should have been taken at 8:00 AM. If the patient skipped his/her evening meal, the dose should have been taken at 8:00 PM. For patients who worked odd hours (e.g., the night shift), medication was to be taken before the patient's scheduled breakfast or evening meal.

### Treatment Compliance

Study drug tablets were dispensed by the investigator (or designee) according to treatment number at the Randomization Visit. Patients were instructed to return all unused study drug at the Week 4, 8, 12 and (if necessary) Follow-up Visits at which times tablet counts of remaining study drug were performed by study personnel. Patients who consumed less than 80% of the intended dose of study drug during the previous 4 weeks were considered noncompliant. Compliance was not evaluated when study drug was not returned.

## Concurrent Medications and Non-Drug Therapies

### Permitted Medications

All concomitant medications used by patients at study entry were recorded at the Screening Visit and an up-to-date record of all concurrent medication used was maintained at each subsequent study visit. Where possible, concurrent medication remained constant throughout the study.

The following classes and individual medications were permitted during the study provided the patient had received stable doses for 30 days prior to randomization:

- antianginals (calcium channel blockers, nitrates)
- antidepressants (except mirtazapine [Remeron])
- antipsychotics
- antihypercholesterolemics (except cholestyramine)
- antihyperglycemies (oral sulfonylureas)
- antihypertensives (e.g., ace inhibitors, β-blockers, α-blockers, diuretics)
- anxiolytics
- bulking agents
- iron supplements
- pancreatic enzymes
- thyroid replacement therapy (e.g., levothyroxine).

Use of an unstable dose(s) constituted a protocol violation.

**Prohibited Medications**

Patients must not have taken the following medications for at least 7 days prior to screening and must have abstained from taking these medications for the duration of the study:

- anticholinergics (e.g., dicyclomine, hyoscyamine, propantheline)
- cholestyramine
- cholinomimetic agents (bethanechol, pyridostigmine, tacrine, physostigmine, anticholinergics)
- codeine and codeine-containing analgesics (> 5 day per 2 months)
- colchicine
- Cytotec
- gastrointestinal preparations:
  5-acetylsalicylic acid (ASA) preparations, antidiarrheal agents, antinausea agents (e.g., benzquinamide, trimethobenzamide, prochlorperazine, promethazine, hydroxyzine)
  antispasmodic agents (e.g., Donnatol, Librax, dicyclomine, propantheline), antacids which include aluminum or magnesium (other than provided
  bismuth compounds, laxatives (see below)
  prokinetic agents (e.g., cisapride, metoclopramide)
  stool softeners (docusate), sulfasalazine
  Exception:
  antidiarrheals (e.g., Immodium) may have been subject to at least a 2-day washout period for those subjects whom the investigator determined would be debilitated by the 7-day washout period followed by the 14-day Screening Phase.
- laxatives unless prescribed by investigator
  Exception:
  compounds given as preparations for the required flexible sigmoidoscopy, colonoscopy, or flexible sigmoidoscopy plus barium enema
- leuprolide
- macrolide antibiotics
- morphine, morphine-containing analgesics, and all other narcotics
- other 5-$HT_3$ antagonists (e.g., ondansetron, tropisetron, granisetron, mirtazapine, dolasetron)
- peppermint oil
- stimulants and amphetamine-like drugs
- tramadol.

### Laxative Use

If a patient experienced constipation, she was to contact the site and discuss the need for laxative intervention with the investigator (or designee). If it was determined that the patient needed a laxative, the investigator (or designee) and the patient agreed on a plan for the use of the

The investigator was instructed to use his or her discretion to prescribe an alternative laxative only under the exceptional circumstance that it would be inappropriate for the patient to use the protocol-specific laxative. If additional was dispensed or if a laxative other than the protocol-specified laxative was used, this information was documented in the patient's records.

Study medication was not to be interrupted during laxative medication use. However, if a patient experienced 4 consecutive days without stool, she was contacted by the site to discuss the use of a laxative as described above. If the patient continued to experience no stool for a total of 8 consecutive days even with the use of the laxative, study medication was discontinued and the patient was withdrawn from the study.

## Measurements and Evaluations

### Demographic and Baseline Characteristics

Demographic and baseline characteristics were collected at the Screening Visit and included date of birth, race, height, weight, IBS subtype, childbearing potential, method of birth control, parity, and date of onset of IBS symptoms.

An up-to-date record of any current medical conditions (and their respective treatments) were noted at the Screening Visit and were recorded in the patient's notes. Intermittent or pro re nata (PRN) use of medication not recorded at baseline which a patient took during the trial indicated the occurrence of an AE or the exacerbation of a pre-existing condition which should have been recorded as an AE in the subject's notes and CRF.

### Study Drugs

The following information was collected regarding study drug:

- start and stop dates of study drug
- status of the treatment blind
- whether study drug was returned
- count of remaining study drug
- whether the patient was at least 80% compliant in taking study drug
- action taken with study drug as related to an AE or SAE.

**Efficacy Measures**

Quality and quantity of IBS symptoms were recorded daily during the Screening, Treatment, and Follow-up Phases utilizing the touch-tone telephone data entry system.

**Primary Efficacy Measure**

The primary efficacy variable, **"satisfactory control of IBS-related bowel urgency,"** was measured via the patients' daily calls to the touch-tone telephone data entry system. Patients were asked to respond to the following query:

**"Have you had satisfactory control of your bowel urgency today (yes/no)?'**

Patients initially responded to this question on the day of screening and then every day thereafter, up to and including the Follow-up Phone Contact at Week 14.

**Secondary Efficacy Measures**

Patients completed a questionnaire at the Week 4, 8, and 12 Visits which included a rating of **IBS Global Improvement and Bowel Urgency Improvement** rated according to a 7-point scale as follows:

Substantially Worse = 1,
Moderately Worse = 2,
Slightly Worse = 3,
No Change = 4,
Slightly Improved = 5,
Moderately Improved = 6,
Substantially Improved 7

In addition, patients answered the following qualitative question during their daily calls to the touch-tone telephone data entry system:

**"Have you had satisfactory control of the sense of incomplete evacuation today (yes/no)?"**

Patients initially responded to this question on the day of screening and then every day thereafter, up to and including the Follow-up Phone Contact at Week 14.

**Quantitative assessment of IBS symptoms** was performed via patients' daily calls to the touch-tone telephone data entry system. Patients were asked to respond to the following question:

**"How many times did you pass stool today (provide number of times)?"**

In addition, **daily stool consistency scores** were recorded according to the following scale:

Very Hard = 1, Hard = 2, Formed = 3, Loose = 4, Watery = 5

**Health Outcomes Measures**

**Satisfaction with Treatment**

At the Screening Visit, patients recorded satisfaction scores on attributes of their current IBS medication using the Satisfaction with IBS Treatment questionnaire. At the Week 12 (or Final) Visit, patients recorded satisfaction scores on attributes of their study medication using the same questionnaire. Satisfaction was rated on a 7-point Liken scale as follows:

Very Satisfied = 1,
Satisfied = 2,
Somewhat Satisfied = 3,
Neutral (Neither Satisfied nor Unsatisfied) - 4,
Somewhat Unsatisfied - 5,
Unsatisfied =6,
Very Unsatisfied - 7

This scale was reversed for analysis purposes.

**Lost Workplace Productivity and Activity Time**

During their calls to the touch-tone telephone data entry system, patients assessed **Lost Workplace Productivity and Activity Time**. Patients initially responded to these questions on Day 8 (and Days 9 and 10, if necessary) and then every 7 days thereafter, up to and including the Week 12 (or Final) Visit.

**Safety Measures**

**Adverse Events**

The investigator was responsible for recording and reporting AEs observed before, during, and after study drug treatment.

**Definition of an Adverse Event and Serious Adverse Event**

An AE was any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which did not necessarily have a causal relationship with this treatment. An AE could therefore have been any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

**An AE included**:

- an exacerbation of a pre-existing illness
- an increase in frequency or intensity of a pre-existing episodic event or condition
- a condition detected or diagnosed after study medication administration even though it may have been present prior to the start of the study
- continuous persistent disease/symptoms present at baseline that worsened following the start of the study
- pre- or post-treatment events that occurred as a result of protocol-mandated procedures (e.g., invasive procedures, modification of patient's existing therapeutic regimen).

**An AE did not include**:

- medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, or transfusion). (The condition that led to the procedure was an AE.)
- pre-existing disease or condition present or detected at the start of the study that did not worsen
- situations where an untoward medical occurrence had not occurred (e.g., hospitalizations for cosmetic or elective surgery or social/convenience admissions)
- the disease or disorder being studied or sign/symptom associated with the disease or disorder unless more severe than expected for the subject's conditions
- overdose of either study drug or concurrent medication without any clinical signs or symptoms. An overdose was defined as any dose that exceeded the maximum allowable dose as stated in the protocol.

**An SAE was any AE occurring at any dose that resulted in any of the following outcomes:**

- death
- a life-threatening AE
- inpatient hospitalization or prolongation of existing hospitalization
- a disability/incapacity
- a congenital anomaly in the offspring of a patient who received drug
- important medical events that may not have resulted in death, been life-threatening, or required hospitalization may have been considered SAEs when, based upon appropriate medical judgement, they may have jeopardized the patient and may have required medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that did not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Abnormal laboratory findings (e.g., clinical chemistry, hematology, urinalysis) or other abnormal assessments (e.g., electrocardiograms [ECGs], X-rays, vital signs) that were judged by the investigator as clinically significant were recorded as AEs or SAEs if they met the definitions of AEs or SAEs. Clinically significant abnormal laboratory findings or other abnormal assessments that were detected after study drug administration or that were present at baseline and worsened following the start of the study were included as AEs or SAEs.

**Bloody Diarrhea, or Rectal Bleeding with Abdominal Pain**

If a patient encountered either bloody diarrhea or rectal bleeding with abdominal pain, the Glaxo Wellcome Medical Monitor was notified immediately by phone. Depending on the clinical presentation of the patient, follow-up evaluations and information, which was recorded in the source documents and CRF, may have included:

- stool cultures for *Escherichia coli* 0157:H7, *salmonella, shigella, yersinia, campylobacter,* ova and parasites, and *Clostridium difficile* toxin. These were performed at a local laboratory at the onset of the event (no later than 7 days after the onset of the event).

- endoscopic evaluation (flexible sigmoidoscopy or colonoscopy). If biopsies were performed, two unstained coated glass slides were sent to Glaxo Wellcome for *E. coli* immunostaining.

- thrombosis panel (including measurements of protein C, protein S, antithrombin III, Factor VIII, and homocysteine). Appropriate blood samples were sent to [redacted]

In addition, the following information was recorded:

- any history of myocardial infarction, ischemic heart disease, or congestive heart failure
- any history of colonic stricture
- any history of thrombosis
- current evidence of amphetamine or cocaine use.

**Hepatic Laboratory Abnormalities during Treatment or Follow-up**

During the Treatment or Follow-up Phases of the study, if a patient's blood chemistry results revealed any of the following laboratory abnormalities: ALT level ≥3-fold ULN (upper limits of normal), alkaline phosphatase ≥2-fold ULN, or total bilirubin ≥2-fold ULN, the Glaxo Wellcome Medical Monitor was notified by phone. Follow-up evaluations included:

- fractionation for direct and indirect bilirubin for all total bilirubin elevations observed during the Treatment Phase
- serology for hepatitis A, B, and C for ALT elevations ≥3-fold ULN during the Treatment Phase. ALT levels were assessed every 2 weeks until values normalized, substantively improved, were deemed stable.
- liver function assessment for alkaline phosphatase elevations ≥2-fold ULN or bilirubin ≥2-fold ULN during the Treatment Phase. Liver function testing occurred every 2 weeks until alkaline phosphatase values normalized, substantively improved, or were deemed stable.

## Recording and Reporting of Adverse Events and Serious Adverse Events

Each AE was promptly recorded and sufficiently documented by the investigator in the CRF. A causal relationship was not necessarily implied by the report of the AE. The investigator attempted to establish a diagnosis based on the presenting signs and symptoms and then gave an assessment based on whether or not there was a reasonable possibility the AE was related to use of the study drug. If the event met the definition of serious, the SAE form was completed. The completeness and accuracy of these forms were monitored by Glaxo Wellcome Inc. personnel.

At each visit, after the patient had an opportunity to spontaneously mention any problems, the investigator was instructed to inquire about AEs by asking the following standard questions:

1) "Have you had any (other) medical problems since your last visit/assessment?"

2) "Have you taken any new medicines, other than those given to you in this study, since your last visit/assessment?"

During the 12-week Treatment and 2-week Follow-up Phases, events meeting the definitions of AEs and SAEs were recorded in patients' CRFs and source documents. All unresolved AEs and SAEs observed at the last study visit were followed by the investigator until the event(s) resolved, stabilized, the patient was lost to follow-up, or the event was otherwise explained. At the last scheduled study visit, the investigator instructed patients to report any subsequent AE which patient or their physicians believed might reasonably have been caused by the study drug.

**Pregnancy**

Patients of childbearing potential must have had a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test at the Screening Visit in order to be randomized to study drug. Patients of childbearing potential also must have had a negative serum β-hCG pregnancy test at the Week 12/Final Visit.

Any patient who became pregnant while participating in the study was followed to determine the outcome of the pregnancy. Generally, the duration of follow-up was no longer than 6 to 8 weeks after the estimated delivery date. The investigator, or his or her designee, collected pregnancy information on the appropriate Glaxo Wellcome form and submitted it to Glaxo Wellcome within 2 weeks of learning of the patient's pregnancy.

While pregnancy itself was not considered to be an AE or an SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons was recorded as an AE or an SAE and was followed-up as such. Furthermore, if the investigator learned, through spontaneous reporting, of any SAE which occurred as a result of a post-study pregnancy and which was reasonably related to the study drug, he or she was advised to notify Glaxo Wellcome Inc.

## Clinical Laboratory Tests

A standard battery of laboratory blood tests including clinical chemistry and hematology was performed at the Screening and Week 12 (or Final) Visits. Laboratory tests included are listed in the following Table 1.

**Table 1**
**Clinical Laboratory Tests**

| Hematology | Serum Chemistries | Other |
|---|---|---|
| Bands | Albumin | Ova and parasites[a] |
| Basophils | Alkaline phosphatase | Hydrogen breath test[b] |
| Eosinophils | ALT (SGPT) | Stool occult blood[a] |
| Hematocrit | AST (SGOT) | Serum β-hCG pregnancy test[c] |
| Hemoglobin | Blood urea nitrogen (BUN) | TSH[d] |
| Lymphocytes | Calcium | |
| Monocytes | Chloride | |
| Neutrophils | Creatinine | |
| Platelets | Glucose | |
| Red blood cells (RBCs) | Magnesium | |
| White blood cells (WBCs) | Phosphorus | |
| | Potassium | |
| | Sodium | |
| | Total bilirubin | |
| | Total protein | |

a. Performed at the Screening Visit if not assessed within the previous 3 months.
b. Performed at the Screening Visit if status was unknown.
c. Performed at the Screening and Week 12 Visits.
d. Performed at the Screening Visit if not assessed within the previous 3 years.

All abnormal laboratory test results that were assumed to be potentially drug related or of uncertain causality were repeated at the investigator's discretion until the abnormal result(s) resolved or were deemed clinically insignificant. If the laboratory studies performed at the Week 12 Visit showed any clinically significant abnormal result(s) that was assumed by the investigator to be drug related or of uncertain etiology, that specific parameter(s) was reassessed when the subject returned for the Follow-up Visit or sooner if deemed necessary by the investigator.

### Other Safety Measures

#### Physical Examination

A physical examination was performed by the principal investigator or a subinvestigator at the Screening and Week 12 Visits. Results were recorded in patients' source documents.

## Data Analysis Methods

### Quality Control Measures

Patients recorded all daily and weekly urgency, bowel symptoms, and productivity and activity data during the Screening, Treatment, and Follow-up Phases via the touch-tone telephone data entry system. These data were captured and electronically transferred by Kendle International Inc. At the clinical study sites, the investigator or designee recorded required patient data in paper CRFs. Self-ratings of patient satisfaction and global improvement were completed via questionnaires administered at the study site.

### Sample Size Considerations

The sample size estimate was based on the primary endpoint, proportion of days with satisfactory control of bowel urgency over 12 weeks. In the Phase III clinical trials, the proportion of days with bowel urgency was estimated at 0.50 for subjects receiving placebo and 0.40 for subjects receiving alosetron. The approximate standard deviation for both groups was 0.30. In the current study, the two treatment groups were compared using a van Elteren test (i.e., stratified Wilcoxon rank-sum test) stratified by cluster. Using the nonparametric Wilcoxon Rank Sum test, 200 patients per treatment group were needed to detect a 0.10 difference in the proportion of days with satisfactory control of bowel urgency with 90% power at the $\alpha$=0.05 significance level. To allow for a 20% dropout rate, a target sample size of 250 per treatment group was needed.

### Interim Analyses and Data Monitoring

No interim analyses were planned for this study.

### General Considerations for Data Analyses

SAS software was used to perform all calculations and to program all statistical analyses, summaries, tables, and patient listings for this report. The SAS analysis database resides at Glaxo Wellcome Inc.

### Analysis Populations

Three populations were considered for analysis as described below:

The **Intent-to-Treat Population** comprised all randomized subjects. Patients who participated in the Screening Phase but who were not subsequently randomized to treatment were excluded from this population.

The **Primary Efficacy Population** consisted of those in the Intent-to-Treat Population who completed at least 8 weeks of treatment or withdrew for reasons other than the sponsor's early termination of the study. This was the primary population used for efficacy analyses.

Patients in the Intent-to-Treat Population who received at least one dose of study drug were included in the **Safety Population**. Patients with no treatment start date were excluded from this population.

### Examination of Subgroups

Satisfactory control of urgency was assessed for the following subgroups of patients:

- age: <50, ≥50, <65, ≥65, <75, and ≥75 years
- race: white and other
- parity: 0 births, 1-3 births, and >3 births
- childbearing potential: potentially able to bear children or sterile/menopausal
- time since IBS diagnosis: <10 years and ≥10 years
- IBS subtype: diarrhea-predominant and alternating constipation/diarrhea
- BMI: <27kg/m$^2$ and ≥27kg/m$^2$

Productivity information was assessed for patients who worked all 12 weeks and for those who worked at least 10 of the 12 weeks in the Treatment Phase.

Adverse events and drug-related AEs were assessed by age and race.

### Handling of Patients Prematurely Discontinued or Missing Data

#### Multicenter Studies

A total of 135 centers were used to recruit patients. Some centers may have enrolled relatively small numbers of patients, thus making tests for treatment effects and treatment-by-center interactions inappropriate. Therefore, statistical management of centers was accomplished via a priori pooling into clusters by geographic region. These

clusters were used for the assessment of treatment-by-center interaction for the primary efficacy parameter. The following geographic clusters were identified for pooling centers:

1. **West**: California, Oregon, Washington, Nevada, Utah, Arizona

2. **North Central**: Colorado, Nebraska, kansas, Missouri, Minnesota, Illinois, Ohio, Wisconsin, Indiana, Michigan, Montana, North Dakota, South Dakota, Iowa, Idaho

3. **South Central**: Tennessee, Alabama, Kentucky, Texas, Arkansas, Louisiana, Mississippi, Oklahoma, New Mexico, Georgia

4. **Southeast**: Florida, South Carolina, North Carolina

5. **Northeast/Mid-Atlantic**: Maryland, Pennsylvania, New York, New Jersey, Connecticut, Massachusetts, Vermont, Delaware, Virginia, District of Columbia, West Virginia, New Hampshire, Maine, Rhode Island

**Multiple Comparisons and Multiplicity**

For statistical analyses, p-values based on two-sided tests were reported for comparing alosetron 1 mg BID and placebo BID.

To control experiment-wise Type 1 error, a stepwise approach was used to adjust for multiple comparisons. First, the primary endpoint, relief of bowel urgency over 12 weeks, was tested at the 0.05 level. If statistical significance was demonstrated for the primary endpoint, then statistical testing proceeded to the first secondary endpoint, IBS Global Improvement at Week 12, which was tested at the 0.05 level. If statistical significance was demonstrated for IBS Global Improvement, statistical testing proceeded to Loss of Productivity over 12 weeks and overall satisfaction with treatment at Week 12 which were tested at the 0.05 level.

The IBS Global Improvement response was collected at three timepoints: Weeks 4, 8, and 12. Within this endpoint, Week 12 was tested at the 0.05 level as described above. If differences between treatment groups were statistically significant at Week 12, then testing proceeded to Week 8, and so on. If differences in IBS Global Improvement were statistically significant between treatment groups at Week 12, testing proceeded to Lost Productivity and overall satisfaction with treatment. Lost Workplace Productivity, Lost Activity Time, and overall satisfaction with treatment were tested at the 0.05 level using the Hochberg approach.

The procedure described above ensured tight family-wise error rate control for relief of urgency, the composite of IBS Global Improvement tests, and the composite productivity and overall satisfaction with treatment tests. In addition, a second family of endpoints was tested independent of the endpoints described above. This included the proportion of subjects reporting satisfactory control of urgency on each of the first 14 days of treatment. This set of fourteen endpoints was tested using the exact step-down permutation tests of PROC MULTTEST of SAS/STAT. The family-wise error rate across all endpoints, including the primary endpoint, the secondary endpoints, and the fourteen daily tests, was no more than 0.10, since 0.05 family-wise error rate was allocated to each family.

All other efficacy endpoints were tested at the 0.05 level. Tight family-wise error was not maintained for these other endpoints, thereby limiting the inferential conclusions that can be drawn from them.

## Protocol Deviations

The number and percentage of patients with protocol violations was tabulated by category in decreasing order of frequency. The following were considered protocol violations:

- violation of inclusion or exclusion criteria
- patient took prohibited medications
- patient was <80% compliant in taking study medication, or had missing compliance data
- patient was <50% compliant with the telephone diary system during the Treatment Phase.

### Compliance

#### Treatment compliance

Treatment compliance was determined using study drug accountability records collected at the Week 4, 8, and 12 Visits, as well as at the Follow-up Visit if the patient did not return study medication at the Week 12 Visit. If the patient did not return study drug at a given visit, then compliance was missing for that visit. The proportion of patients who were at least 80% compliant during the previous 4 weeks was summarized by treatment group and visit.

**Touch-tone telephone data entry system compliance**

Compliance with the telephone diary system was evaluated throughout the 12-week Treatment Phase. The proportion of days that a patient was compliant with the telephone diary system was determined by summing the number of days that the patient completed a call to the system divided by the number of days on treatment. Patients who were less than 50% compliant were considered protocol violators.

**Other Descriptions of Study Population**

The following demographic and baseline characteristics were summarized by treatment group for the Primary Efficacy and Intent-to-Treat Population as well as for screening failures: age, race, height, weight, BMI, IBS subtype, childbearing potential, method of birth control, parity, and date of onset of IBS symptoms. Current medical conditions were collected at baseline and summarized by treatment group. Concurrent medications and IBS medications (coded using the in-house THERAPY dictionary) were summarized by treatment group and sorted in descending frequency.

## IV. Proposed Analyses

### A. Efficacy Analyses

**Primary Efficacy Measure –**

**Satisfactory Control of Bowel Urgency over 12 Weeks**

The primary efficacy measure was satisfactory control of bowel urgency over the 12-week Treatment Phase. Data were collected daily via the touch-tone telephone system and the proportion of days a subject had satisfactory control of bowel urgency was calculated using the following formula:

$$\frac{\text{Number of days with satisfactory control of bowel urgency}}{\text{Number of days patient could have answered the bowel urgency question}}$$

The proportion of days with satisfactory control of bowel urgency was compared between treatment groups using the van Elteren method of the Wilcoxon rank-sum test with stratification by cluster. The null and alternative hypotheses for the van Elteren test were stated as:

$H_0$: The proportion of days patients had satisfactory control of bowel urgency was independent of treatment when adjusted for cluster.

$H_1$: The proportion of days patients had satisfactory control of bowel urgency was not independent of treatment when adjusted for cluster.

*To ensure inclusion of subject data for the entire 12-week Treatment Phase, the last observation carried forward (LOCF) principle was employed in which days with missing data had the previous day's data carried forward up until the treatment stop date.* If the first day was missing, it was assumed the patient did not have satisfactory control of urgency. The same analysis was also performed on observed data. Only data collected through Day 91 (Week 12 Visit plus 7 days) were included in the primary efficacy calculation.

**Supportive Analysis –**

**Change from Baseline in Satisfactory Control of Bowel Urgency over 12 Weeks**

A supportive analysis of the primary measure assessed the change from baseline in the proportion of days with satisfactory control of bowel urgency by week for each patient. The proportion of days with satisfactory control of bowel urgency for the 2 weeks of screening and for each week during treatment were calculated. Screening included Days -14 to -1, Week 1 included Days 1 to 7, Week 2 included Days 8 to 15, and so on. For the small subset of patients who were antidiarrheal-dependent, the proportion of days with satisfactory control of bowel urgency during screening was calculated for a 5-day Screening Phase. If a patient had a colon procedure, the 14 days prior to the procedure (5 days prior if antidiarrheal-dependent) were used for screening.

The weekly proportion of days with satisfactory control of bowel urgency was calculated using all available daily response data, provided there was a response for at least 1 day within that week. *If all data were missing for a particular week, the average proportion from the previous week was used (LOCF).* Weekly data were not carried forward to a follow-up week, but *the first follow-up week was carried forward if the second follow-up week was missing.* Change from baseline was calculated by week for each patient. For each week, change from baseline was compared between treatment groups using a van Elteren test stratified by cluster. The same analysis was performed on observed data.

## Secondary Efficacy Measures

### Irritable Bowel Syndrome Global Improvement Responders

Every 4 weeks (Weeks 4, 8, and 12) patients were asked the IBS Global Improvement question. IBS Global Improvement Responders were those patients who demonstrated substantial or moderate improvement on this endpoint. These assessments were collected at specific visits ±7 days (i.e.. Week 4 was Day 28, Week 8 was Day *56,* and Week 12 was Day 84). Data collected outside these windows were considered unscheduled. These data were used in LOCF analyses but not in observed analyses. *For LOCF analyses, if Week 4 was missing, the last treatment assessment prior to Week 4 was carried forward. If Week 8 was missing, the last treatment assessment prior to Week 8 was carried forward, and if Week 12 was missing, the last treatment assessment prior to Week 12 was carried forward.*

Proportions of Responders and Nonresponders were compared between treatment groups at Week 12 using a Mantel-Haenszel test stratified by cluster. If statistical significance was demonstrated at Week 12, testing proceeded to Week 8, and if statistically significant, to Week 4.

**Supportive analysis –**

### Irritable Bowel Syndrome Global Improvement Scale

Treatment group effects were compared across the 7-point IBS Global Improvement scale at Weeks 4, 8, and 12 using the extended Mantel-Haenszel mean score test stratified by cluster.

### Daily Analysis of Satisfactory Control of Bowel Urgency

The proportion of patients with satisfactory control of bowel urgency was calculated daily over the first 14 days of treatment with no imputation of missing values. This set of fourteen endpoints was tested using the exact step-down permutation tests of PROC MULTTEST of SAS/STAT which calculates adjusted p-values using the step-down Bonferroni method of Holm. Significance on all 14 days was assessed and trends were noted.

#### Lower Gastrointestinal Functions

The baseline averages of stool consistency and stool frequency were calculated using information collected during the Screening Phase. Averages were calculated for Weeks 1 though 12 using LOCF imputation and observed data.

The proportion of days that patients experienced a sense of incomplete evacuation was calculated for the Screening Phase and for Weeks 1 through 12. Data were analyzed as described previously for weekly calculation of satisfactory control of bowel urgency.

*The method for applying LOCF was the same as that described for the primary endpoint, satisfactory control of bowel urgency.* For each gastrointestinal function described above, weekly change from baseline was summarized by treatment group for the Treatment and Follow-up Phases. Treatment group effects were compared using a van Elteren test stratified by cluster.

**Other Efficacy Measures: Exploratory Endpoints**

**Bowel Urgency Improvement Responders**

Every 4 weeks (Weeks 4, 8, and 12) patients were asked the Bowel Urgency Improvement question. Bowel Urgency Improvement Responders were those patients who demonstrated substantial or moderate improvement on this endpoint. *The method for applying LOCF was the same as that described for the secondary endpoint, IBS Global Improvement.* Proportions of Responders and Nonresponders were compared between treatment groups at Weeks 4, 8, and 12 using a Mantel-Haenszel test stratified by cluster.

**Supportive Analysis: Bowel Urgency Improvement Scale**

Treatment group effects were compared using the 7-point Bowel Urgency Improvement scale at Weeks 4, 8, and 12 using the extended Mantel-Haenszel mean score test stratified by cluster.

**Correlations between Control of Bowel Urgency and Other Endpoints**

Since a strong relationship exists between bowel urgency and the other lower gastrointestinal functions (stool frequency, stool consistency, and sense of incomplete evacuation), the relationship among clinical endpoints was quantified using Spearman rank correlation statistics on observed data. In addition, associations between clinical endpoints and satisfaction with treatment were explored. The scale used to rate satisfaction with treatment was reversed for analysis purposes.

## Health Outcomes Analyses

### Satisfaction with Treatment

At screening and the Week 12 (or Final) Visit, patients recorded a satisfaction score for a set of IBS medication attributes, with each attribute rated on a 7-point Likert scale. Treatment group effects were compared at the Week 12 (or Final) Visit using the extended Mantel-Haenszel mean score test stratified by cluster. In addition, satisfaction with treatment at the Week 12 (or Final) Visit was similarly compared with subjects' satisfaction with their usual IBS medication.

The 7-point scale used to rate satisfaction with treatment was reversed for analysis purposes. Therefore, analyses were performed with improvement and satisfaction scales ranging from "Very Unsatisfied = 1" to "Very Satisfied = 7".

### Lost Workplace Productivity and Activity Time

#### Last Workplace Productivity

Lost Workplace Productivity was calculated as:

$$A + (B * [1-(C/100)])$$

Where:

A = Total time missed from paid job(s) because of IBS symptoms in the past 7 days

B = Total time worked at paid job(s) with IBS symptoms in the past 7 days

C = Percent effectiveness while working with IBS symptoms at paid job(s)

Average weekly time missed was calculated using both imputed and observed data. Only subjects who worked at least 1 week were included in the analysis. If a patient was included and recorded that she did not work for an individual week, that week was assigned a value of 0. *If a value for a week was missing, the average of the non-missing weeks for that patient was imputed for the missing week.* The total time was summed for the entire Treatment Phase.

Treatment group effects were compared with respect to total time missed over 12 weeks and for each week using a van Elteren test controlling for cluster. The number of hours missed per week was also summarized. In addition, the subgroup of subjects who worked all 12 weeks was analyzed.

Two post hoc analyses were performed;

1) Percent Lost Workplace Productivity
calculated as Lost Workplace Productivity divided by time planned to work.

2) Lost Workplace Productivity among subjects working full time as defined by at least 10 of 12 weeks with ≥30 hours of planned work.

Both post hoc endpoints were analyzed similarly to Lost Workplace Productivity, described above.

### Lost Activity Time

Lost Activity Time was calculated as follows:

$$D+(E * [1-(F/100)])$$

Where:

D = Total time prevented from doing normal activities because of IBS symptoms in the past *7* days

E = Total time carried on normal activities with IBS symptoms in the past 7 days

F = Percent effectiveness while carrying on normal activities with IBS symptoms

Average weekly Lost Activity Time was calculated using both imputed and observed data. Data were imputed similarly to Lost Productivity Time. Treatment effects were compared over 12 weeks using a van Elteren test controlling for cluster. The number of hours missed per week was also summarized.

### Total Lost Productivity

For patients who recorded both Lost Workplace Productivity and Lost Activity Time, the two endpoints were summed to characterize Total Lost Productivity. The average weekly time missed was calculated using both imputed and observed data. Treatment effects were compared over 12 weeks using a van Elteren test controlling for cluster. The number of hours missed by week was also summarized.

## B. Safety Analyses

### Extent of Exposure

Extent of exposure to study drug (i.e., the number of days the subject received treatment during the study) was computed as the difference between trial medication stop at start dates plus one day. Days of exposure were categorized and summarized by treatment group.

### Adverse Events

Adverse events were coded using the Glaxo Wellcome MIDAS dictionary and grouped using the Coding Symbols for the Thesaurus of Adverse Reactions (COSTART) dictionary. Adverse events occurring on or after the start of treatment were considered separately from AEs occurring during the Screening Phase. For each body system, and over all body systems, the frequency of patients reporting at least one treatment emergent AE was summarized by treatment group. If the patient had more than one occurrence of an AE within a preferred term, body system, or overall, the patient was counted only once The number and percentage of patients with any Treatment Phase AE in any body system were summarized by treatment group.

In addition, the number of patients reporting at least one drug-related treatment-emergent AE (as judged by the investigator as having a reasonable possibility that the event may have been caused by the trial medication) and the most frequent AEs ($\geq$5%) were summarized by treatment group.

### Deaths and Serious Adverse Events

The frequency of SAEs was summarized by body system and treatment group. In addition, details regarding deaths and SAEs were derived from information contained in listings and North American Product Surveillance case narratives.

### Adverse Events Leading to Discontinuation of Study Drug and/or Withdrawal from Study and Other Significant Adverse Events

Adverse events leading to discontinuation from study procedures were tabulated by body system. Information regarding premature discontinuation of study drug and other significant AEs was derived from listings.

### Pregnancies

Pregnancies were summarized using information in listings and North American Product Surveillance case narratives.

### Clinical Laboratory Evaluations

Blood samples for laboratory tests were collected at the Screening and Week 12/Final Visits. For the purposes of statistical analyses, the final value of the laboratory test prior to the start of randomized treatment was used as the baseline value, and only those laboratory tests with a numeric normal range and at least one follow-up value were analyzed.

The frequency of patients with an abnormal baseline laboratory value among those patients with a baseline laboratory value and a follow-up laboratory value was summarized by treatment group.

The frequencies of transitions from prestudy values to abnormal values at any follow-up visit were summarized for each treatment group. "Shift" categories included changes:

1) from normal or low to high,
2) from normal or high to low, and
3) to normal or no change.

Laboratory values exceeding the threshold limits were defined in terms of a multiplicative factor of the testing laboratory's normal range. A laboratory value that was above the upper limit factor multiplied by the ULN was considered a high threshold value. A laboratory value below the lower limit factor multiplied by the lower limit of the normal range (LLN) was considered a low threshold value.

Baseline threshold laboratory values were summarized by the frequency of patients with a beyond-threshold baseline value among those subjects with a baseline laboratory value and a follow-up laboratory value.

The frequencies of transitions to beyond threshold from baseline at any follow-up visit were summarized for each treatment. The "threshold" categories presented included changes to 1) high threshold, 2) low threshold, and 3) normal or no change.

### Other Safety Measures

### Physical Examinations

Results of physical examinations were not tabulated.

**Study Populations Results**

**Subject Accountability**

Eleven hundred one (1101) patients were screened for participation in the study. Of these 1101 patients, 609(55%) were not randomized to treatment. The most common reasons for failure to randomize subjects were (from Sponsor's Table 6.1):

- 50% of days with lack of satisfactory control of bowel urgency entry criterion not met (300/609, 49%)
- noncompliance with the touch-tone telephone data entry system (179/609, 29%)
- abnormal serum creatinine, ALT, AST, or TSH values (77/609, 13%)

Forty-five percent (45%, 492/1101) of the patients screened were randomized to treatment, with 50% (246/492) randomized to the placebo group and 50% (246/492) randomized to the alosetron-treatment group, making up the Intent-To-Treat (ITT) Population. Seventeen percent (17%, 86/492) of the patients withdrew due to the sponsor's early termination of the study. Therefore, the Primary Efficacy (PE) Population consisted of those in the ITT Population who completed at least 8 weeks of treatment or withdrew for reasons other than the sponsor's early termination of the study. The PE Population was comprised of 89% (436/492) of the ITT Population with 49% (213/436) in the placebo group and 51% (223/436) in the alosetron group (Sponsor's Table 6.2).

The percentage of patients in the PE Population who completed the study was 65% (282/436) overall, including 63% (135/213) in the placebo group and 66% (147/223) in the alosetron group. Thirty-five percent (35%, 154/436) of the patients withdrew from the study during the Treatment or Follow-up Phases, including 37% (78/213) of the placebo group and 34% (76/223) of the alosetron group. The same number (282) of patients in the ITT Population completed the study. The percentage of patients in the ITT Population who withdrew from the study was 43% (210/492) overall, including 45% (111/246) from the placebo group and 40% (99/246) from the alosetron group. The difference in completion/withdrawal status in the PE and ITT Populations was entirely attributed to the additional number of patients withdrawing due to the sponsor's early termination of the study.

The most common reason for withdrawal from the study in the alosetron group was constipation, which led to the premature discontinuation of 38/223(17%) alosetron-treated patients. The most common reasons for early withdrawal among placebo-treated patients were AEs which occurred among 21/213 (10%) of patients and lack of efficacy, which affected 21/213 (10%) patients.

The next most common reason for withdrawal from the study in both treatment groups was the sponsor's early termination of the study (Other); 17/213 (8%) of placebo-treated patients and 13/223 (6%) of alosetron-treated patients. Similar results were found for the ITT Population except reason for withdrawal from the study due to the sponsor's early termination of the study (Other) was greater in both treatment groups; 50/246 (20%) of placebo-treated patients and 36/246 (15%) of alosetron-treated patients. Reasons for premature withdrawal from the study in the PE population are summarized in Table 2.

**Table 2**
**Premature Study Withdrawals by Reason**
**Primary Efficacy Population, S3B40031**

| | Placebo BID n/213 (%) | Alosetron 1mg BID n/223 (%) | Total n/436 (%) |
|---|---|---|---|
| Number of subjects withdrawing prematurely | 78 (37%) | 76 (34%) | 154 (35%) |
| Adverse event | 21 (10%) | 38 (17%) | 59 (14%) |
| Consent withdrawn | 9 (4%) | 7 (3%) | 16 (4%) |
| Lost to follow-up | 7 (3%) | 8 (4%) | 15 (3%) |
| Protocol violation | 3 (1%) | 6 (3%) | 9 (2%) |
| Lack of efficacy | 21 (10%) | 4 (2%) | 25 (6%) |
| Other[a] | 17 (8%) | 13 (6%) | 30 (7%) |

Source data: Table 6.3 and Listing 3.
a. All subjects were discontinued by the sponsor due to early termination of the study.

**Protocol Deviations**

Protocol violations occurred at similar frequency between treatment groups. The most common protocol violation in both groups was use of prohibited medications during the study, which occurred among 42/213(20%) patients in the placebo group and 57/223 (26%) patients in the alosetron group. In each case, these prohibited medications were initiated on or before the treatment stop date. Other protocol violations included:

- <80% compliance in taking study medication: 33/213 (15%) patients in the placebo group and 38/223 (17%) patients in the alosetron group
- failure to meet inclusion/exclusion criteria: none patients in the placebo group and 8/223 (4%) patients in the alosetron group
- <50% compliance with the telephone data entry system: 2/213 (<1%) patients in the placebo group and 4/223(2%) patients in the alosetron group.

The treatment blind was broken by the investigator for a total of two patients during the study, one in the placebo group and one in the alosetron group.

### Populations Analyzed

Forty-five percent (45%, 492/1101) of the patients screened were randomized to treatment, constituting the Intent-to-Treat Population. Of these, 50% (246/492) were randomized to each of the placebo group and the alosetron group. All randomized patients received at least one dose of study drug. As such, the Safety Population was identical to the Intent-to-Treat Population.

Eighty-nine percent (89%, 436/492) of the subjects in the ITT Population completed at least 8 weeks of treatment or withdrew for reasons other than the sponsor's early termination of the study, constituting the Primary Efficacy Population. Of these, 49% (213/436) were randomized to the placebo group and 51% (223/436) were randomized to the alosetron group.

### Demographic and Baseline Characteristics

### Demographics

The PE Population ranged in age from 19.5 to 84.6 years, 89% (390/436) of patients were white, 5% (23/436) were black, and the remainder were Hispanic (18/436, 4%), Asian (2/436, <1%), or 'other' descent (3/436, <1%). Treatment groups were well matched with regard to demographic characteristics. Patients in the placebo group had a mean ( standard deviation) age of 49.40 $\pm$13.84 years (range = 20.3 to 81.4 years). In the alosetron group, mean age was 48.70 $\pm$15.29 years (range = 19.5 to 84.6 years). The racial composition of each of the treatment groups reflected that of the overall population. The group of patients who failed screening did not differ notably from those patients in the PE Population with regard to demographic characteristics.

### Baseline Characteristics

Body mass index was similar between treatment groups. In the PE Population the mean BMI was 30.53 $\pm$8.81 kg/m$^2$ in the placebo group and 28.75 $\pm$7.86 kg/m$^2$ in the alosetron group. Approximately one-third of patients in each group were potentially able to bear children (67/213, 31% in the placebo group and *72/223,* 32% in the alosetron group) and the remainder were sterile or post-menopausal. Among those women who were able to conceive children, the most common method of birth control was oral contraceptives and abstinence.

Patients in both groups had suffered from IBS for an average of about 12 years. Eighty-nine percent (89%, 390/436) of patients in the PE Population were characterized by the investigator as suffering from the diarrhea-predominant IBS subtype. The remaining 11% (46/436) of patients had alternating constipation/diarrhea IBS. The distribution of IBS subtype was similar in each of the placebo and alosetron-treated groups.

Ten percent (10%, 42/436) of the patients were reported to have [redacted] as their healthcare provider. Eighty-nine percent (89%, 386/436) reported other providers as their healthcare provider, and less than 2% (8/436) were missing this information or had no healthcare provider. The distribution of healthcare provider status was similar in each of the placebo and alosetron-treated groups. Current paid work status showed that 52% (225/436) worked full-time, 14% (63/436) worked part-time, and 34% (148/436) did not work at a paid job. The distribution of paid work status was similar in each of the placebo and alosetron-treated groups.

Baseline characteristics were similar between screen failures, the patients who were randomized, and the PE Population.

**Medical Conditions**

The distribution of current medical conditions was uniform between treatment groups. The most common underlying conditions involved the following: allergies, the musculoskeletal system, and gastrointestinal conditions other than IBS.

**Concurrent Medications and Non-Drug Therapies**

Most (395/436, 91%) patients in the PE Population reported taking other medications during the study. The most commonly reported concurrent medications acted via the nervous system (reported by 150/213, 70% of patients in the placebo group and 156/223, 70% of patients in the alosetron group) and endocrine and metabolic system (reported by 127/213, 60% of patients in the placebo group and 138/223, 62% of patients in the alosetron group). Other concomitant medications which were commonly used included those affecting the gastrointestinal and cardiovascular systems (Table 3).

**Table 3**
**Summary of Concurrent Medications P E Population**
**Protocol S3B40031**

| Medication Class by Body System | Placebo BID 193/213 (91%) | Alosetron 1 mg BID 202/223 (91%) |
|---|---|---|
| **Nervous** | 150 (70%) | 156 (70%) |
| **Endocrine & Metabolic** | 127 (60%) | 138 (62%) |
| **Gastrointestinal** | 80 (38%) | 102 (46%) |
| **Cardiovascular** | 79 (37%) | 81 (36%) |
| **Nutrition** | 57 (27%) | 58 (26%) |
| **Anti-Infectives & Immunologicals** | 30 (14%) | 42 (20%) |
| **Skin, Ear, & Eye** | 7 (3%) | 2 (<1%) |
| **Cytotoxic & Anti-Neoplastics** | 2 (<1%) | 0 (0%) |
| **Various drugs** | 35 (16%) | 31 (14%) |

Adapted from Sponsor's Table 6.7

### Compliance

### Treatment Compliance

Treatment compliance for the PE Population was comparable between treatment groups, with 86-94% of placebo-treated pts and 85-94% of alosetron-treated patients demonstrating ≥80% compliance during each of the three 4-week periods in the Treatment Phase. Treatment compliance data were missing for a minority of patients who did not return study drug . Similar results were found in the ITT Population.

### Touch-tone Telephone Data Entry System Compliance

Mean subject compliance with the touch-tone telephone data entry system was 87.2± 13.2% in the placebo group and 87.0 ± 14.4% in the alosetron group. Similar results were found in the ITT Population

## VII. Study Results

### A. Efficacy Results

The Primary Efficacy Population (n=436) was utilized for efficacy analyses. The Intent-to-Treat Population (n=492) was utilized for supportive efficacy analysis.

**Primary Efficacy Measure:**
**Satisfactory Control Of Bowel Urgency Over 12 Weeks**

Analysis using LOCF imputation of the PE data revealed that the median proportion of days with satisfactory control of urgency over the 12-week Treatment Phase was 0.56 in the placebo BID group and 0.69 in the alosetron 1mg BID group, representing a statistically significant therapeutic gain of alosetron 1 mg BID over placebo BID of 13 % ($p \leq 0.001$). Identical analysis using ITT data showed the median proportion of days with satisfactory control of urgency over the 12-week Treatment Phase was 0.56 in the placebo BID group and 0.69 in the alosetron 1 mg BID group, representing a statistically significant therapeutic gain of alosetron 1 mg BID over placebo BID of 13 % ($p \leq 0.001$).

The following Tables summarize the data and present the statistically significant benefit of alosetron 1 mg BID over placebo(Table 4 presents the PE data and Table 5 presents the ITT data)

**Table 4**
**Summary of the Proportion of Days with Control of Urgency over 12 Weeks (LOCF)**
**Study S3B40031**

| Primary Efficacy Population | Treatment Groups | | p-value * | Therapeutic Gain |
|---|---|---|---|---|
| | Placebo n=213 | Lotronex n=223 | | |
| **Proportion of Days** | | | | |
| N | 213 | 223 | | |
| Mean | 0.49 | 0.59 | ≤0.001 | 10% |
| Standard error | 0.021 | 0.022 | | |
| Median | 0.56 | 0.69 | ≤0.001 | 13% |
| Minimum | 0.00 | 0.00 | | |
| Maximum | 1.00 | 1.00 | | |

* p-value obtained using a van Elteren Test stratified by cluster (Sponsor's Table 7.1, modified).

**Table 5**
**Summary of the Proportion of Days with**
**Satisfactory Control of Urgency over 12 Weeks (LOCF)**
**Study S3B40031**

| Intent-to-Treat Population | Placebo n=246 | Lotronex n=246 | p-value * | Therapeutic Gain |
|---|---|---|---|---|
| **Proportion of Days** | | | | |
| N | 246 | 246 | | |
| Mean | 0.48 | 0.59 | <0.001 | 11% |
| Standard error | 0.019 | 0.021 | | |
| Median | 0.56 | 0.69 | <0.001 | 13% |
| Minimum | 0.00 | 0.00 | | |
| Maximum | 1.00 | 1.00 | | |

* p-value obtained using a van Elteren Test stratified by cluster
(Sponsor's Table 7.1.1, modified).

Alosetron 1 mg BID was more effective than placebo BID in increasing the proportion of days with satisfactory control of urgency over 12 weeks.

Subgroup analyses of the proportion of days with satisfactory control of urgency within age, race, parity, childbearing potential, time since IBS diagnosis, IBS subtype, and BMI demonstrated benefit for alosetron (when sufficient sample size was available to draw conclusions) and no evidence of differential treatment effects across the subgroup categories.

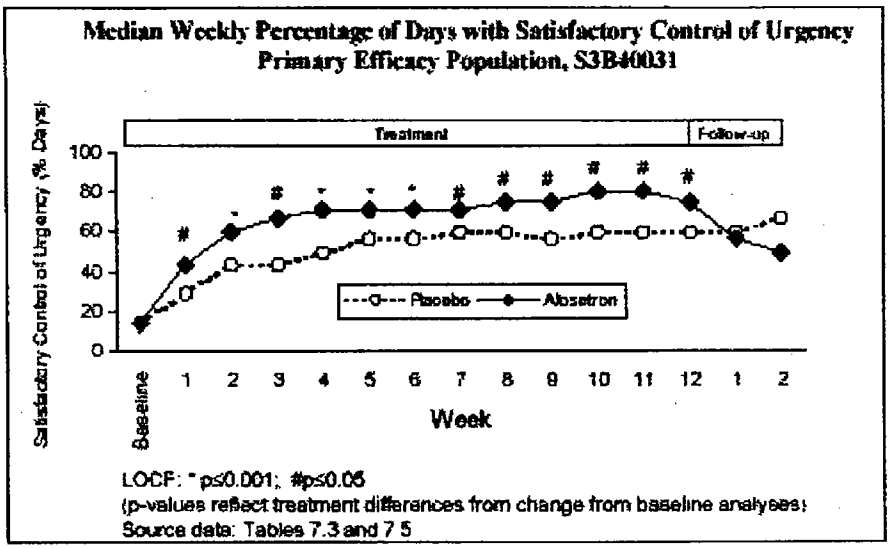
**Supportive Analysis:**

**Change from Baseline in Satisfactory Control of Bowel Urgency over 12 Weeks**

Compared with placebo BID-treated patients, alosetron 1 mg BID-treated patients demonstrated a statistically significantly greater change from baseline in the proportion of days with satisfactory control of urgency at each week of the 12-week Treatment Phase. This effect diminished rapidly following the cessation of treatment.

Figure 1 presents weekly LOCF values for the proportion of days with satisfactory control of urgency, expressed as a percentage. P-values reflect treatment differences from weekly change from baseline analyses.

**Figure 1**




Results were similar in the ITT analysis.

## Secondary Efficacy Measure(s):
## Irritable Bowel Syndrome

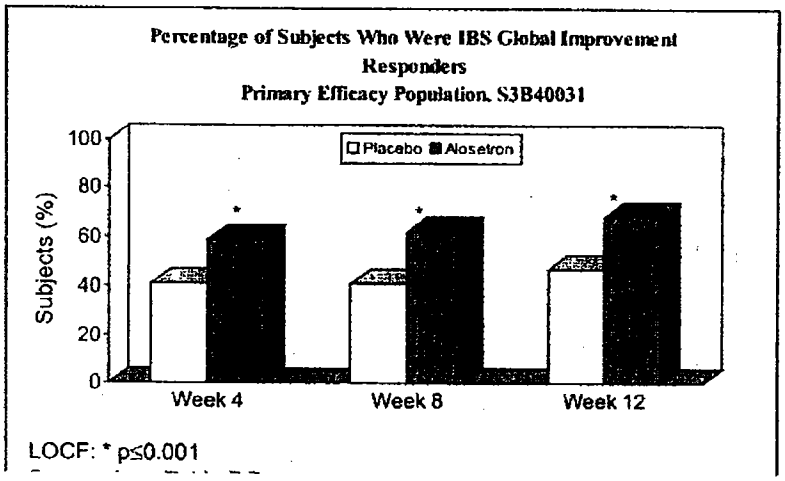
### Global Improvement Responders

A statistically significantly greater percentage of patients in the alosetron 1 mg BID group were IBS Global Improvement Responders compared with the placebo BID group at:

Week 12 68%, 143/210 versus 47%, 94/201, respectively( $p \leq 0.001$
Week 8 62%, 131/210 versus 41%, 82/201, respectively($p \leq 0.001$)
Week 4 59%, 118/201 versus 41%, 78/191, respectively($p \leq 0.001$).

These results are shown in Figure 2.

**Figure 2**




Source: Sponsor's Table 7.7

The beneficial effect of alosetron 1 mg BID on self-assessment of IBS Global improvement was present during each 4 week period of treatment.

**Supportive Analysis - Measured:**

**Irritable Bowel Syndrome Global Improvement Scale**- Treatment responses were different between groups across the IBS Global Improvement scale. The result shown above for IBS Global Improvement Responders was driven by the proportion of Responders who were substantially improved as opposed to those who were only moderately improved for each time measured.

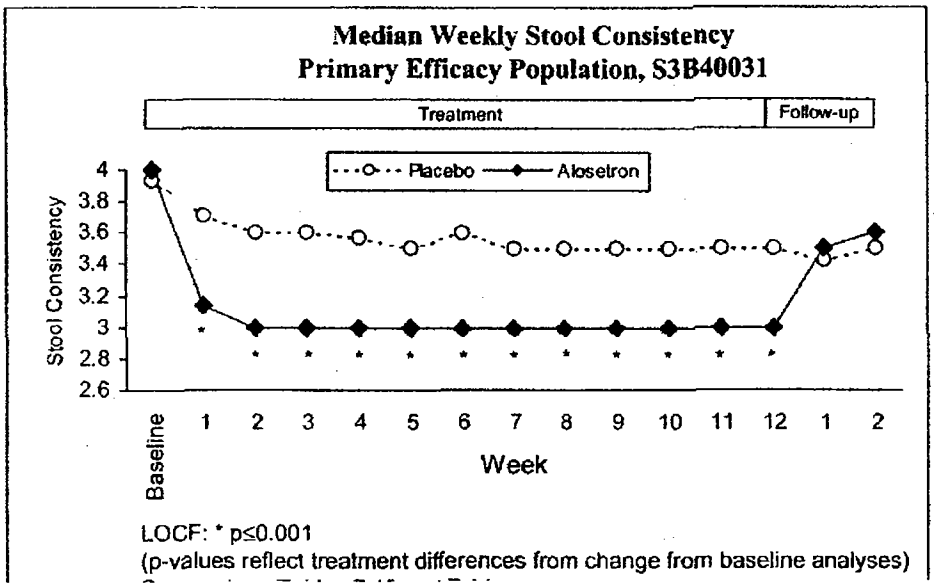
**Daily Analysis of satisfactory Control of Bowel Urgency** - Within the first 14 days of the study, the proportion of patients with satisfactory control of urgency was greater among alosetron-treated patients than among placebo-treated patients. The difference between treatments attained statistical significance on Day 12 using adjusted p-values (step-down Bonferroni method of Holm) and on Day 2 using unadjusted p-values. In the ITT analysis, statistical significance was seen on Day 3 using adjusted p-values.

**Lower Gastrointestinal Functions were measured:**

**Stool Consistency** - Relative to baseline, stool was statistically significantly firmer among alosetron-treated patients than among placebo-treated patients during each week of the Treatment Phase ($p \leq 0.001$ for all assessments). As demonstrated in the Figure 3, this effect persisted until treatment ceased, then diminished within the first week of

follow-up. LOCF values for stool consistency are presented along with p-values which reflect treatment differences from weekly change from baseline analyses (Note: lower values indicate firmer stool.)

**Figure 3**

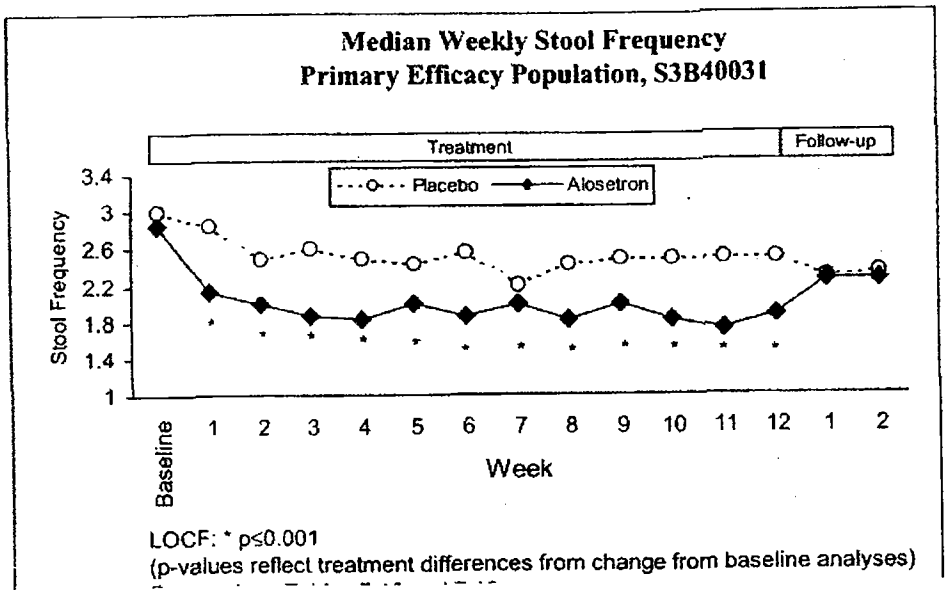



Lower values indicate firmer stool.
Source: Sponsor's Tables 7.12 and 7.14

**Stool Frequency** - Patients who were treated with alosetron reported statistically significantly fewer stools than placebo-treated patients during all weeks of the 12-week Treatment Phase ($p \leq 0.001$ for all assessments). The statistically significant treatment difference in frequency of stool passage disappeared by Week 1 of the Follow-up Phase.

Figure 4 displays LOCF values for weekly stool frequency with p-values from weekly change from baseline analyses.

**Figure 4**

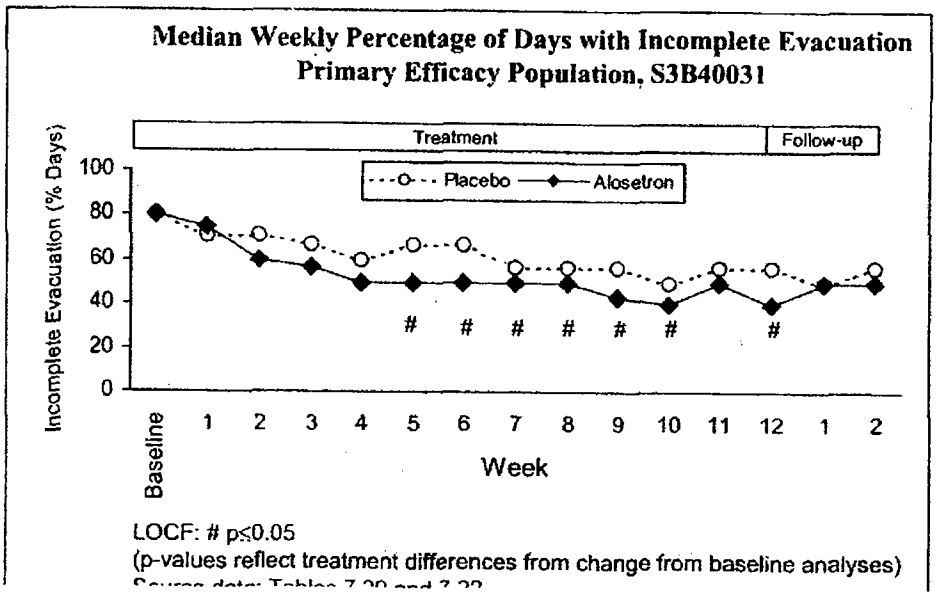



Source data: Sponsor's Tables 7.16 and 7.18

**Sense of Incomplete Stool Evacuation** - Patients in the alosetron 1 mg BID group, compared with patients in the placebo BID group, experienced a reduction from baseline in the proportion of days with a sense of incomplete evacuation. Treatment effects became statistically significantly different in favor of alosetron 1 mg BID at Week 5. This statistically significant effect was maintained through 6 of the remaining 7 weeks of the Treatment ($p \leq 0.05$).

Figure 5 presents weekly LOCF values for the proportion of days with a sense of incomplete evacuation, expressed as a percentage. P-values reflect treatment differences from weekly change from baseline analyses.

**Figure 5**



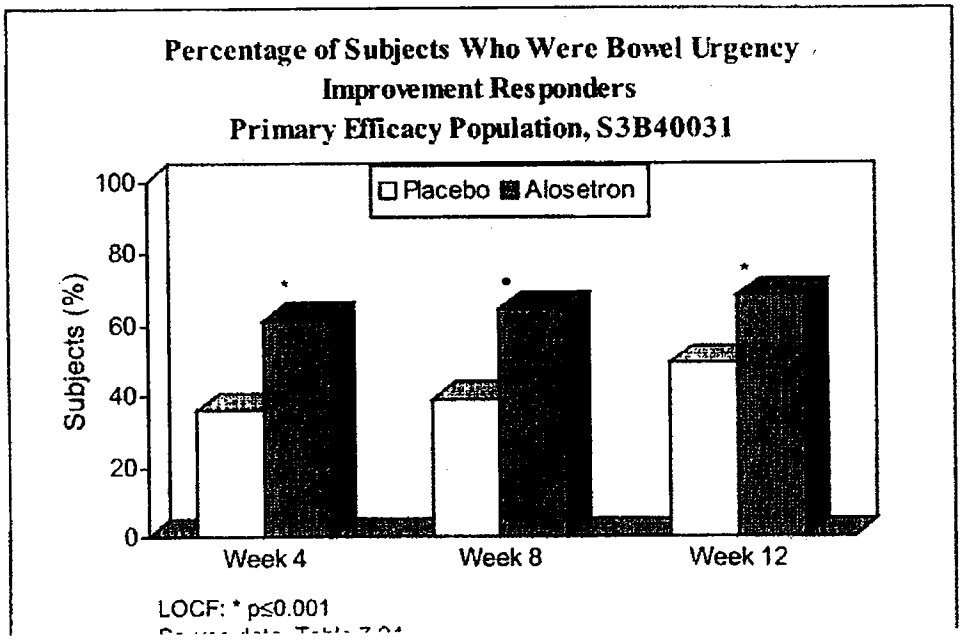

Source: Sponsor's Tables 7.20 and 7.22

**Bowel Urgency Improvement - Responders** in the alosetron 1 mg BID group were statistically significantly greater than that of the placebo BID group at:

Week 12 68%, 142/210 versus 49%, 97/200, respectively( $p \leq 0.001$)
Week 8 64%, 134/210 versus 39%, 78/200, respectively ($p \leq 0.001$)
Week 4 61%, 122/201 versus 36%, 69/190, respectively ($p \leq 0.001$)

This is shown for LOCF data in Figure 6:

**Figure 6**




Source data: Sponsor's Table 7.24

**Bowel Urgency Improvement Scale** provided Supportive Analysis, as the result shown above for Bowel Urgency Responders was driven by the proportion of patients who reported substantial improvement in the control of urgency for each time measured.

**Correlation Between Control of Bowel Urgency and Other Endpoints**

Spearman rank correlation coefficients indicated a consistent relationship (i.e., $r>0.20$ in all cases) between: satisfactory control of urgency and improvement in other lower gastrointestinal symptoms, overall satisfaction with treatment, Bowel Urgency Improvement, and IBS Global Improvement. Specifically, increased satisfaction with control of urgency was associated with:

- firmer stools ($r = 0.467$),
- less frequent bowel movements ($r = 0.431$),
- smaller proportion of days with a sense of incomplete evacuation ($r = 0.591$),
- greater overall satisfaction with treatment ($r = 0.481$) at 12 weeks of treatment.

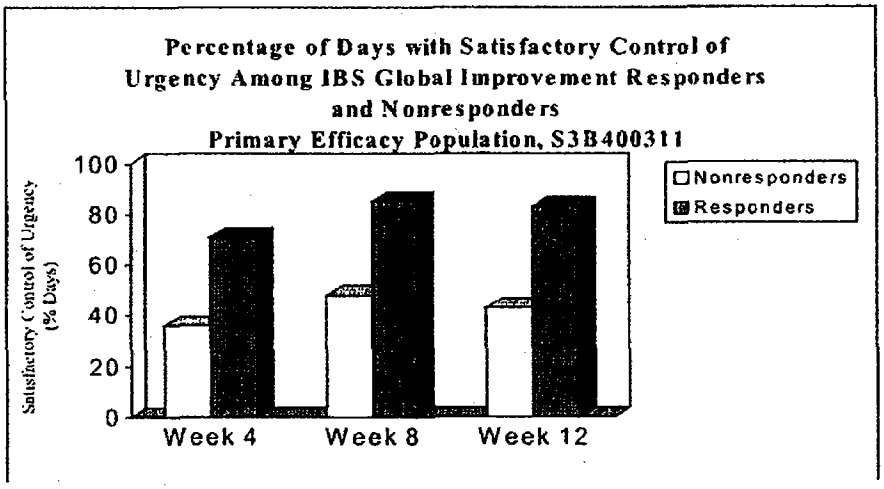
Satisfactory control of urgency was directly correlated with the Bowel Urgency Improvement Scale, indicating agreement between responses to the daily urgency query and the queries that retrospectively assessed each 4-week period (r = 0.540-0.619).

Satisfactory control of urgency was directly correlated with the IBS Global Improvement scale for each 4-week period (r = 0.498-0.546) and Global Improvement Responders demonstrated higher median values for satisfactory control of urgency than Nonresponders. These values, expressed as a percentage, for Responders and Nonresponders, respectively, were:

Week 4 71 % for Responders and 36 % Nonresponders,
Week 8 85 % for Responders and 48 % Nonresponders,
Week 12 83% for Responders and 43% Nonresponders.

Figure 7 displays the relationship between the proportion of days, expressed as a percentage, with satisfactory control of urgency and IBS Global Improvement Responders for subjects from both treatment groups combined:

**Figure 7**




Source data: Sponsor's Table 7.32

These findings indicate that patients' perception of improvement included control of urgency. However, several other gastrointestinal symptoms (stool consistency, stool frequency, and proportion of days with a sense of incomplete evacuation) were inversely related to the IBS Global Improvement scale, indicating that perceived improvement included a reduction in each of these symptoms as well. IBS Global Improvement was positively correlated with the overall satisfaction at Week 12 (r = 0.814).

**Efficacy Conclusions**

Key efficacy findings were as follows:

1. Patients in the alosetron group had a statistically significantly greater proportion of days with satisfactory control of urgency compared with the placebo group over the 12-week Treatment Phase (medians 0.69 versus 0.56, respectively ($p \leq 0.001$). This effect was present regardless of age, race, parity, childbearing potential, time since IBS diagnosis, IBS subtype, or BMI.

2. A statistically significantly greater percentage of patients in the alosetron group versus the placebo group were IBS Global Improvement Responders at Week 12 (68% and 47%, respectively), and all other timepoints measured ($p \leq 0.001$).

3. Alosetron 1 mg BID use resulted in statistically significantly firmer stools, fewer stools per day, and a smaller proportion of days with a sense of incomplete evacuation compared with placebo. These effects emerged rapidly and persisted throughout the Treatment Phase then diminished upon cessation of therapy.

4. Efficacy endpoints were consistently favorably correlated, indicating a positive interdependency of factors associated with the concept of improvement.

**Health Outcome Results**

The Primary Efficacy Population (n=436) was utilized for health outcomes analyses. The Intent-to-Treat Population (n=492) was utilized for supportive health outcomes analysis.

**Satisfaction with Treatment**

**Importance of Specific Medication Attributes**

The medication attributes which patients most often rated as important or very important at baseline were:

relief of urgency
prevention of return of urgency
time to return to normal activities
speed of relief
prevention of return of abdominal pain/discomfort

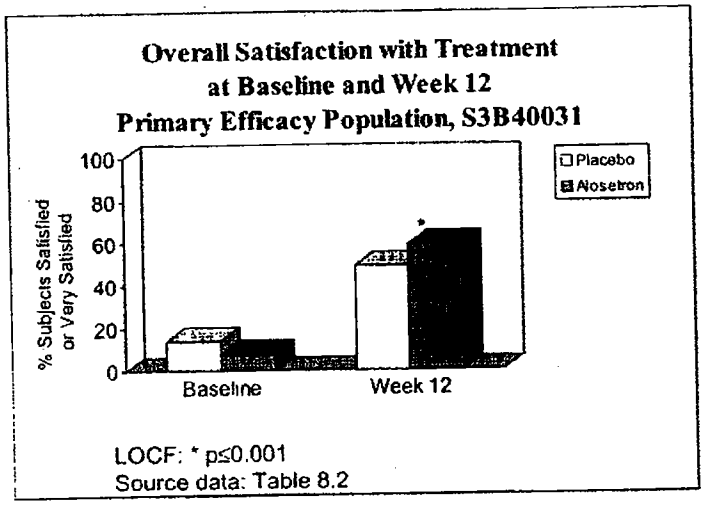
Attributes rated as important or very important by fewer patients included:
relief of abdominal pain/discomfort
prevention of return of other IBS symptoms
relief of other IBS symptoms
convenience of dosing
time to return to normal eating habits
number of doses needed for relief

**Overall Satisfaction**

At baseline, patients' ratings of overall satisfaction with their prestudy IBS therapy did not differ between treatment groups. Only 14% (22/156) of patients assessed in the placebo group and 8% (13/164) of patients assessed in the alosetron group indicated that they were satisfied or very satisfied with their prestudy IBS medication.

At the end of the 12-week Treatment Phase, 49% (94/192) of patients assessed in the placebo group compared with 59% (117/200) of patients assessed in the alosetron group reported that they were satisfied or very satisfied with the medication they used during the study ($p \leq 0.001$). This is shown in Figure 8.

**Figure 8**



**Satisfaction with Specific Medication Attributes**

At the Screening Visit a minority of patients in each group rated themselves as satisfied or very satisfied with their prestudy medication for each of the 11 medication attributes.

At the end of the 12-week Treatment Phase, statistically significantly more patients in the alosetron group compared with the placebo group indicated that they were satisfied or very satisfied with the medication they used during the study for 9 of the 11 medication attributes ($p \leq 0.05$) as demonstrated in Figure 9. Favorable satisfaction ratings for alosetron were assigned to the five medication attributes that patients considered to be most important. Figure 9 presents these data.

These included:

- relief of urgency (61% alosetron; 36% placebo)
- prevention of return of urgency (59% alosetron; 43% placebo)
- time to return to normal activities (66% alosetron; 49% placebo)
- speed of relief (62% alosetron; 44% placebo)
- prevention of return of abdominal pain/discomfort (57% alosetron; 46% placebo)

**Figure 9**

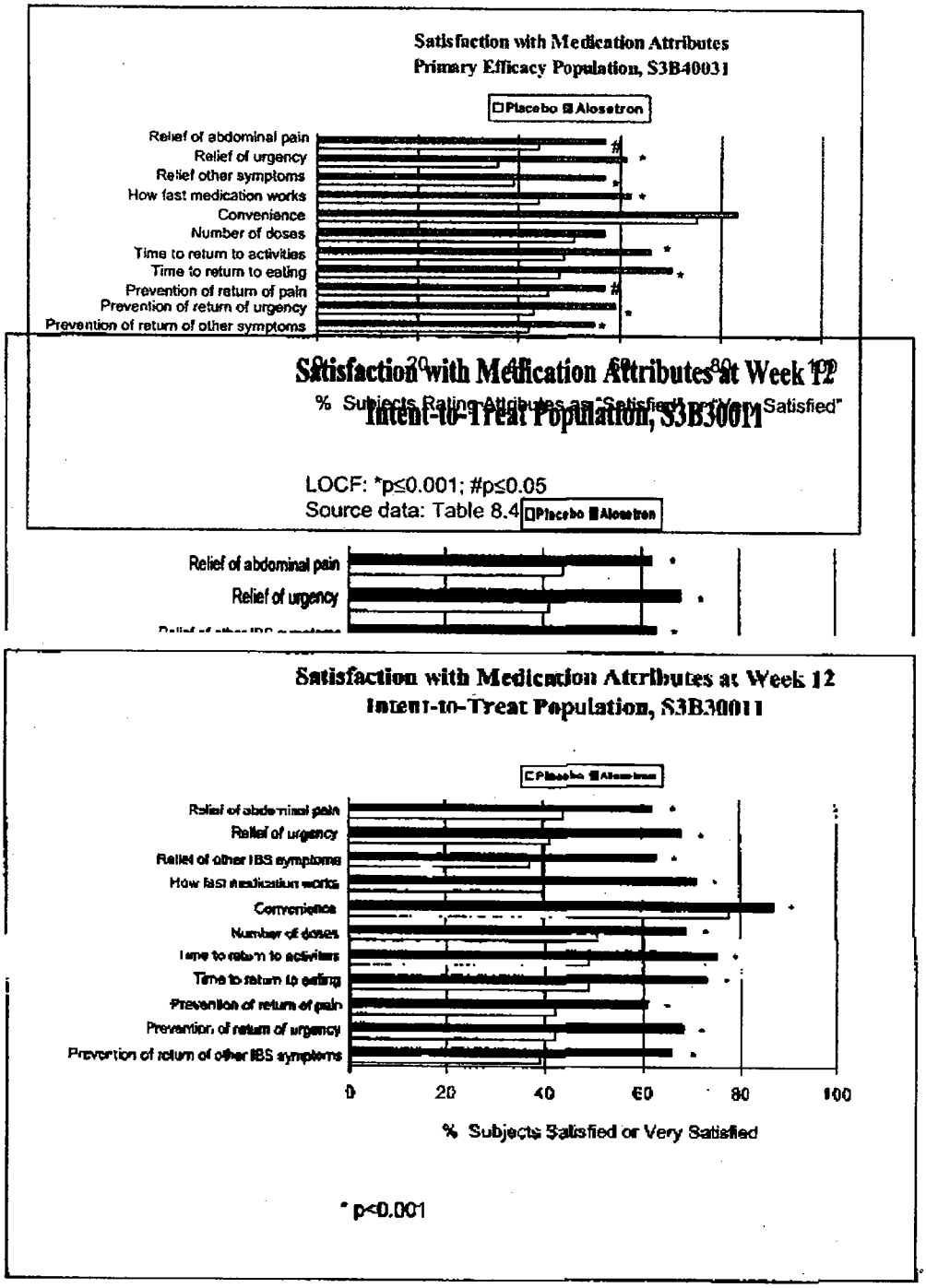
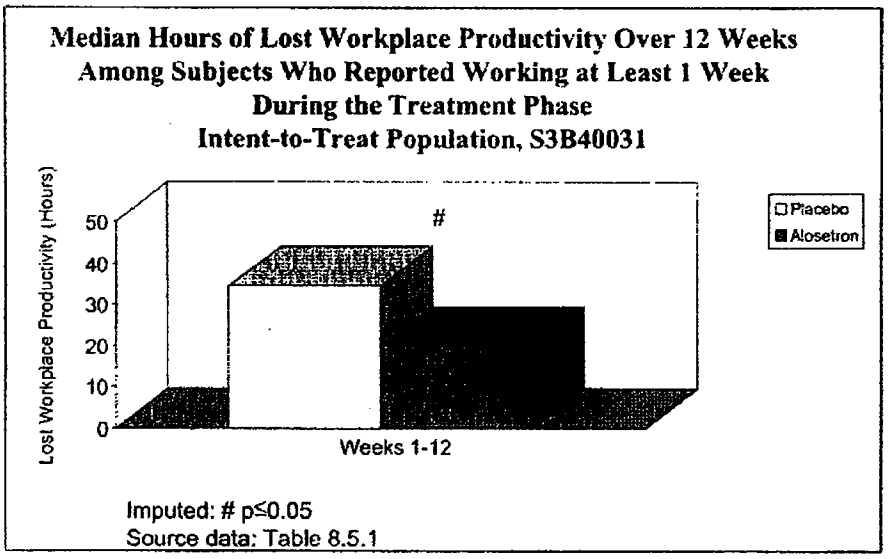

Satisfaction with Medication Attributes
Primary Efficacy Population, S3B40031
Placebo Alosetron
Relief of abdominal pain
Relief of urgency
Relief other symptoms
How fast medication works
Convenience
Number of doses
Time to return to activities
Time to return to eating
Prevention of return of pain
Prevention of return of urgency
Prevention of return of other symptoms
Satisfaction with Medication Attributes at Week 12
% Subjects Rating Attributes as "Satisfied" or "Very Satisfied"
Intent-to-Treat Population, S3B30011
LOCF: *p≤0.001; #p≤0.05
Source data: Table 8.4
Placebo Alosetron
Relief of abdominal pain
Relief of urgency
Satisfaction with Medication Attributes at Week 12
Intent-to-Treat Population, S3B30011
Relief of abdominal pain
Relief of urgency
Relief of other IBS symptoms
How fast medication works
Convenience
Number of doses
Time to return to activities
Time to return to eating
Prevention of return of pain
Prevention of return of urgency
Prevention of return of other IBS symptoms
0
20
40
60
80
100
% Subjects Satisfied or Very Satisfied
* p<0.001

**Figure 10**




The benefit of alosetron versus placebo in reducing Lost Workplace Productivity was not apparent among patients who worked all 12 weeks. Explorative analyses of percent Lost Workplace Productivity over 12 weeks did not show statistically significant differences in favor of alosetron-treated subjects who worked at least 1 week during the Treatment Phase or among alosetron-treated subjects who worked all 12 weeks (Sponsor's Tables 8.8 and 8.9). The ITT analysis showed statistically significant differences in favor of patients who took alosetron for percent of Lost Workplace Productivity over 12 weeks for patients who worked at least 1 week during the Treatment Phase, but not among patients who worked all 12 weeks.

Explorative analysis investigated Lost Workplace Productivity among patients working full time as defined by at least 10 of 12 weeks with $\geq$30 hours of planned work. Results of imputed and observed analyses revealed statistically significantly less Lost Workplace Productivity for alosetron-treated patients compared with placebo-treated patients ($p \leq 0.05$). Results were similar in the ITT analysis.

**Lost Activity Time**

Lost Activity Time was lower among alosetron-treated patients (median = 100.64 hours lost) than among placebo-treated patients (median = 114.87 hours lost), over the 12-week Treatment Phase ($p=0.173$) representing a difference of 12%. lower loss of activity time in the alosetron-treatment group as compared with the placebo-treatment group. A treatment difference in medians of 14.23 hours was

detected, but statistical significance was not reached in the PE Population. The ITT analysis showed that Lost Activity Time was statistically significantly lower among alosetron-treated patients (median = 100.56 hours lost) than among placebo-treated patients (median = 124.78 hours lost) over the 12-week Treatment Phase ($p \leq 0.05$). This represented a 19% lower loss of activity time in alosetron group as compared with the placebo group. Results from observed data did not show a statistically significant difference for either the PE or ITT Populations.

**Total Lost Productivity**

Total Lost Productivity Time was statistically significantly lower in the alosetron group (median = 119.00 hours lost) compared with the placebo group (median = 155.22 hours lost) ($p \leq 0.05$). This finding represents a 23% difference in favor of the alosetron group. The ITT analysis showed a similar difference of 27% ($p \leq 0.05$); median = 115.80 hours lost in the alosetron group and median = 158.43 hours lost in the placebo group. Results from observed data did not show a statistically significant difference for either the PE or ITT Populations.

**Health Outcomes Conclusions**

Key health outcomes findings follow and are summarized in Table 6.

1. A statistically significantly greater percentage of alosetron-treated patients (117/200, 59%) compared with placebo-treated patients (94/102, 49%) were satisfied or very satisfied with their IBS therapy following 12 weeks of treatment ($p \leq 0.001$). In comparison, only 11% of patients [14% (22/156) in the placebo group and 8% (13/164) in the alosetron group] were satisfied or very satisfied with their IBS medication at baseline .

2. Alosetron was associated with greater satisfaction than placebo for 9 of the 11 medication attributes assessed ($p \leq 0.05$) and favorable satisfaction ratings for alosetron were assigned to the five medication attributes that patients considered to be most important:
   - relief of urgency
   - prevention of return of urgency
   - time to return to normal activities
   - speed of relief
   - prevention of return of abdominal pain/discomfort

3. Alosetron-treated patients experienced 40% less Lost Workplace Productivity ($p \leq 0.05$), 19% less Lost Activity Time ($p \leq 0.05$), and 27% less Total Lost Productivity Time ($p \leq 0.05$) compared with placebo-treated patients over the 12-week Treatment Phase as seen for the ITT Population.

**Table 6**
**Health Outcome Conclusions (ITT Population)**
**Study S3B40031**

| Key Health Outcomes | Placebo-Treated | | Alosetron-Treated | | Therapeutic Gain |
|---|---|---|---|---|---|
| | PreStudy Rx | Post 12 Weeks Rx | PreStudy Rx | Post 12 Weeks Rx | |
| **Overall satisfaction with IBS Rx** | 14 % | 49 % | 8 % | 59 % | 10 % |
| **Satisfaction with the five most important attributes** | | 36-49 % | | 57-66 % | 11-25 % |
| **Total lost workplace Productivity- Median hours** | | 34.08 | | 20.34 | 40 % |

Medical Reviewer's Table

## B. Safety Results

### Extent of Exposure

The Safety Population utilized 492 patients for the safety analyses. The majority of patients (64%, 314/492) participated in the study for 89 or more days. The median number of days that patients were exposed to study drug was 83.0 days in the placebo group and 83.5 days in the alosetron group. This duration corresponds to the 12-week Treatment Phase of the study.

### Adverse Events

Fifty-two percent (52%, 127/246) of patients in the placebo group reported AEs during the Treatment Phase. Within the alosetron group 59% (145/246) of subjects reported AEs.. A summary of the AEs that were reported most commonly during treatment are summarized in Table 7.

C Treatment group effects were similar with regard to the proportion of patients experiencing AEs for all body systems except the gastrointestinal system. The number of placebo-treated patients who reported gastrointestinal AEs was 71/246 (29%) compared with 103/246 (42%) patients in the alosetron-treated group. Constipation, a class effect of 5-HT3 receptor antagonists, was the most frequently reported side effect in both treatment groups and the difference was primarily due to *constipation which was experienced by 22/246 (9%) patients in the placebo group and 69/246 (28%) patients in the alosetron group. Of the 69 patients reporting constipation in the alosetron group, 11% of the events were mild, 75% were moderate, and 14% were severe.*

Other notable gastrointestinal system AEs included gastrointestinal discomfort and pain, which occurred among 14/246 (6%) patients in the placebo group and 36/246 (15%) patients in the alosetron group. The occurrence of AEs of special interest, including rectal bleeding, are presented in the section on AEs of special interest.

**Most Commonly Reported Adverse Events**

The most common AEs were defined as those that occurred among >5%_of patients in either group. Constipation was the most frequently reported side effect in both treatment groups. As a class effect of 5-HT3 receptor antagonists, constipation was reported more frequently by patients in the alosetron 1 mg BID group (69/246, 28%) than in the placebo BID group (22/246, 9%). Gastrointestinal discomfort and pain was also reported more frequently by patients in the alosetron 1 mg BID group (36/246, 15%) than in the placebo BID group (14/246,6%). The frequencies of other AEs reported by >5% of patients were generally similar between groups, with most reflecting the underlying disease, or common ailments. A summary of the AEs that were reported most commonly during treatment is presented in Table 7.

**Table 7**
**Summary of Commonly Reported Adverse Events in Protocol S3B40031**
**(Events Greater Than 5 % Among Study Patients)**

| Body System Event | Placebo (n = 246) | | Lotronex (n = 246) | |
|---|---|---|---|---|
| **Constipation** | **22** | **9%** | **69** | **28%** |
| **GI discomfort & pain** | **14** | **6%** | **36** | **15%** |
| **Diarrhea** | **15** | **6%** | **16** | **7%** |
| **Headaches** | **12** | **5%** | **17** | **7%** |

Adapted from Sponsor's Table 9.2

### Drug-Related Adverse Events

Adverse events included in drug-related AE analyses included those judged by the investigator as having a reasonable possibility that the event may have been caused by the trial medication.

Twenty-one percent (21%, 52/246) of patients in the placebo group and 38% (93/246) of patients in the alosetron group experienced drug-related AEs during the Treatment Phase. This difference between groups was driven by the lower frequency of drug-related gastrointestinal AEs in the placebo group (17%, 41/246) compared with the alosetron group (35%, 86/246). In particular, the incidence of drug-related constipation differed between groups: 9% (22/246) in the placebo group versus 27% (66/246) in the alosetron group. The incidence of gastrointestinal discomfort also differed between groups: 3% (7/246) in the placebo group versus 12% (30/246) in the alosetron group. Drug-related AE frequencies were similar between treatments for all other body systems

## Adverse Events in Subgroups of the Population

Constipation occurred at a greater rate among alosetron treated patients than among placebo treated patients within both racial categories, although sample size was small within the "other races" stratum. The same is true for gastrointestinal discomfort and pain within the white population. Similarly, a greater proportion of patients treated with alosetron experienced constipation and gastrointestinal discomfort and pain compared with patients who received placebo regardless of age. All other AEs occurred with similar frequency between race and age categories. Results from subgroup analyses of drug-related AEs were comparable.

## Deaths

No deaths occurred during the study:

### Serious Adverse Events

Two percent (4/246) of patients in the placebo group and <1% (2/246) of patients in the alosetron group experienced SAEs during or after treatment. No case of constipation met the criteria for classification as an SAE. The nature of SAEs was varied within both treatment groups. None of the SAEs in either treatment group were judged by the investigator as having a reasonable possibility of having been caused by the trial medication.

The SAEs observed during the study are shown in Table 8.

**Table 8**

**Serious Adverse Events
Safety Population, S3B40031**

| Serious adverse event (group term) | Placebo BID | Alosetron 1mg BID |
|---|---|---|
| Depressive disorders | 167823 | |
| Diverticulitis | 170941 | |
| Fractures | | 170938 |
| Gastric ulcers | 171358 | |
| Hypertension | | 167635 |
| Increased drug levels | 167823 | |
| Menstruation symptoms | 169891 | |
| | Subjects=4<br>SAEs=5<br>Drug-related SAEs[a]=0 | Subjects=2<br>SAEs=2<br>Drug-related SAEs[a]=0 |

Source of data: Sponsor's listings 17 and 18

a Judged by the investigator as having a reasonable possibility that the event may have been caused by the trial medication.

Four subjects, three in the placebo group and one in the alosetron group, experienced non-fatal SAEs which led to their withdrawal from the study. These patients and the SAEs which resulted in withdrawal are identified in the following Table 9.

**Table 9**

**Subjects with Serious Adverse Events Leading to Withdrawal from the Study
Safety Population, S3B40031**

| Subject number | Serious adverse event(s) | Treatment group | Related to study drug?[a] |
|---|---|---|---|
| 167823 | Depressive disorders<br>Increased drug levels | Placebo BID | No<br>No |
| 169891 | Menstruation symptoms | Placebo BID | No |
| 171358 | Gastric ulcers | Placebo BID | No |
| 167635 | Hypertension | Alosetron 1mg BID | No |

Source of data: Sponsor's listings 17 and 18

a Judged by the investigator as having a reasonable possibility that the event may have been caused by the trial medication.

### Adverse Events Leading to Discontinuation of Study Drug and/or Study Withdrawal

Ten percent (10%. 25/246) of patients in the placebo group and 15% (38/246) of patients in the alosetron group were withdrawn during the course of the study due to AEs. This difference was driven by a higher frequency of withdrawals due to gastrointestinal AEs (specifically constipation and gastrointestinal discomfort and pain) between treatments, with 7% (18/246) of patients withdrawn due to gastrointestinal AEs in the placebo group and 14% (35/246) of patients withdrawn due to gastrointestinal AEs in the alosetron group. The incidence of constipation leading to withdrawal from the study was 1% (3/246) in the placebo group versus 9% (22/246) in the alosetron group. The incidence of gastrointestinal discomfort and pain leading to withdrawal from the study was 1% (3/246) in the placebo group versus 6% (14/246) in the alosetron group.

Four patients, three in the placebo group and one in the alosetron group, experienced non-fatal SAEs which led to their withdrawal from the study.

## Special Adverse Events

### SAE of Ischemic Colitis

No cases of SAE of ischemic colitis were reported within this study.

### SAE of Serious Complications of Severe Constipation

No cases of SAE of Serious Complications of Severe Constipation were reported within this study.

**Adverse Events Involving Bleeding Associated with Bowel Function**

Eleven patients experienced a total of 11 AEs involving bleeding associated with bowel function during the study. (Aloserton-associated AEs in **BOLD**)
In the placebo group, three patients reported three AEs:
blood in the stool (patient 168565)
rectal bleeding (patients 168958 and 170287).
In the alosetron group, 8 patients reported 8 AEs:
hematochezia (patients **168417** and **170549**)
blood in the stool (patients **171357**, and **171685**),
blood clot in the stool (patient **171398**),
rectal bleeding (patients **168182** and **168931**), and
bleeding hemorrhoids (patient **170161**).
None of the events in either group was considered serious and two led to patient withdrawal from the study (alosetron-treated patients **170549**, hematochezia and **170161**, bleeding hemorrhoids). All events were of mild or moderate intensity, with 7 of the 11 AEs resolving in $\leq$3 days.

Six of the 8 AEs documented in the alosetron group were judged possibly related to study drug by the investigator.
These events were:
hematochezia (patients **168417** and **170549**),
blood in stool (patients **171357**, and **171685**),
rectal bleeding (patient **168182**) and
bleeding hemorrhoids (patient **170161**).
One AE of hematochezia coincided with an AE of constipation. The other case of hematochezia (patient **170549**) was followed up with stool collection, hepatitis panel, antithrombin, protein C, protein S and Von Willebrand Factor Antigen testing. Results for all of these tests were normal or negative with the exception of a high Von Will Ag of 156% (normal range: 50% - 150%). All cases of rectal bleeding coincided with constipation and or hemorrhoids.

**Pregnancies**

Three pregnancies occurred during the study:

Patient 167790: A 22-year-old female in the alosetron group was found to be pregnant after completing 3 months of study medication. Her last menstrual period occurred 13 days after stopping study drug, suggesting that conception occurred after completing her last dose of study medication. The outcome was unknown at the time that this report was prepared.

Patient 16812 1: A 34-year-old female in the placebo BID group was found to be pregnant during the study. The outcome was unknown at the time that this report was prepared.

Patient 168576: A 32-year-old female in the alosetron group was determined to be pregnant 5 days after discontinuing study drug treatment. The subject received study medication for three days. The outcome was unknown at the time that this report was prepared.

### Clinical Laboratory Evaluations

### Changes in Summary Laboratory Data Over Time

Transaminases, alkaline phosphatase, and total bilirubin levels were comparable between treatment groups and remained constant from baseline to the end of the study. No notable hematology findings were apparent during the study. Clinical chemistry values were similar between treatments throughout the study. No clinically significant laboratory abnormalities were noted during the study.

### Safety Conclusions

Key safety findings were as follows:

1. The most commonly documented AE among alosetron 1 mg BID-treated patients was constipation. No serious AE cases of constipation were reported. The majority of constipation events were mild or moderate and did not result in withdrawal from the study.
2. Alosetron 1 mg BID was well tolerated during the study as determined by the following AE and laboratory assessment findings:
   - The incidence of all AEs was 52% and 59% in the placebo and alosetron groups. respectively. Gastrointestinal AEs were more common among alosetron-treated patients than among placebo-treated patients, a result which was driven primarily by the incidence of constipation (9% with placebo versus 28% with alosetron) and gastrointestinal discomfort and pain (6% with placebo and 15 % with alosetron).
   - Adverse events and drug-related AEs did not vary within age or race categories.
   - Serious adverse events occurred at a similar frequency between treatments. None were judged by the investigator as having a reasonable possibility of having been caused by the trial medication.
   - The incidence of study drug discontinuation and withdrawal from the study due to adverse events was low in both groups.
   - One patient in the placebo group and two patients in the alosetron group became pregnant during the study. The outcomes were unknown at the time of reporting.
   - Clinical laboratory value profiles were comparable between treatment groups

## VI. Discussion and Analysis of Data

This study demonstrated that alosetron 1 mg BID given for 12 weeks, significantly improved the control of urgency as well as other relevant clinical and health outcome-related measures in nonconstipated women with IBS. Improvement was fairly rapid and persisted throughout the 12 week treatment period. Improvement was unaffected by constipation, laxative use, and a host of demographic and baseline variables including age, race, parity, childbearing potential, time since IBS diagnosis, IBS subtype, and BMI.

Bowel urgency is among the most bothersome of the IBS-related symptoms. In the present study, randomized patients had a significant burden of illness (≥50% of days with lack of satisfactory control of urgency) and when treated with alosetron they experienced statistically significantly more days with satisfactory control of urgency compared with patients receiving placebo. This statistically significant effect diminished soon after the cessation of therapy. The percentage of Bowel Urgency Improvement Responders, patients who reported moderate and substantial improvement in bowel urgency over the previous 4 weeks, was statistically significantly greater with alosetron than with placebo. Also noted, was the high placebo effect observed for the primary endpoint, a common finding in IBS trials. This high placebo effect may be due to normal fluctuations in urgency or differences in the explanation or interpretation of "satisfactory control".

In addition to the benefit of alosetron on urgency, a statistically significantly greater percentage of patients who took alosetron versus placebo were IBS Global Improvement Responders, reporting moderate or substantial improvement in IBS symptoms. Like Bowel Urgency Improvement Responders, alosetron-treated patients who were IBS Global Improvement Responders more often reported substantial improvement of symptoms.

Based on the Guidelines regarding clinical trial design for functional gastrointestinal disorder therapies recently published by the Rome II Working Group on Functional Gastrointestinal Disorders, the guidelines recommended the assessment of multiple symptoms, patient integration of symptoms, and disease-related quality of life measures to serve as the basis for clinical efficacy. The IBS Global improvement endpoint attempted to fulfill these recommendations by assessing multiple symptoms of IBS with single, patient-defined ratings. Although IBS Global Improvement was statistically significantly associated with control of urgency, numerous other clinical endpoints (stool consistency and stool frequency, but not proportion of days with a sense of incomplete evacuation) played a significant role in patients' self-perception of overall IBS improvement. Therefore, the IBS Global Improvement endpoint represented a clinically meaningful assessment of alosetron effectiveness across the spectrum of IBS symptoms that are most relevant for patients.

Alosetron statistically significantly improved multiple individual bowel-related functions by decreasing the number of stools per day and improving stool consistency. Patients in the alosetron group had statistically significantly firmer stools than patients in the placebo group indicating that alosetron increased stool firmness across a range of baseline stool consistencies. Relief from gastrointestinal symptoms usually occurred within 1 week of treatment. These favorable effects remained statistically significant throughout the 12 weeks of therapy. Then following treatment cessation, they diminished quickly.

Several statistical methods, usually utilized for analysis of these kinds of data and applied to the data obtained from this study, actually tend to enhance the efficacy demonstrated by studies. These techniques include: LOCP (last observation carried forward) to replace missing data with prior data, or utilize an average of the non-missing data to "fill in a missing gap in the data."

In the pre-approval Phase III studies, alosetron provided relief of abdominal pain and discomfort and increased the proportion of pain-free days in female subjects with diarrhea-predominant IBS. Adequate relief of IBS pain and discomfort is considered to be a scientifically valid endpoint for measuring improvement in the symptoms of IBS.

Clinicians and health care investigators increasingly recognize patient satisfaction as an essential outcome measure for evaluating the usefulness of a therapeutic intervention. Only 11% of patients at the beginning of the study ( 8% in the placebo group and 14% in the alosetron group) reported that they were satisfied or very satisfied overall with their prestudy IBS therapy. After 12 weeks of study treatment, 59% of patients reported that they were satisfied or very satisfied with alosetron (versus 49% of patients with placebo). A similar pattern of results was observed for the 11 specific medication attributes studied. Favorable satisfaction ratings for alosetron were assigned to the five medication attributes that patients considered to be most important in the management of IBS symptoms:

- relief of urgency
- prevention of return of urgency
- time to return to normal activities
- speed of relief
- prevention of return of abdominal pain

Patients' high degree of satisfaction with relief of urgency was consistent with the primary efficacy results. The finding of strong positive correlation between patient ratings of overall satisfaction and satisfactory control of bowel urgency ($r=0.481$) and global improvement of IBS symptoms ($r=0.814$) supports the proposition that the clinical efficacy of alosetron is largely responsible for the favorable satisfaction ratings. Conversely, the finding that efficacy and patient satisfaction measures are

not perfectly correlated, demonstrated that efficacy did not fully explain patients' level of satisfaction.

Due to the sponsor's early termination of the study, treatment comparisons in the primary efficacy populatIon were powered at less than 50% for Lost Workplace productivity and Lost Activity Time. (alosetron vs. placebo)

- 23% less Lost Workplace Productivity hours (12.75 vs.16.60)
- 13% less Total Lost Productivity Time in hours (89.80 vs. 103.53)
- 4% more Lost Activity Time in hours (81.80 vs.78.70)

However, analyzing the ITT Population, statistical significance was reached for several endpoints. As determined by the Quality of Life (QOL) median measures, alosetron-treated patients experienced significantly greater benefit than placebo-treated patients:

- 40% less Lost Workplace Productivity hours (20.34 vs.34.08)
- 12% less Lost Activity Time in hours (100.64 vs.114.87)
- 23% less Total Lost Productivity Time in hours (119.00 vs. 155.22)

A summary of the efficacy of alosetron-treatment of IBS patients with urgency compared to placebo-treated patients over the 12-week Treatment Phase in this study is shown in Medical Reviewer's Table 10.

**Table 10 S3B40031**
**12 Week Control of Urgency Study Efficacy Summary - PE Population**

| Efficacy Measures | Placebo BID N=213 | Alosetron 1 mg BID N=223 | p-value |
|---|---|---|---|
| **Primary - over 12 weeks** 1 | | | |
| Proportion of days with satisfactory control of urgency (median) | 56 % | 69 % | ≤0.001* |
| **Secondary – by month** | | | |
| IBS global - substantial or moderate improvement (LOCF) 2 | | | |
| Week 4 | 78/191 (41%) | 118/201 (59%) | ≤0.001† |
| Week 8 | 82/201 (41%) | 131/210 (62%) | ≤0.001† |
| Week 12 | 94/201 (47%) | 143/210 (68%) | ≤0.001† |
| IBS global - substantial or moderate improvement (Observed) 3 | | | |
| Week 4 | 76/174 (44%) | 115/188(61%) | <0.001† |
| Week 8 | 64/143 (45%) | 111/170 (65%) | <0.001† |
| Week 12 | 72/133 (54%) | 103/139 (74%) | <0.001† |
| Stool Consistency – mean change from baseline (LOCF) 4 * | | | |
| Week 4 | -0.36 | -0.89 | <0.001* |
| Week 8 | -0.35 | -0.90 | <0.001* |
| Week 12 | -0.37 | -0.83 | <0.001* |
| Stool Frequency – mean change from baseline (LOCF) 5 * | | | |
| Week 4 | -0.47 | -0.96 | <0.001* |
| Week 8 | -0.45 | -1.01 | <0.001* |
| Week 12 | -0.44 | -0.92 | <0.001* |
| Sense of Incomplete Evacuation - mean change from baseline (LOCF) 6 * | | | |
| Week 4 | -0.59 | -0.53 | N.S. |
| Week 8 | -0.55 | -0.47 | N.S. |
| Week 12 | -0.54 | -0.45 | N.S. |

* p-value obtained using a van Elteren Test stratified by cluster

† p-value obtained using a Mantel-Haenszel test stratified by cluster

N.S. Not statistically significant

1 Sponsor's Table 7.6 2 Sponsor's Table 7.7 3 Sponsor's Table 7.8

4 Sponsor's Table 7.12 5 Sponsor's Table 7.16 6 Sponsor's Table 7.22

**Table 10 (continued) S3B30011**
**12 Week Control of Urgency Study Efficacy Summary - PE Population**

| Efficacy Measures | Placebo BID N=213 | Alosetron 1 mg BID N=223 | p-value |
|---|---|---|---|
| **Other Efficacy Measures** | | | |
| Bowel Urgency Responders (LOCF) [7] | | | |
| Week 4 | 36% (69/190) | 61% (122/201) | <0.001† |
| Week 8 | 39% (78/200) | 64% (134/210) | <0.001† |
| Week 12 | 49% (97/200) | 68% (142/200) | <0.001† |
| **Satisfaction with Treatment** | | | |
| Overall Satisfaction with Therapy (satisfied or very satisfied) | | | |
| Baseline (Pre-Study) | 8% (13/164) | 14% (22/156) | |
| Week 12 (Post-Study) [8] | 49% (94/192) | 59% (117/200) | <0.001† |
| BMI <27 (mean) [9] | 48 % | 55 % | N.S. |
| BMI >27 (mean) [9] | 50 % | 63 % | N.S. |
| Lost Workplace Productivity (patients who worked all 12 weeks) | | | |
| Median Hours Lost [10] | 16.60 | 12.75 | 0.076* |
| Median % Lost Productivity [11] | 6.84 % | 4.92 % | 0.130* |
| Lost Activity Time [12] | | | |
| Median Hours Lost | 78.70 | 81.80 | 0.306* |
| Total Lost Productivity [13] | | | |
| Median Hours Lost | 103.53 | 89.80 | 0.144* |

* p-value obtained using a van Elteren Test stratified by cluster

† p-value obtained using a Mantel-Haenszel test stratified by cluster

7 Sponsor's Table 7.24 8 Sponsor's Table 8.2 9 Sponsor's Table 7.7
10 Sponsor's Table 8.6 11 Sponsor's Table 8.9 12 Sponsor's Table 8.13
13 Sponsor's Table 7.15

Medical Reviewer's Table

Similar to the clinical endpoints, alosetron-associated improvements were maintained throughout the Treatment Phase. The beneficial effects of alosetron on Lost Workplace Productivity, Lost Activity Time, and Total Lost Productivity did not attain statistically significant levels as they did in Protocol S3B30011. In future studies, treatment should be administered beyond 12 weeks in order to assess the time course of alosetron-associated improvement for these QOL attributes.

Productivity data in the placebo group revealed a substantial impact of IBS on patients' daily functioning in patients not treated with alosetron. These data are consistent with known IBS-associated impairment in workplace attendance and functioning. In both the alosetron and placebo-treated groups, the impact of IBS on Lost Activity Time was greater than the impact of IBS on Lost Workplace Productivity. In fact, for the PE Population, placebo-treated IBS patients lost four-fold more time from non-work activities (median 78.70 hours in 12 weeks) than they did from workplace productivity hours (median 16.60 hours in 12 weeks). The greater impact of IBS on non-work compared with work activities (an effect observed regardless of whether patients received alosetron or placebo) may reflect the fact that non-work time is generally less rigidly scheduled than work time and therefore more susceptible to disruption by illness.

The most commonly reported side effect following both 12-week and 12-month alosetron administration remains constipation. *Within clinical studies*, it seems to be milder in severity, transient, and manageable with a short course of over-the-counter laxative, as demonstrated in study S3B30011, or a brief interruption in treatment as shown in other studies.

The majority of constipation reports in the present study were mild or moderate and patients typically continued treatment with or without laxative use. Furthermore, no SAEs or sequelae of constipation were reported. Constipation incidence in the present study was 28% in the alosetron and 9% in the placebo groups, comparable to previous studies where frequencies have approximated 30% in the alosetron groups and 5% in the placebo groups.

Aside from the well-documented difference in the frequency of constipation between alosetron and placebo, AE and clinical laboratory value profiles were similar between treatment groups. Cases of ischemic colitis have been reported in alosetron clinical trials (1 in 700 incidence). No AEs of ischemic colitis were reported in the present study. In general, alosetron has been well tolerated in this clinical study of nonconstipated or diarrhea-predominant women with IBS.

This study S3B40031 replicated Glaxo Wellcome protocol S3B30011 with a few differences:

S3B40031 - utilized patients seeing physicians in an IPA model managed care
S3B30011- evaluated intervention directed at managing constipation and enabling patients to continue therapy

Results from both studies were similar as demonstrated by statistically superior benefit of treatment with alosetron 1 mg BID over placebo for:

- Control of bowel urgency
- IBS global improvement
- Lower gastrointestinal functions
  - Stool consistency
  - Stool frequency
- Overall satisfaction with treatment

Results from both studies were dissimilar as demonstrated by statistically superior benefit of treatment with alosetron 1 mg BID over placebo in S3B30011 and not in S3B40031 for:

- Lower gastrointestinal function
  - Sense of incomplete evacuation
- Lost Workplace Productivity
- Lost Activity Time
- Total Lost Productivity

**Conclusions**

Findings from Protocol S3B40031 of 492 female patients (246 treated with alosetron and 246 treated with placebo) with nonconstipated IBS demonstrated that, relative to placebo, alosetron 1mg BID for 12 weeks:

1. Provided persistent, statistically significant improvement in multiple clinical symptoms of IBS including more days with satisfactory control of bowel urgency, firmer stools and fewer stools per day. In addition, alosetron provided a statistically significant increase in IBS Global Improvement, a patient-rated measure related to clinical and quality of life-associated dimensions of IBS.

2. Resulted in statistically significantly greater overall satisfaction with IBS treatment and satisfaction with specific IBS medication attributes that patients consider important.

3. Did not confer statistically significant reductions in Lost Workplace Productivity, Lost Activity Time, and Total Lost Productivity Time.

4. Was well tolerated, exhibiting, with the exception of constipation and gastrointestinal discomfort and pain, similar rates of AEs and laboratory abnormalities as placebo.

Constipation as an AE, was reported in 28% (69/246) of patients in the alosetron–treatment group. Of the 69 patients in the alosetron-treated group, constipation as an AE was reported to be mild in 11%, moderate in 75%, and severe in 14%. Fifteen percent (38/246) of patients in the alosetron–treatment group and ten percent (25/246) of patients in the placebo–treatment group reported constipation as an AE severe enough to result in discontinuation of treatment.

It should be noted that that the incidence of drug related constipation and of withdrawal due to the occurrence of constipation as an AE in this study among the alosetron-treated patients is identical with that observed in the pivotal pre-approval studies. (Table 11).

**Table 11**

**Comparison of The Incidence of Constipation–Related AEs and Withdrawal Due to The AEs Within The Current Alosetron Study and The Pre-Approval Alosetron Studies**

| **Constipation–Related AEs** | **Pre-Approval Protocols 3001 & 3002** | **Current Protocol S3B40031** |
|---|---|---|
| **Within Alosetron-Treated Patients** | | |
| Incidence within study | 28 % | 28 % |
| Incidence of cause for withdrawal | 10 % | 9 % |
| **Within Placebo-Treated Patients** | | |
| Incidence within study | 5% | 14% |
| Incidence of cause for withdrawal | 1% | 1% |

Medical Reviewer's Table

Constipation incidence in the present study in both the alosetron-treated (28%) and placebo-treated (9%) groups was comparable to the previous studies where frequencies were 28% in the alosetron group and 5% in the placebo group. Apart from the well-documented difference in the frequency of constipation between alosetron and placebo, AE and clinical laboratory value profiles were similar between treatment groups.

Cases of ischemic colitis, a SAE had been reported in previous alosetron clinical trials (approximating an incidence of 1 in 700). In this study, no cases of ischemic colitis were recognized within patients in both the placebo and alosetron-treated patients. Eleven (11) patients experienced rectal bleeding in this study, eight (8) in the alosetron-treated and three (3) in the placebo-treated group. Unfortunately, the diagnostic evaluation performed for each case was not as thorough as would have been desired. Thus, exclusion of ischemic colitis and analysis of possible causality for each case was made difficult. .

In summary, the results of this study demonstrated clinical benefit of alosetron 1 mg BID in the treatment of women with nonconstipated IBS. Alosetron provided statistically significant, rapid control of bowel urgency and improvement of other bothersome clinical symptoms. Additionally, alosetron was associated with a high degree of patient satisfaction. Statistically significant reductions in lost workplace productivity and activity time were not shown. Excluding the frequent occurrence of constipation, alosetron was associated with minimal side effects.

Table 12 summarizes the efficacy results demonstrated within Protocol S3B40031.

**Table 12**
**Summary - Efficacy Results Protocol S3B40031 PE Population**

| | Study in Weeks | Placebo | Alosetron | Therapeutic Gain |
|---|---|---|---|---|
| **Primary Efficacy Measure DP-IBS [LOCF]** | | | | |
| **Satisfactory Control of Urgency (mean)** | **12** | **48%** | **59%** | **11%** |
| **Satisfactory Control of Urgency (median)** | **12** | **56%** | **69%** | **13%** |
| **Supportive Analysis - Secondary Efficacy Measures** | | | | |
| **Global Improvement Responders** | **12** | **47%** | **68%** | **21%** |
| **Lower GI Function** | | | | |
| **Stool Consistency** | **12** | **-0.37** | **-0.83** | **+0.46** |
| **Stool Frequency** | **12** | **-0.44** | **-0.92** | **+0.48** |
| **Incomplete Stool Evacuation** | **12** | **-0.54** | **-0.45** | **-0.09** |

* p-value obtained using a van Elteren Test stratified by cluster

† p-value obtained using a Mantel-Haenszel test stratified by cluster

N.S. = Not statistically significant

Medical Reviewer's Table

## VII. Medical Officer's Conclusions

Based on the findings from study S3B40031 of 492 female patients with nonconstipated IBS (246 treated with alosetron and 246 treated with placebo), analysis of the results demonstrated that relative to placebo, alosetron 1 mg BID for 12 weeks:

1. Provided persistent, statistically significant improvement in multiple clinical symptoms of IBS including more days with satisfactory control of urgency (the primary endpoint), firmer and fewer stools per day. In addition, alosetron provided a statistically significant increase in IBS Global improvement, a subject-rated measure related to clinical and quality of life-associated dimensions of IBS.

2. Resulted in statistically significantly greater overall satisfaction with IBS treatment and satisfaction with specific IBS medication attributes that patients consider important

3. Alosetron-treated patients experienced no cases of serious ischemic colitis and constipation occurred in 28% of alosetron-treated patients. Constipation AEs were transient and mild to severe. No SAEs related to severe constipation were observed in this study population. The conduct of this study supports the impression that constipation within clinical studies has not been particularly problematic. That information is useful, as it reinforces the generally held opinion of those of us within the Agency who have always believed that with proper physician and patient vigilance, the serious complications of constipation that occurred post-marketing should have been mostly preventable. Rates for other AEs and laboratory abnormalities were similar for alosetron and placebo-treated patients.

Within this study population, no constipated patient experienced any of the SAEs that were observed post marketing, suggesting that complications of constipation should be preventable with proper physician and patient vigilance. To improve the Risk-Benefit ratio for serious complications of severe constipation, it should be possible to design a major customized mutually acceptable Restricted Distribution Program-Restricted Management Plan that can achieve measurable reductions in the incidence and severity of constipation-related SAEs including hospitalizations, hemorrhages, operations, and deaths associated with the use of alosetron. On the other hand, we still know very little about risk factors responsible for ischemic colitis and therefore can not offer patients advice for prevention of ischemic colitis and its serious sequelae.

Scheldon Kress, M.D.

March 6, 2001

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

/s/

Scheldon Kress
3/7/02 02:09:29 PM
MEDICAL OFFICER

Hugo Gallo Torres
3/8/02 07:47:10 AM
MEDICAL OFFICER

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

# ADDENDUM

| | |
|---|---|
| **NDA:** | **NDA 21-207** |
| **Applicant:** | **GlaxoSmithKline** |
| **Drug:** | **LOTRONEX (alosetron)** |
| **Pharmacological Category:** | **5HT-$_3$ Receptor antagonist** |
| **Drug Study:** | **"Post-hoc" evaluation of the frequency of significant therapeutic benefit from alosetron 1 mg BID among the more severely symptomatic non-constipated IBS patients in Protocols S3B30011 and S3B40031, those with satisfactory control of urgency on 30% or less of days at baseline, and satisfactory control of urgency for both 75% and 85% of days over 12 weeks of therapy** |
| **Material Reviewed:** | **January 31, 2002 Response (Attachment 1) to January 24, 2002 Request for Additional Information to Protocols S3B30011 and S3B40031** |
| **Reviewer:** | **Scheldon Kress, M.D.** |
| **Date:** | **March 4, 2002** |


## Executive Summary

A "post-hoc" evaluation of the frequency of significant therapeutic benefit was performed among the more severely symptomatic non-constipated IBS patients, those with satisfactory control of urgency on 30% or less of days at baseline from Protocols S3B30011 and S3B40031.

Over 12 weeks of therapy in these two protocols, the therapeutic gain of alosetron over placebo in improved satisfactory control of urgency from < 30% of days at baseline to >75% and > 85 % of days was 18%-19% and 14-17% of patients. Thus, evidence of efficacy does exist to support the use of alosetron 1 mg BID for IBS patients with severely symptomatic non-constipated urgency.

A "post-hoc" evaluation of the frequency of significant therapeutic benefit was performed among the more severely symptomatic non-constipated IBS patients, those with satisfactory control of urgency on 30% or less of days at baseline from Protocols S3B30011 and S3B40031. The inclusion criteria for purposes of this evaluation was stricter than the original inclusion criteria for both studies which was control of bowel urgency on 50% or less of days at baseline. Satisfactory control of urgency for these severe patients was arbitrarily selected to be determined if patients subsequent to treatment with alosetron 1 mg BID experienced satisfactory control of urgency for both 75% and 85% of days. These results are shown in Tables 1 and 2.

**Table 1**

**Summary of Satisfactory Control of Urgency for Severely Symptomatic Patients (Patients With Satisfactory Control of Urgency on 30% or Less Days at Baseline) By Month and Over 12 Weeks in Protocol S3B30011 (Intent-to-Treat Population LOCF)**

| Days With Satisfactory Control of Urgency At | Placebo-Treated (N=181) | | Lotronex-Treated (N=327) | | p-value * | Therapeutic Gain |
|---|---|---|---|---|---|---|
| **Month 1** | 180 | | 327 | | | |
| 75% | 19 | 11% | 86 | 26% | <0.001 | 15% |
| **85%** | 8 | 4% | 48 | 15% | <0.001 | **11%** |
| **Month 2** | 180 | | 327 | | | |
| 75% | 51 | 28% | 160 | 49% | <0.001 | 21% |
| **85%** | 32 | 18% | 113 | 35% | <0.001 | **17%** |
| **Month 3** | 180 | | 327 | | | |
| 75% | 51 | 28% | 175 | 54% | <0.001 | 26% |
| **85%** | 32 | 18% | 134 | 41% | <0.001 | **23%** |
| **Overall (12 Weeks)** | 180 | | 327 | | | |
| 75% | 37 | 20% | 127 | 39% | <0.001 | 19% |
| **85%** | 15 | 8% | 83 | 25% | <0.001 | **17%** |

* p-values obtained using Mantel-Haenszel mean score test controlling for cluster

**Table 2**
**Summary of Satisfactory Control of Urgency for Severely Symptomatic Patients**
**(Patients With Satisfactory Control of Urgency on 30% or Less Days at Baseline)**
**By Month and Over 12 Weeks in Protocol S3B40031**
**(Intent-to-Treat Population LOCF)**

| Days With Satisfactory Control of Urgency At | Placebo-Treated (N=171) | | Lotronex-Treated (N=169) | | p-value * | Therapeutic Gain |
|---|---|---|---|---|---|---|
| **Month 1** | 171 | | 168 | | | |
| 75% | 23 | 13% | 43 | 26% | 0.007 | 13% |
| **85%** | 9 | 5% | 23 | 14% | 0.007 | **9%** |
| **Month 2** | 171 | | 168 | | | |
| 75% | 47 | 27% | 69 | 41% | 0.009 | 13% |
| **85%** | 20 | 12% | 49 | 29% | <0.001 | **17%** |
| **Month 3** | 171 | | 168 | | | |
| 75% | 51 | 30% | 73 | 43% | 0.009 | 13% |
| **85%** | 30 | 18% | 55 | 33% | 0.001 | **15%** |
| **Overall (12 Weeks)** | 171 | | 169 | | | |
| 75% | 28 | 16% | 58 | 34% | <0.001 | **18%** |
| **85%** | 11 | 6% | 33 | 20% | <0.001 | **14%** |

* p-values obtained using Mantel-Haenszel mean score test controlling for cluster

Alosetron 1 mg BID provided statistically significant therapeutic benefit over placebo in increasing the percent of days of satisfactory control of urgency among the more severely symptomatic IBS patients. Based on the results of the analyses from these two protocols, significant therapeutic benefit among the more severely symptomatic IBS patients tended to improve with each additional month of treatment with alosetron (over the 1 to 3 months studied). Over 12 weeks of therapy in these two protocols, the therapeutic gain of alosetron demonstrated over placebo in improved satisfactory control of urgency from < 30% of days at baseline to >75% of days was 18%-19% of patients and > 85 % of days was 14-17% of patients. Thus, evidence of efficacy does exist to support the use of alosetron 1 mg BID for IBS patients with severely symptomatic non-constipated urgency.

**Scheldon Kress, M.D.**

**March 4, 2002**

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

/s/
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Division of Gastrointestinal and Coagulation Drug Products

Medical Officer's Review

**The Randomized Clinical Trial Experience**

| | |
|---|---|
| **NDA:** | 21-107/S-005 |
| **Date Submitted:** | December 7, 2001 |
| **Sponsor:** | Glaxo SmithKline<br>Research Triangle Park, N.C. |
| **Drug:** | LOTRONEX® (alosetron hydrochloride)<br>Tablets for oral administration |
| **Pharmacological Category:** | 5-$HT_3$ antagonist |
| **Proposed Indication:** | LOTRONEX is indicated only for women with diarrhea-predominant irritable bowel syndrome (IBS) who have failed to respond to conventional therapy and who have signed the Patient-Physician Agreement (see BOXED WARNING, CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS).<br><br>In men the safety and effectiveness of LOTRONEX has not been established (see CLINICAL TRIALS). |
| **Material Reviewed:** | Final Clinical Study Reports (CSRs) for **all studies** in NDA 21-107.<br><br>All 40 new CSRs submitted in the sNDA of December 7, 2001.<br><br>Summaries from the Randomized Clinical Trials completed before approval of the original NDA.<br><br>Although the main emphasis is on safety, some information on efficacy is included. |
| **Reviewer:** | Hugo E. Gallo-Torres, M.D., Ph.D.<br>Medical Team Leader, GI Drugs<br>HFD-180 |

# LOTRONEX®:

## The Randomized Clinical Trial Experience

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# LOTRONEX®
## The Randomized Clinical Trial Experience
## EXECUTIVE SUMMARY

The objective of this review is to assess all the available safety data from the Randomized Clinical Trials (RCTs) in NDA 21-107. Review of the final Clinical Study Reports (CSRs) for 40 total new studies (not included in the original NDA and submitted as part of the December 7, 2001 sNDA) was accomplished in the shortest possible time by using a cooperative approach involving several reviewers. Results of these new evaluations were analyzed in conjunction with CSRs submitted in the original NDA, which were reviewed by Dr. J. Senior (primary review) and Dr. H. Gallo-Torres (secondary review). Emphasis in this review was focused on the reporting of deaths, serious adverse events [SAEs, particularly ischemic colitis (IC) and serious complications of severe constipation (SCSC), withdrawals (particularly those due to AEs) and other significantly or potentially significant AEs, such as bloody stool/bloody diarrhea occurring in temporal association with abdominal pain, which could have been an indication that the patient is experiencing IC. Standard definitions of SAEs, as they applied to IC and SCSC were used.

Efficacy reviews were limited to a few studies evaluating **severe urgency** [Studies **S3B30011** and **–40031**, reviewed by Dr. Kress], and two with either mebeverin or trimebutine as active concurrent controls [**studies S3BB3001** and **–3002**, reviewed by Dr. E. Kaminskas] and **study S3B30020**, where a rather large number of SAEs of IC (n=10) and SCSC (n=6) were reported [reviewed by Dr. S. Kress]. The newly gathered experience was analyzed in conjunction with final CSRs submitted in the original (pre-marketing) NDA (primary review by Dr. J. Senior, secondary review by Dr. H. Gallo-Torres). The emphasis was on safety although, some efficacy information assessing severe urgency and quality of life (QoL) was also considered, in order to determine if the sponsor-proposed revisions to the labeling, re: efficacy, are supported by these data.

The primary safety data are derived from 26 IBS trials including 10,805 alosetron-treated patients, 2935 treated with placebo, 772 treated with active concurrent control and 889 given misc. IBS treatments. [Refer to Table 1]. Half of the trials were completed while the other half were terminated early. Most of the trials randomized only females while in 5 the study population consisted of males and females. One study randomized only male patients. The overall conclusions apply to the target population (females with constipation-predominant IBS = CP-IBS). The duration of treatment ranged from 14 days to 1 year, but it most trials, the length of treatment was 12 weeks. Most of the trials were multicenter, randomized and double-blind. In 11, the comparator control was placebo while in the other 4 an active concurrent control was used. In 3 trials, the indications evaluated were other than CP-IBS [these trials were not included in calculations of incidence rates]. The clinical trials comprising the secondary safety data (Table 2) included a total of 624 alosetron-treated patients. No AEs of concern were reported among these Phase I-II patients (Appendix 1).

**ISCHEMIC COLITIS (IC)**

- All in all, a total of 19 cases of IC were reported, 18 in association with alosetron: 10 in Study – 30020, a multicenter, repeat-dose, 6 month, open-label study (vs. traditional therapy), one in each of 7 PL-controlled trials, and 1 in another open-label 2-part study.
- One case of IC was reported in a patient that received placebo (Table 3, Appendix 2).
- Similar to that observed in the 4 pre-marketing cases, the newly described patients had a clinical syndrome characterized by a) bloody stool/bloody diarrhea occurring in association with abdominal pain; b) increased white blood cells (not always); c) sometimes showing signs suggestive of colitis on CT scan; d) colonoscopic/ sigmoidoscopic findings consistent with ischemic colitis; and e) sometimes confirmation on histopathological examination.
- In all patients experiencing IC, the test medication was discontinued and the patient was eventually withdrawn from the trial.
- 14 of the 18 alosetron cases of IC had to be hospitalized; 1 (from study-30020) underwent surgical intervention; no patient died.

- The IC, occurring in temporal association with alosetron, can continue to be described as mild (meaning superficial, non-transmural) and self-limiting. In the majority of cases the event represented a **positive dechallenge** since the patient responded well to drug discontinuation.

- In Study-30020 nearly all patients experiencing IC (like in most other cases in other trials) reported use of concurrent medications (such as antidepressants, NSAIDs and estrogens) but, at this point in time, risk factors for IC are yet to be identified.

- The data from Study-30020, together with data from spontaneous reports reaffirms the supposition that IC is more likely to occur with the initiation of therapy with alosetron. This lends support to the newly proposed approach of administering a lower than the recommended dose of ALOSETRON® for 2 to 4 weeks, assess safety/efficacy results at the end of this period and intervene accordingly.

- For the 4 pre-approval cases of IC, the calculated incidence rate, in terms of proportion of clinical trial patients experiencing IC in apparent association with alosetron, without considering time to event, was 1 in 700 [Confidence Intervals 1/100 to 1/1000]. The newly appraised experience yielded similar incidence rates. Details of an assessment of whether the hazard rates of these SAEs were constant, increased or decreased over time, is found in Dr. D. Hoberman's statistical review (separate document).

**SEVERE CONSTIPATION**

- A total of 14 patients experienced SAEs related to serious constipation
  :11 alosetron-treated and 3 placebo-treated patients (Table 7, Appendix 3).

- In study -**30020** the incidence of drug-related constipation was higher among the alosetron-treated patients (36%) compared to traditional therapy (<1%). From within the alosetron-treated group, 18% withdrew due to GI AEs. These findings are consistent with the previously observed withdrawal rate of one-third of constipated patients. SAEs of severe constipation were reported in 6 patients randomized to alosetron (details in Appendix 3) and none of the traditional therapy patients. All 6 of the patients experiencing SCSC had to be hospitalized. One of these patients (# 67694) developed toxic megacolon, fulminant, secondary, ischemic gangrenous (transmural) colitis and septicemia and required a **total colectomy and ileostomy**. As already mentioned, nearly all patients reported use of concurrent medications **(Appendix 3)** the most common groups were anti-depressants (30% specifically SSRIs), NSAIDs (13%) and estrogens (30%).

- Although, in this review, emphasis is put on the occurrence of serious complications of severe constipation it is worth mentioning that the bulk of the cases of constipation rarely led to hospitalization and surgery. No patient experiencing SAEs related to constipation died.

- From Dr. Hoberman's computations, there seems to be a relation between age and weight to the risk of severe constipation (by quartiles).

**EVENTS OF RECTAL BLEEDING, BLOODY STOOLS/DIARRHEA WITH ABDOMINAL PAIN/GI PAIN IN ALL IBS TRIALS**

- A review of the evidence (section V. of this review, Tables 8, 9 and 10) allows the conclusion that the incidence rate of these events was higher in patients on alosetron (0.68%) than on placebo (0.37%), or active comparators. But there was no qualitative difference in the severity of reported events, the majority of which were mild to moderate in intensity and resolved spontaneously, some even with continued alosetron administration. Most of the events seemed to be associated with constipation and (external or internal) hemorrhoidal bleeding.

- In the absence of colonoscopic visualization of the colonic mucosa, these events do not provide sufficient evidence to support or exclude a diagnosis of ischemic colitis.

- There are nonetheless persistent concerns that at least some of these cases of "unexplained" rectal bleeding may represent forma frustrae cases of ischemic colitis. These lingering concerns support the conservative approach included in the revised LOTRONEX® labeling and in the Patient Medication Guide of discontinuing the drug as soon as the patient experiences bloody stools/diarrhea that cannot be explained by overt causes, such as the presence of hemorrhoids, and fissures.

**NOTES ON EFFICACY**

It is worth noting, the efficacy of LOTRONEX® is well established. To determine whether there are data that could be used as a refinement of the appraisal of effectiveness, additional efficacy information in patients with "severe" manifestations of IBS (i.e. "severe" urgency) and significant disruption of the patient's quality of life (QoL) was assessed.

**URGENCY**

Results of "urgency trials" **[S3B30011** and **–40031]**, two previously reported multicenter randomized placebo-control trials were analyzed. A "post-hoc" evaluation of the frequency of significant therapeutic benefit was performed among the more severely symptomatic non-constipated IBS patients, those with satisfactory control of urgency on 30% or less of days at baseline. The inclusion criteria for purposes of this evaluation was **stricter** than the original inclusion criteria for both studies which was control of bowel urgency on 50% or less of days at baseline. Satisfactory control of urgency for these **severe patients** was arbitrarily selected to be determined if patients subsequent to treatment with alosetron 1 mg bid experienced satisfactory control of urgency for both 75% and 85% of days. Alosetron 1 mg bid provided statistically significant therapeutic benefit over placebo in increasing the percent of days of satisfactory control of urgency among the **more severely symptomatic IBS patients**.

Based on the results of the analyses from these two protocols, significant therapeutic benefit among the more severely symptomatic IBS patients tended to improve with each additional month of treatment with alosetron (over the 1 to 3 months studied). Over 12 weeks of therapy in these two protocols, the therapeutic gain of alosetron demonstrated over placebo in improved satisfactory control of urgency from < 30% of days at baseline to >75% of days was 18 to 19% of patients and >85% of days was 14 to 17% of patients. In conclusion, efficacy does exist to support the use of alosetron 1 mg bid for IBS patients with severely symptomatic non-constipated urgency.

**QUALITY OF LIFE (QoL)**

QoL results of the two previously reported pivotal multicenter, randomized, placebo-control trials **[S3B3001** and **–3002]** were analyzed by Dr. D. Hoberman (Biometrics). These data indicate that the alosetron-treated patients do better[a] than patients on

placebo in all noted aspects of the scales of evaluation used. In terms of the absolute benefit as defined by the percentage of alosetron patients who are severely affected and who experience marked relief, between 10 to 20% can expect to get this margin of benefit on **Social scales** and approximately 5% on the **Work scales**. It is to be noted that the QoL scales appear to indicate a clear benefit compared to placebo. However, in these trials, the results are less impressive when actually counting the number of school or workdays lost as a result of the patient's IBS. The full distributions of lost days are statistically different when alosetron and placebo are compared. However, comparison before-and-after weekly strata reveals that there is little difference between the groups in terms of the actual number of days lost.

- Alosetron appears to be no less efficacious than mebeverine or trimebutine, drugs approved for the treatment IBS in Europe and used as positive concurrent controls in two clinical trials.

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[a] "Better" is defined as the change in the percentage of alosetron-treated patients who are severely affected at baseline and who then experience market improvement within 3 months of therapy.

# LOTRONEX®:

## The Randomized Clinical Trial Experience

## I. BACKGROUND/APPROACH TO THE REVIEW

The objective of this review is to assess all the available Randomized Clinical Trial (RCT) safety data existing in NDA 21-107. In addition to Dr. J. Senior's reviews on safety[1] and a secondary review[2] by Dr. H. Gallo-Torres of the original NDA, the current appraisal includes reviews of the 40 **new** RCTs not included in the original NDA. In response to the Agency request for early receipt of the **completed sections** of the proposed sNDA, GSK submitted first the **final clinical Study Reports (CSRs)** for 28 of the 40 total new studies. The additional final study Reports were submitted as part of the correspondence on 10/25/01. All 40 studies were again submitted as part of the sNDA on 12/07/01.

To review the submission in the shortest possible time a cooperative review of the data, involving several reviewers, was initiated. As indicated in memorandum from the Medical Team Leader (MTL) to the then HFD-180 Division Director, each reviewer was assigned certain studies[3]. Only final CSRs were included. Emphasis was put on the reporting of deaths, serious adverse events [SAEs, particularly ischemic colitis (IC) and serious complications of severe constipation (SCSC)], withdrawals (particularly those due to AEs) and other significant or potentially significant AEs (such as bloody stool/bloody diarrhea occurring in association with abdominal pain, which could have been an indication that the patient is experiencing IC.

Standardized definitions of SAEs, as they applied to SCSC and IC were used. SAE was any AE occurring at any dose that resulted in any of the following outcomes: 1) death; 2) life-threatening event; 3) inpatient hospitalization or prolonged existing hospitalization; 4) disability/incapacity; 5) congenital anomaly in the offspring of the patient receiving the drug and 6) additional important medical events that may not have resulted in death, been life-threatening or required hospitalization. Additional events were considered SAE when, based upon appropriate medical judgement, they may have jeopardized the patient and may have required medical or surgical intervention to prevent one of the outcomes listed in this definition. One example of the latter is the occurrence of **fecal impaction** in a patient that was **disimpacted** in the Doctor's office, although the event did not result in hospitalization.

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[1] Dr. John Senior's reviews include:
a. Safety Review of the original NDA (October 22, 1999)
b. Review of 90-day Safety Update (November 30, 1999)
c. Review of Supplemental Safety Update-2 (April 6, 2000)

[2] Dr. Hugo E. Gallo-Torres. Secondary Multidisciplinary Review and Recommendations for Regulatory Action. Memorandum to Director, Office of Drug Evaluation III, HFD-103 (November 17, 1999).

[3] Dr. Hugo Gallo-Torres. Division of Labor; sNDA 21-107, submission of August 23, 2001 (GlaxoSmithKline= GSK) (August 30, 2001)

The definition, etiology and pathogenesis, clinical features, findings on diagnostic testing, and management and course of **ischemic colitis**, a form of colitis due insufficient arterial blood flow to in the colonic mucosa, are discussed in detail in the MTL secondary review of November 17, 1999. This description includes Escherichia coli 015: H7-associated colitis. Also included are clinical summaries [clinical presentations: similarities and dissimilarities (Table 15)] of the 4 cases of ischemic colitis in the alosetron safety database before approval of the drug. These descriptions incorporate comments from Dr. Kay Washington (Vanderbilt University), who on behalf of the sponsor, carried out histopathological evaluation of all four cases that had been reported as IC. She concluded that in at least 2 of these 4 cases the findings represent infectious colitis. The MTL's conclusion (eventually incorporated in the labeling) was that all four patients had a clinical syndrome of IC that was **confirmed** on endoscopy but not always (as it may happen in many cases in clinical practice) supported by histopathological findings[4]. In summary, the MTL concluded that the 4 pre-approval cases were indeed IC. Based on the information available at that time it could not be concluded that these cases of IC were induced by alosetron, although there was a strong suspicion that this might be so because of the temporal relationship, positive dechallenge and due to the fact that no case was reported among patients taking placebo. The calculated incidence rate, in terms of proportion of clinical trial patients experiencing IC in apparent association with alosetron, without considering time to event, was 1 in 700 [Confidence Intervals 1/100 to 1/1000].

Also included in the MTL's secondary review was a list of drugs known to produce colonic ischemia[5] to which atherosclerosis, hyperlipidemia and surgical interventions, specially those that reduce blood supply to the gut, should be added. The aim was to identify any risk factors that might predict increased likelihood for the development of IC (e.g. nested case control evaluation).

Except as specified below, no detailed reviews of the results of individual RCTs were performed by the Medical Officer. More complete reviews (eventually signed off into DFS) were done for studies of special interest. These included those evaluating severe urgency [**Studies S3B30011 and S3B40031**], review carried out by Dr. S. Kress], two with active concurrent control, either mebeverin or trimebutine [**Studies S3BB3001 and S3BB3002;** review carried out by E. Kaminskas] and Study **S3B30020** where a rather large number of cases of IC (n=10) and SCSC (n=6) were reported [reviewed by Dr. S. Kress].

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[4] This IC may coexist or even be the consequence of some form of E. coli infection, an infection that is somewhat common [W.F. Marshall et al. Results of a 6-month survey of stool cultures for Escherichia coli 0157:H7. Mayo Clinic Proc. 65:787-792 (1990)]

[5] These include use of oral contraceptives (which may be associated with mesenteric and venous thrombosis, typically presenting as IC); estrogen (which may produce hypercoagulability, mesenteric vasospasm, and endothelial proliferation with subendothelial fibrosis); vasopressin (which causes colonic ischemia by reducing blood flow) cocaine and dextroamphetamine (which may evoke intense mesenteric spasm). Ergot preparations produce colonic vasospasm whereas ergotamine suppositories can cause rectal ulcers with obliteration of small vessels, endothelial proliferation, and thickening of the vascular wall. IC has been reported after the use of neuroleptic and tricyclic antidepressants. Digitalis preparations are associated with colonic ischemia, in part because of the low-flow states (e.g. CHF) that produce colonic hypoperfusion. Many if not all of these agents produce mesenteric vasoconstriction in animal models however, and may directly contribute to consequent ischemia.

To facilitate the process, the individual reviewers maintained regular communication about their reviews with other members of the team, the MTL and Mr. Paul Levine Jr., the project Manager. Close communication was also maintained with members of the Biometrics Division (Drs. T. Permutt and D. Hoberman). As shown below, evaluations include (a) a formal incidence rate of the SAEs (mainly IC) with an appropriate Confidence Interval (compare with the pre-marketing approval rate) and (b) an assessment of whether the hazard rates of these SAEs were constant, increased or decreased over time. Dr. Hoberman also carried out additional evaluations on urgency and Quality of Life (QoL) information.

## II. Clinical Trials (Tables 1 and 2 )

The sponsor elected to present the safety data arising from two types of trials: Those comprising the primary safety data (Table 1) and those identified under the heading of secondary safety data.

- The primary safety data are derived from 26 (**not 24,** as stated by the sponsor) IBS trials including a total of 15,401 patients, distributed as follows:

| **Treatment** | **# of Patients** |
|---|---|
| Alosetron | 10, 805 |
| placebo | 2,935 |
| mebeverine | 390 |
| trimebutine | 382 |
| misc. IBS Txs | 889 |
| | 15,401 |

- 13 of the trials were **completed** while the other 13 were **terminated early**.

- Most of the trials included only females while in 5 **[S3BP12, S3BA2001, S3BA3003, S3B30019** and **S3B20015]** the study population consisted of males and females. S3B20023 randomized only male patients.

- In most trials, the duration of treatment was 12 weeks but ranged from 14 days **[S3B20012]** to 1 year **[S3BA3003** and **S3B30006].**

- The bulk of the trials were randomized, double-blind.

- In 11, the comparator was placebo; four **[S3BB3001** and **–3002, S3B30026** and **30033]** used an active concurrent control.

- In 3 trials, the indications evaluated were other than IBS **[S3B30004**=anxiety; **S3B20012**= non-cardiac chest pain; **S3B20015**= non ulcer dyspepsia (NUD)].

- Trials of special interest include: **S3BA3001** and **–3002** the 2 pivotal trials submitted in the original NDA (reviewed by Dr. Senior), **S3B30011** and –40031, bowel urgency trials apparently demonstrating effectiveness in patients with **severe** IBS (reviewed by Dr. S. Kress), the two completed active concurrent control trials **(S3BB3001**=mebeverine; -3002= **trimebutine**); (reviewed by Dr. E. Kaminskas), the two long-term trials, **S3BA3003** which enrolled M & F patients, (reviewed by Dr. J. Senior) and **S3B30006** (reviewed by Dr. M. Barreiro) and finally, **S3B30020;** (reviewed by Dr. S. Kress) a multicenter, repeat-dose, 6-month open-label trial (vs. traditional therapy) where 10 cases of ischemic colitis and 6 of serious complications of severe constipation were reported among the 1817 patients treated with alosetron.

  The secondary safety data are derived from the Phase I, II, and other trials (Table 2). These trials are only listed for purpose of completeness and will be briefly discussed here. Results from 18 PK/PD nearly reported studies are summarized in Appendix 1[6].

  In the sections that follow, the primary safety data are analyzed with regards to the occurrence of a) ischemic colitis; b) serious complications of severe constipation; c) events of rectal bleeding, bloody stool/diarrhea with abdominal/GI pain; and d) other SAEs.

[6] Overall, no SAEs were reported. There were no cases of ischemic colitis, serious complications of severe constipation or bloody diarrhea reported.

# Table 1

## sNDA 21-107/S-005
## Studies Comprising the Primary Safety Data

## I. Controlled Studies

| Study No. | C Or T | Duration Weeks | Sex | D-B | Random | Dose Ranging | Division of Labor (Reviewer)/ COMMENTS |
|---|---|---|---|---|---|---|---|
| **A. Studies with Concurrent Placebo Control** | | | | | | | |
| **S3BP12** | C | 12 | M & F | X | X | X | JS (Original NDA) |
| **S3BA2001** | C | 12 | M & F | X | X | X | JS (Original NDA) |
| **S3B20023** | C | 12 | M | X | X | X | MB |
| **S3BA3001** | C | 12 | F | X | X | | JS: one of 2 pivotal trials in original NDA |
| **S3BA3002** | C | 12 | F | X | X | | JS: The other pivotal trial in original NDA |
| **S3B30011** | C | 12 | F | X | X | | SK (urgency) |
| **S3B30013** | T | 12 | F | X | X | | MB |
| **S3B30015** | T | 8 | | X | X | | RJ (adolescents) |
| **S3B30025** | T | 24 | F | X | X | | MB |
| **S3B30028** | T | 12 | F | X | X | | MB |
| **S3B30031** | T | 8-12 | F | X | X | | MB |
| **S3B40031** | T | 12 | F | X | X | | SK (the other urgency trial) |
| **B. Studies with Active Concurrent Control** | | | | | | | |
| **S3BB3001** | C | 12 | F | X | X | | EK: One of 2 active concurrent control trials (vs mebeverine) |
| **S3BB3002** | C | 12 | F | X | X | | EK: The other active concurrent control trial (vs trimebutine) |
| **S3B30026** | T | 8 | F | X | X | | MB |
| **S3B30033** | T | 12 | F | X | X | | MB |
| **C. Long-Term Studies** | | | | | | | |
| **S3BA3003** | T | 1 year | M&F | X | X | | JS (original NDA) |
| **S3B30006** | C | 1 year | F | X | X | | MB |
| **D. Open-Label Studies** | | | | | | | |
| **S3B30012** | C | 6 | F | | | | MB (2-part study) |
| **S3B30017** | T | 8+ | F | X | X | X | MB (2-part study) |
| **S3B30019** | T | 16 | M&F | | | | MB |
| **S3B30020** | T | 24 | F | | | | SK: A multicenter, Repeat-Dose, 6- month study (vs traditional therapy) where 10 cases of IC and 6 of SCSC were reported in apparent association with alosetron |
| **E. Indications Other Than IBS** | | | | | | | |
| **S3B30004** | C | 8 | F | X | X | | MB(anxiety) (vs PL) |
| **S3B20012** | C | 14 days | F | X | X | | MB (non-cardiac chest pain)(vs PL) |
| **S3B20015** | C | 12 | M&F | X | X | X | RJ(Non-ulcer dyspepsia) (vs PL) |
| **II. Other Uncontrolled Studies** | | | | | | | |
| | | | | | | | |
| **S3B40032** | T | | | | | | |

Abbreviations: C= Completed; T= Terminated; M = males; F = females; Random.= Randomized:
JS = Dr. John Senior; M.B. = Dr. Marcelo Barreiro; SK = Dr. Scheldon Kress; RJ = Dr. Raymond Joseph; EK = Dr. Edvardas Kaminskas; IC = Ischemic Colitis; SCSC Serious Complications of severe constipation; PL = Placebo

**Table 2**
**SNDA 21-107/S-005**
**Clinical Alosetron Studies Comprising The Secondary Safety Data**

| COMLETED STUDIES | | Sex | D-B | Random | Dose Ranging | Duration (Days) | # Alosetron-Treated Patients |
|---|---|---|---|---|---|---|---|
| Repeated-dose Pharmacokinetics | | | | | | | |
| GPK:90:02 | | M | X | X | | 9.5 | 12 |
| S3B-101 | | M | X | X | X | 3.5 | 36 |
| -102 | | M & F | X | X | | | 36 |
| -B1011 | | | | | | 27.5 | 0 |
| AS-02 | | M | SB | X | | 7 | 6 |
| Potential Interactions with Food & Drugs | | | | | | | |
| S3BA1001 | Cisapride | M & F | X | X | | 4 | 12 |
| -A1002 | Min-Ovral | F | | | | 21 | 16 |
| -10948 | Oral contraception | F | | | | 21 | 18 |
| -A1004 | Food | F | X | X | | 15.5 | 13 |
| -201 | Halperidol | M & F | X | X | | 14 | 11 |
| -A1003 | Mebeverine | F | | X | | 7 | 28 |
| -10935 | Fluositine Fluoxitine | M & F | | | | 14 | 12 |
| -10936 | Amitriptyline | M & F | | | | 5 | 12 |
| -10938 | Alprazolam | M & F | | X | | 2 | 13 |
| Pharmacodynamics & Mechanisms of Action | | | | | | | |
| -H05 | GI transit time | M | X | X | | 8 | 11 |
| -H06 | Ibid | M &F | X | X | | 8 | 12 |
| -B2011 | Ibid | M &F | X | X | X | 4 weeks | 20 |
| -10906 | Ibid | M &F | | X | | 6 weeks | 32 |
| C94-014 | Intestinal motility | M &F | X | X | | 7 | 21 |
| S3BA2003 | Ibid | M &F | X | X | | 7 | 10 |
| -B1001 | Ibid | M &F | X | X | | 7.5 | 12 |
| -B1007 | Ibid | M &F | X | X | | 7 | 30 |
| -B1002 | Ibid | M & F | X | X | | 7.5 | 8 |
| -A1006 | Ibid | M &F | X | X | | 14 | 20 |
| C93-059 | Visceral sensitivity | M &F | X | X | X | 6.5 | 19 |
| S3B-H04 | Ibid | | | | | | 0 |
| -H08 | Ibid | | | | | | 0 |
| -B1003 | Ibid | M & F | X | X | X | 6.5 | 10 |
| -B1006 | Ibid | M | X | X | | 6.5 | 2 |
| -10945 | Ibid | F | X | X | | 15 | 23 |
| -B1009 | Gastrointestinal bloating | F | X | X | | 14 | 12 |
| -10932 | QT and QTc changes | F | X | X | X | 4 | 60 |
| -10901 | Serotonin synthesis rates | M & F | X | X | | 2 weeks | 14 |
| -10948 | Oral contraceptive | | | | | | 0 |
| -A2002 | Brain activity & sigmoid sensation | M & F | X | X | X | 21 | 24 |
| Efficacy- Diarrhea-Associated Carcinoid Syndrome | | | | | | | |
| S3BMDIND | | M & F | X | X | X | 3 weeks | 27 |
| S3BMDEXT | | M & F | | | | 1 Year | 9 |
| Efficacy-Unexplained Chest Pain (Non-cardiac chest pain) | | | | | | | |
| S3B20012 | | F | X | X | | 14 | 4 |
| Efficacy- Dumping Syndrome | | | | | | | |
| S3B20013 | | F | X | X | | 21 | 9 |
| | | | | | TOTAL PATIENTS | | 624 |

Not listed: Bioavailability/ Bioequivalence, single dose and other studies in healthy volunteers.
0=No patients for this entry or number not available

## III. ISCHEMIC COLITIS

All in all, a total of 19 cases of ischemic colitis were reported, with the following distribution:

**Ischemic Colitis [Total n=19]**

| ALOSETRON mg b.i.d. [n=18] | | | PLACEBO b.i.d. [n=1] |
|---|---|---|---|
| 0.5 | 1.0 | 2.0 | |
| [n=1][a] | [n=16][b] | [n=1][c] | [n=1][d] |

a) Study S3B20023
b) 10 cases in Study S3B30020;
c) Study S3BA2001
d) Study S3BA3003

- In **Table 3**, each individual patient experiencing ischemic colitis is identified by Pt.#, treatment assigned, type and number of study, age, sex, and whether the event was reported as being serious or not.

## Table 3
## sNDA 21-107/S-005
## Patients Experiencing Ischemic Colitis

| ALOSETRON mg. b.i.d. | Age, Sex | Patient # | Study Number and Type | Serious |
|---|---|---|---|---|
| 0.5 | 41M | 40398 | S3B20023: Concurrent PL Control | N |
| 2.0 | 33F | 2829 | -A2001: Concurrent PL Control | Y |
| 1.0 | 48F | 7195 | -A3002: PIVOTAL (PL Control) | Y |
| 1.0 | 41F | 15687 | -A3001: PIVOTAL PL Control | Y |
| 1.0 | 61F | 34069 | -30011: Concurrent PL Control | Y |
| 1.0 | 54F | 32451 | -30013: Concurrent PL Control | Y |
| 1.0 | 64F | 182603 | -30031: Concurrent PL Control | N |
| 1.0 | 31F | 49203 | -30012: Open-Label, 2- part | N |
| 1.0 | 54F | 63223 | -30020: Open-Label (vs Traditional Therapy) | Y |
| 1.0 | 75F | 66556 | Ibid | Y |
| 1.0 | 36F | 69433 | Ibid | N |
| 1.0 | 37F | 71843 | Ibid | N |
| 1.0 | 64F | 72823 | Ibid | Y |
| 1.0 | 57F | 72824 | Ibid | Y |
| 1.0 | 20F | 78134 | Ibid | Y |
| 1.0 | 50F | 80357 | Ibid | Y |
| 1.0 | 61F | 82125 | Ibid | Y |
| 1.0 | 67F | 65443 | Ibid | Y |
| PLACEBO | 27F | 8245 | -A3003: Long-Term (PL Control) | N |

- The case summaries for each of the patients experiencing ischemic colitis are given in **Appendix 2**. The information in the case summaries is displayed in a fashion similar to that used for the 4 cases (the 1996 case, the 1998a and b cases and the 1999 case) described in utmost detail in the MTL's secondary multidisciplinary review of November 17, 1999. These 4 cases are also included in this Appendix, to facilitate comparisons. Just as the 4 original cases, the newly described patients had a clinical syndrome characterized by a) bloody stool/bloody diarrhea occurring in association with abdominal pain (sometime of different character when compared to their usual IBS pain); b) increased white blood cells (not always); c) sometimes showing signs suggestive of colitis on CT scan; d) sigmoidoscopic/colonoscopic findings consistent with ischemic colitis **(the most important diagnostic feature)** and e) sometimes confirmation on histopathological examination.

- In all patients experiencing ischemic colitis, the test medication was discontinued and the patient was eventually withdrawn from the trial.

- Details of the outcome of these cases of ischemic colitis are given in **Table 4**. Fourteen of the 18 cases had to be hospitalized, one (from Study **S3B30020**) underwent **surgical intervention**, because of IC, but no patient died. The ischemic colitis occurring in **temporal association** with alosetron, can continue to be described as mild (meaning superficial, **non transmural**) and self-limiting. This is because in the majority of cases, the event represented a **postive dechallenge** since the patient responded well to drug discontinuation. The event usually resolved within 2 weeks with no overt sequelae.

- Results from Study **S3B30020**, a 24-week randomized, open label trial of Health Care Resource Use, Quality of Life and Productivity are of special interest. The effects of alosetron 1 mg twice daily were compared to traditional therapy in females with IBS whose predominant bowel symptom was diarrhea. Enrollment was discontinued when a total of 2706 patients (67% to alosetron; 33% to the comparator) were randomized to treatment. The proportion of patients completing the trial (53%) was substantially impacted by the sponsor's decision to terminate the study prematurely. Reasons for premature discontinuation (36% of the patients) included adverse events (10%) consent withdrawn (5%), lost to follow-up (4%), protocol violation (2%), insufficient therapeutic effect (2%) and "other" reasons (12%).

- Ischemic colitis occurred as SAEs in 10 alosetron-treated patients (1:180 patient exposures) and none of those treated with traditional therapy. As shown in Appendix 2, one of the patients with IC developed a colonic perforation, peritonitis and sepsis and required a sigmoid resection and **colostomy.** She subsequently suffered a stroke. Although 6 of the 10 patients developing IC required hospitalization, in 9 the event resolved with **conservative treatment**.

## Table 4
## sNDA 21-107/S-005
## Detail of Outcome: Serious Adverse Events in 26 Alosetron Studies Comprising the Primary Safety Data

| Protocol Number | Patients On Alosetron | Ischemic Colitis | Serious Complications of Constipation | Miscellaneous Vasculopaties | Miscellaneous GI Bleeding[a] | Hospitali-zation | Surgical Procedures | Deaths |
|---|---|---|---|---|---|---|---|---|
| S3BP12 | 345 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| S3BA2001 | 290 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| -20023 | 534 | 1 | 0 | 0 | 7 | 0 | 0 | 0 |
| -A3001 | 309 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| -A3002 | 324 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| -30011 | 532 | 1 | 0 | 0 | 12 | 1 | 0 | 0 |
| -30013 | 280 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| -30015 | 33 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| -30025 | 1028 | 0 | 1 | 0 | 0 | 1 | 0 | 0 |
| -30028 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| -30031 | 276 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| -40031 | 246 | 0 | 0 | 0 | 8 | 0 | 0 | 0 |
| -B3001 | 319 | 0 | 0 | 0 | 3 | 0 | 0 | 0 |
| -B3002 | 402 | 0 | 3 | 0 | 3 | 3 | 0 | 0 |
| -30026 | 957 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| -30033 | 94 | 0 | 0 | 0 | 3 | 0 | 0 | 0 |
| -30012 | 426 | 1 | 0 | 0 | 14 | 0 | 0 | 0 |
| -A3003 | 649 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| -30006 | 351 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| -30017 | 876 | 0 | 1 | 0 | 2 | 0 | 0 | 0 |
| -30019 | 8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| -30020 | 1817 | 10 | 6 | 0 | 64 | 12 | 2 | 0 |
| -40032 | 587 | 0 | 0 | 0 | 7 | 0 | 0 | 0 |
| -30004 | 32 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| -20012 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| -20015 | 239 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **TOTALS** | **10960** | **18** | **11** | **0** | **123** | **17** | **2** | **0** |

[a)] Irrespective of whether this event occurred in temporal association with abdominal pain.

- Searching for risk or predisposing factors existing at baseline, it has been found that in study S3B30020 (like in most other cases described in Appendix 2) nearly all patients reported use of concurrent medications. The most common of these were grouped as anti-depressants (30% specially SSRIs), NSAIDs (31%), and estrogens (30%). If any pattern can be suggested from these data, reviewed by Dr. Kress, it would be that vulnerability for IC is highest at the onset of therapy. Six of the ten cases of IC associated with alosetron therapy for 24 weeks occurred **within the first 3 weeks** of therapy. This finding is reproduced in Dr. Barreiro's review of the spontaneous reporting cases of IC (December 13, 2001) where 70% of the cases of IC occurred with the first 2 weeks after dosage with alosetron.

  **NOTE:** These data from Study S3B30020 together with the data from the spontaneous reports appear to lend support to the newly proposed approach of administering a lower than the recommended dose of ALOSETRON®, such as 1 mg per day for 2 to 4 weeks assess safety/efficacy results at the end of this period and, intervene accordingly (details in MTL Review of Risk Management Plan).

- Calculations related to time-to-event and hazard ratios for the entire database were carried out by Dr. Hoberman (Biometrics). Details of his evaluations are given in his review dated March 14 2002. **Table 5** contains **person-time** and events for the 20 trials with at least 100 patients. The overall estimate of the **incidence density (Table 6)** is based on pooling all 20 studies. [Some reviewers argue against pooling of data] Of the two 1-year long studies, **S3B30006** yielded one alosetron case while the other **[S3BA3003]** yielded no alosetron – associated case of IC, but a case of ischemic colitis in association with placebo treatment (Table 3). All cases of IC occurred within 162 days of randomization.

**Table 5**
**sNDA 21-107/S-005**
**Person-Time and Events for Trials with at least 100 Patients[a]**

| Study | n | Person-Days | Weeks | IC |
|---|---|---|---|---|
| S3B-P12 | 345 | 24,335 | 12 | - |
| S3B20015 | 239 | 17,432 | 12 | - |
| S3B20023 | 534 | 39,871 | 12 | 1 |
| S3B30006 | 348 | 84,875 | 48 | - |
| S3B30011 | 533 | 40,278 | 12 | 1 |
| S3B30012 | 422 | 45,279 | 12 | 1 |
| S3B30013 | 280 | 19,616 | 12 | 1 |
| S3B30017 | 876 | 53,993 | 20 | - |
| S3B30020 | 1 828 | 216,714 | 24 | 10 |
| S3B30025 | 1028 | 94,005 | 24 | - |
| S3B30026 | 957 | 58,240 | 32 | - |
| S3B30031 | 277 | 14,589 | 20 | 1 |
| S3B40031 | 246 | 16,480 | 12 | - |
| S3B40032 | 577 | 38,044 | 12 | - |
| S3BA2001 | 287 | 20,160 | 12 | 1 |
| S3BA3001 | 310 | 22,282 | 12 | 1 |
| S3BA3002 | 324 | 23,209 | 12 | 1 |
| S3BA3003 | 640 | 155,136 | 52 | - |
| S3BB3001 | 318 | 23,442 | 12 | - |
| S3BB3002 | 402 | 29,768 | 12 | - |
| | 10,775 | 1,037,748 | | 18 |

[a]Computations by Dr. D. Hoberman (Biometrics)

**Table 6**
**sNDA 21-107/S-005**
**Overall Estimate of the Incidence Density based on pooling all 20 Trials[a]**

| Study | Incidence density (/per-month) |
|---|---|
| S3B20023 | 1/1329 |
| S3B30011 | 1/1343 |
| S3B30012 | 1/1509 |
| S3B30013 | 1/654 |
| S3B30020 | 1/803 |
| S3B30031 | 1/486 |
| S3BA2001 | 1/672 |
| S3BA3001 | 1/743 |
| S3BA3002 | 1/774 |

**Overall- 1/1921 person-months over 20 studies**

[a]Computations by Dr. D. Hoberman (Biometrics)

## IV. SEVERE CONSTIPATION (Table 7)

- In this Table, each individual patient experiencing serious complications of **severe constipation** is identified by Pt. #, treatment assigned, type and number of study, age, sex, and whether the event was reported as being serious or not.

**Table 7**
**in NDA 21-107**
**Patients Experiencing Serious**
**Complications of Severe Constipation**

| ALOSETRON mg b.i.d. | Age, Sex | Patient # | Study Number and Type | Serious |
|---|---|---|---|---|
| | | | | |
| 1.0 | 56F | 176167 | S3B30025: Concurrent PL Control | Y |
| 1.0 | 45F | 2330 | - B3002: Active Concurrent Control | Y |
| 1.0 | 29F | 2541 | Ibid | Y |
| 1.0 | 54F | 3773 | Ibid | Y |
| 1.0 | 21F | 174139 | -30017: Open-label; 2 part | N |
| 1.0 | 76F | 65385 | -30020: Open-Label (vs Traditional Therapy) | Y |
| 1.0 | 56F | 67694 | Ibid | Y |
| 1.0 | 26F | 80655 | Ibid | Y |
| 1.0 | 47F | 83206 | Ibid | Y |
| 1.0 | 67F | 87373 | Ibid | Y |
| 1.0 | 50F | 88034 | Ibid | Y |
| | | | | |
| Placebo | 31F | 6582 | S3BA3002: PIVOTAL (PL Control) | Y |
| Placebo | 67F | 34911 | -30011: Concurrent PL Control | Y |
| Placebo | 71F | 23647 | -30006: Long-Term (PL control) | Y |

- The case summaries for each of the 14 patients experiencing serious complications of severe constipation are given in **Appendix 3**. Once again, the information in these case summaries is presented in a fashion similar to that used for ischemic colitis cases. Details of the outcome of these 14 cases of SCSC are given in Table 4.

- Once again, results from study **S3B30020**, reviewed by Dr. Kress, are of interest.

- In study **S3B30020** the incidence of drug-related constipation was higher among the alosetron-treated patients (36%) compared to traditional therapy (< 1%). From within the alosetron-treated group, 18% withdrew due to GI AEs. These findings are consistent with the previously observed withdrawal rate of one-third of constipated patients. SAEs of severe constipation were reported in 6 patients randomized to alosetron (details in Appendix 3) and none of the traditional therapy patients. All 6 of the patients experiencing SCSC had to be hospitalized. One of these patients (# 67694) developed toxic megacolon, fulminant secondary ischemic gangrenous (transmural) colitis and septicemia and required a **total colectomy and ileostomy**. But no patient died. As already mentioned, nearly all patients reported use of concurrent medications **(Appendix 3)** the most common groups were anti-depressants (30% specifically SSRIs), NSAIDs (13%) and estrogens (30%).

- Although, in this review, emphasis is put on the occurrence of serious complications of severe constipation it is worth mentioning that the bulk of the cases of constipation rarely led to hospitalization and surgery. From Dr. Hoberman's computations, there seems to be a relation between age and weight to the risk of severe constipation (by quartiles).

## V. EVENTS OF RECTAL BLEEDING, BLOODY STOOLS/DIARRHEA WITH ABDOMINAL/GI PAIN IN ALL IBS TRIALS

- The total database was searched for patients with **abdominal pain and discomfort** or gastrointestinal pain and discomfort who also reported either **bloody diarrhea** or blood in their stools. The total n is 13,740.

- These individual events were reported by a total of 86 patients, with the following distribution:

| ALOSETRON | PLACEBO | HYOSCYAMINE-LOPERAMIDE |
|---|---|---|
| **74/10,805 (0.68%)** | **11/2935 (0.37%)** | **1** |

- 66 of these 86 patients experienced pain/discomfort **within 7 days** of the onset of rectal bleeding or bloody stools. The distribution of these 66 patients in whom rectal bleeding was temporally related to abdominal pain was:

| | ALOSETRON[a] | PLACEBO | TRADITIONAL THERAPY |
|---|---|---|---|
| | 56 | 9 | 1 |
| Considered Serious[b] | 3 | 2 | 0 |

[a]Patient # 78134 [Study S3B30020] identified as probable or possible diagnosis of IC, is not included in the discussion that follows.
[b]All the 5 cases resulted in treatment discontinuation

- The remaining 65 patients were further assessed to determine whether their clinical presentations suggested an etiology of G.I. bleeding[7]. Further analysis was made to select subsets with concurrent AEs related to constipation (itself) or with other identified sources of G.I. bleeding.

- The results of these evaluations are summarized in Table 8.

Table 8
**NDA 21-107/S-005**
Concurrent Events in Patients Who Reported Rectal Bleeding Within 7 days of Abdominal/Gastrointestinal Pain and Discomfort

| | Placebo [n=9] | Alosetron [n=56] | Total [n=65] |
|---|---|---|---|
| Constipation | 2 | 31 | 33 |
| Hemorrhoid | 0 | 4 | 4 |
| Anal Fissure | 0 | 1 | 1 |
| Straining | 0 | 1 | 1 |
| Ischemic colitis | 0 | 1 | 1 |
| Diverticulitis | 0 | 1 | 1 |
| Digoxin | 0 | 0 | 0 |
| Mesalamine | 0 | 0 | 0 |
| NSAID use within 7 days | 2 | 11 | 13 |
| Estrogen use within 7 days | 5 | 29 | 34 |

Source: Listing 5.9.4.1

[7] Physician reports were reviewed for patient's symptoms of constipation and hemorrhoidal bleeding. The observation of a source of bleeding on physical examination or endoscopy, or the use of concomitant medications clinically associated with an increased incidence of gastrointestinal bleeding. These concomitant medications included NSAIDs, estrogen, digoxin and mesalamine.

- After exclusion of those patients with constipation (which is not a typical presenting symptom of primary IC) as well as those with drug use or AE reports consistent with a potential source of rectal hemorrhage, 8 patients remained without an identified potential etiology for the bleeding event. The results of these evaluations are summarized in Table 9.

Table 9
NDA 21-107/S-005
**Results (Additional Information) of Searching for an Etiology of Rectal Bleeding**

| **PLACEBO** [n=1] | **ALOSETRON** [n=7] |
|---|---|
| | • In 3 patients the information suggested the involvement of either an AE or pre-existing conditions.<br>• For 2 patients, investigators omitted AE reporting for Abnormal findings observed during the follow-up of The AE [sigmoidoscopy performed in response to the Event of rectal bleeding identified **internal hemorrhoids** without evidence of IC].<br>• For 1 patient **(Pt. 74354 in S3B30020)**[a], findings at the time of the baseline examination suggested a potential source of rectal bleeding during therapy. |

[a] This subject was noted by the investigator to be **HEMOCCULT positive** at baseline, a finding the investigator related to **anusitis.**

- As summarized in Table 10, the sponsor's analysis further reduced from 8 to 5 the number of patients without investigator reports suggesting an alternative source of bleeding related to an evident cause. The events in these 5 patients were rated as mild or moderate and none as severe (Table 10). Although the majority of these events resolved (4 of 5), 2 of these patients were withdrawn from the trial as a result of these symptoms.

**Table 10**
NDA 21-107/S-005
Results of Further Evaluations

| | PLACEBO | TRADITIONAL THERAPY | ALOSETRON |
|---|---|---|---|
| Patients without investigator reports suggesting an alternative source of bleeding related to evident cause[a] | 1 | 1 | 3 |
| Severity of Bleeding Events | | | |
| - Mild | 1 | 1 | 1 |
| - Moderate | 0 | 0 | 2 |
| - Severe | 0 | 0 | 0 |
| Events Resolving | 1 | 1 | 2 |
| Withdrawal due to the Event | 0 | 0 | 2 |

[a] This cause could be either: 1) constipation, 2) hemorrhoids, 3) a potential source of rectal bleeding on endoscopy, 4) a pre-existing condition or 5) the use of a concomitant therapy associated with an increased risk of enteric bleeding.

- The sponsor's analysis also showed that there was a wide range for time to the onset of symptoms of rectal bleeding or bloody diarrhea from 2 to 335 days from the start of study therapy. The majority of the events on active therapy, however, occurred within one month of the onset of treatment (32 of a total of 56 patients) and 76.7% of these events occurred within 60 days of the initiation of drug therapy (43 of 56 patients).

## ADDITIONAL REVIEWER'S COMMENTS

Although the incidence rate of AEs of rectal bleeding or blood in stools seen in associated with symptoms of abdominal or gastrointestinal pain was higher in patients on alosetron (0.68%) than on placebo (0.37%) (or active comparators) the reviewer agrees with the sponsor there was no qualitative difference in the severity of reported events. In addition, the reviewer agrees with the sponsor's analysis, which showed that the majority of these events were mild to moderate in intensity and resolved spontaneously even with

continued alosetron therapy. Most of these events seemed to be associated with constipation and (external or internal) hemorrhoidal bleeding. The evidence at hand demonstrates that the concomitant use of NSAIDs and estrogen therapy may have contributed to some of the reported instances of the self-limiting rectal bleeding or hematochezia associated with constipation or hemorrhoids in these alosetron-treated patients.

The reviewer agrees with the sponsor that the clinical characteristics of all of these events are generally minor AEs. In the absence of colonoscopic visualization of the colonic mucosa, These events do not provide sufficient evidence to support or exclude a diagnosis of ischemic colitis.

NOTE: There are nonetheless lingering concerns that at least some of these cases of "unexplained" rectal bleeding may represent **forma frustrae** cases of ischemic colitis.

Another reviewer (S. Kress) added an addendum to his review of clinical study Report for Protocol S3B30011 (Bowel Urgency in females with non-constipated IBS). After assessing additional information provided, this Medical Officer attempted to ascertain the extent of investigation in each case and to assess the possibility of additional cases of IC. The Reviewer concluded that due to the lack of detailed clinical data and/or classification criteria, definitive assessment of alosetron-causality and severity of each case remains impractical. In the 2 patients that experienced bloody diarrhea in Study S3B30011, neither the possibility of mild ischemic colitis nor the possibility that alosetron contributed to these AEs can be excluded. The MO reviewer arrived at the same conclusions after his evaluation of the occurrence of unexplained bloody diarrhea in study S3B30020.

Although these findings do not provide definite conclusions, they support the conservative approach included in the revised LOTRONEX® labeling and in the Patient Medication Guide of discontinuing the drug as soon as the patient experiences bloody diarrhea that cannot be easily explained by overt causes, such as the presence of hemorrhoids, anal fissures or be the result of the passage of hard stool due to constipation.

## VI. Other SAEs

The database was searched for occurrence of SAEs that were neither IC nor serious complications of severe constipation as well as extraintestinal AEs.

### A. Other intestinal SAEs

Under this category, there were a few cases that could not be categorized as IC or serious complications of constipation with certainty. Two examples are included in Appendix 4. One [**Pt. # 174138 (S3B30017)**] was a 50 y-old woman that experienced transient, patchy **non-specific colitis**.

The other **[Pt. # 190586 (S3B30033)]** was a 61y-old female in who the final diagnosis was from previous surgery. In both instances, alosetron cannot be completely exonerated as having a contributing role.

**B. Extra-intestinal AEs**

During the assessment of the individual cases experiencing SAEs in the LOTRONEX® database, instances of chest pain, arrhythmia, sudden death, TIAs and strokes, syncope and near syncope and thrombosis, in apparent temporal association with test medication, were seen. This prompted a preliminary review of 19 clinical trials in the December 7, 2002 sNDA by Dr. M. Barreiro.

The above-mentioned cardiovascular events were sought for a cause as SAEs. According to the reviewer, a total of 66 SAEs met criteria for inclusion in his evaluation (alosetron, n=48; placebo/active control, n=18. The distribution of events is displayed in Table 11.

**TABLE 11**
**SUMMARY OF CARDIOVASCULAR**
**(n=66 SAEs)[a]**

| Event | ALOSETRON [n=10,083] | P/C [n=3,433] |
|---|---|---|
| **Chest pain** | **26 (0.26%)** | **10 (0.29%)** |
| **Cardiac arrhythmia** | **10 (0.10%)** | **4 (0.12%)** |
| **TIA/Stroke** | **4 (0.04%)** | **2 (0.06%)** |
| **Syncope/near-syncope** | **6 (0.06%)** | **1 (0.03%)** |
| **Thromboses** | **2 (0.02%)** | **1 (0.03%)** |
| **TOTALS** | **48 (0.48%)** | **18 (0.52%)** |

This Table corresponds to Table 2 in Dr. Barreiro's March 5, 2002 review.

Dr. Barreiro calls attention to the fact that there were cases of cardiovascular events that were not judged to be serious, although the patients were W/D from the trial because they "withdrew consent."

- It is concluded that there is no statistically significant difference between the Alosetron and the Placebo/Control-treated patients, with respect to the five cardiovascular SAEs studied, in these 19 research protocols.

## VII. NOTES ON EFFICACY

Although, as stated in section I. BACKGROUND/APPROACH TO THE REVIEW of the present document, the emphasis is on the appraisal of safety data, some evaluations on efficacy, briefly summarized below, were carried out.

It is worth noting, the efficacy of LOTRONEX® is well established[8].

- The objective of the present exercise is to look for additional efficacy information in patients with "severe" manifestations of IBS as manifested by pronounced symptoms and very significant disruption of the patient's quality of life (QOL). In addition, results from two active comparator trials were briefly evaluated.

### A. URGENCY

Of the two studies assessing urgency, and reviewed by Dr. Kress, one [S3B30011 was completed]. The other, [S3B40031] was terminated early.

- Both studies were designed to evaluate the efficacy and safety of alosetron 1 mg b.i.d. in a 12-week, randomized, double-blind against placebo for control of **bowel urgency** in females with lack of satisfactory control of urgency on less than 50% of days with non-constipated IBS. In this study –30011, **satisfactory control of urgency** (the primary endpoint) and IBS global improvement were assessed in patients who did/did not report constipation and who did/did not use laxatives during the study. Study – 40031 replicated – 30011 with a few important differences: 40031 utilized patients seeing physicians in an IPA model managed care whereas-30011 evaluated intervention directed at managing constipation and enabling patients to continue therapy. In both trials, treatment groups were well matched with regard to demographic characteristics including age, race, parity, childbearing potential, time since IBS diagnosis, IBS subtype, and body mass index.

- A "post-hoc" evaluation of the frequency of significant therapeutic benefit was performed among the more severely symptomatic non-constipated IBS patients, those with satisfactory control of urgency on 30% or less of days at baseline from Protocols S3B30011 and S3B40031. The inclusion criteria for purposes of this evaluation was **stricter** than the original inclusion criteria for both studies which was control of bowel urgency on 50% or less of days at baseline. Satisfactory control of urgency for these **severe patients** was arbitrarily selected to be determined if patients subsequent to treatment with alosetron 1 mg BID experienced satisfactory control of urgency for both 75% and 85% of days. Results of these evaluations are summarized in Table 12.

[8] The issue of efficacy was thoroughly addressed by Dr. R. Prizont, in this review of the original NDA, Dr. H. Gallo-Torres multidisciplinary secondary review of November 17, 1999, discussions at Acs and literature publications.

- Alosetron 1 mg BID provided statistically significant therapeutic benefit over placebo in increasing the percent of days of satisfactory control of urgency among the **more severely symptomatic IBS patients**.

- Based on the results of the analyses from these two protocols, significant therapeutic benefit among the more severely symptomatic IBS patients tended to improve with each additional month of treatment with alosetron (over the 1 to 3 months studied). Over 12 weeks of therapy in these two protocols, the therapeutic gain of alosetron demonstrated over placebo in improved satisfactory control of urgency from < 30% of days at baseline to >75% of days was 18 to 19% of patients and >85% of days was 14 to 17% of patients.

- The clinical reviewer believes [and the MTL agrees] that evidence of efficacy does exist to support the use of alosetron 1 mg BID for IBS patients with severely symptomatic non-constipated urgency.

- Furthermore, in a global assessment on urgency, carried out by Dr. D. Hoberman it was noted that, in the clinical trials, urgency was measured by calculating the proportion of days over an interval in which a patient experienced "urgency". The baseline period was one week. Data from 4 trials were analyzed: the 2 original studies (3001 and 3002) and the 2 so-called "urgency" trials (30011 and 40031). The results are summarized in Fig. 1.

- The statistician addresses the issue of "what percentages of patients have a 'response', which lasts for a defined period?" As explained by Dr. Hoberman, the threshold of the response is the following: **only patients who had at least 70% urgency at baseline are included** in order to address the issue of the most severely affected patients. In the upper graph of Fig. 1, a stringent condition is used. This is that the response must be for all 4 weeks of a month to be counted as a monthly responder, while in the lower graph of this Fig. The "monthly responder" standard is relaxed by saying that one must respond **any 2 weeks out of the month,** not all 4 weeks. Since IBS is a fluctuating disease where symptoms, including urgency, may wax and wane, the latter approach may be more applicable to the clinical situation. From these evaluations, LOTRONE® is shown to be more effective than placebo with both approaches but more so when the 2 weeks out of a month approach is used.

**Table 12**

**Summary of Satisfactory Control of Urgency for Severely Symptomatic Patients (Patients With Satisfactory Control of Urgency on 30% or Less Days at Baseline) By Month and Over 12 Weeks (Intent-to-Treat Population LOCF)**

## I. Study S3B30011

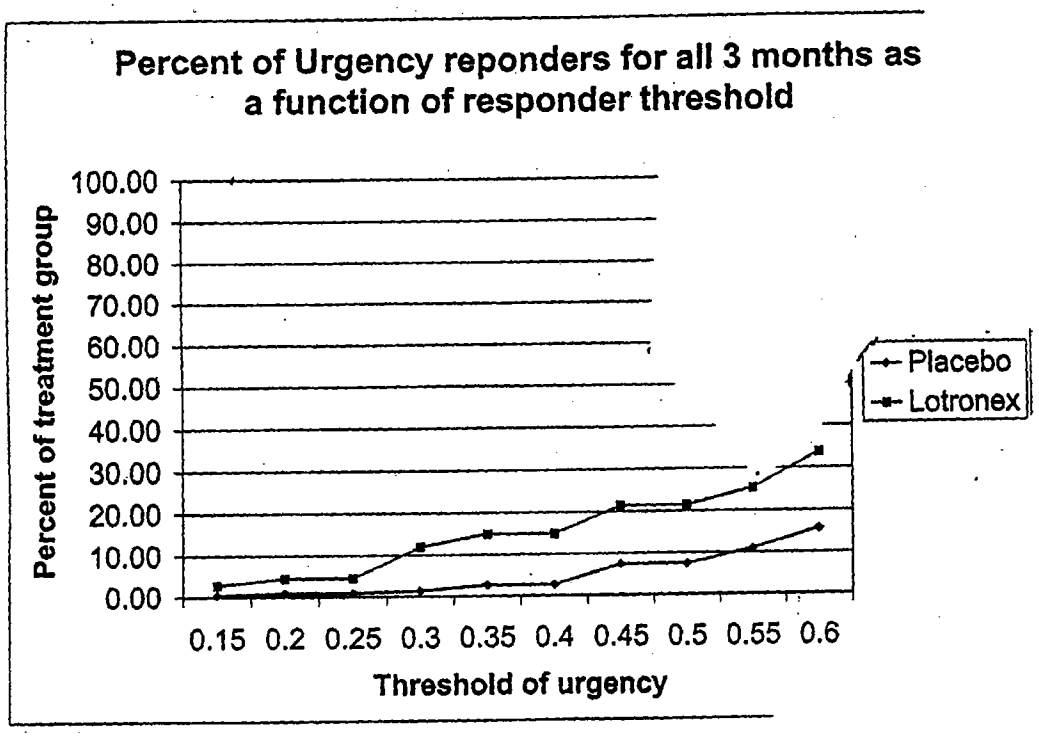
| Days With Satisfactory Control of Urgency At | Placebo-Treated (N=181) | | Lotronex-Treated (N=327) | | p-value * | Therapeutic Gain |
|---|---|---|---|---|---|---|
| **Month 1** | 180 | | 327 | | | |
| 75% | 19 | 11% | 86 | 26% | <0.001 | 15% |
| **85%** | 8 | 4% | 48 | 15% | <0.001 | **11%** |
| **Month 2** | 180 | | 327 | | | |
| 75% | 51 | 28% | 160 | 49% | <0.001 | 21% |
| **85%** | 32 | 18% | 113 | 35% | <0.001 | **17%** |
| **Month 3** | 180 | | 327 | | | |
| 75% | 51 | 28% | 175 | 54% | <0.001 | 26% |
| **85%** | 32 | 18% | 134 | 41% | <0.001 | **23%** |
| **Overall (12 Weeks)** | 180 | | 327 | | | |
| 75% | 37 | 20% | 127 | 39% | <0.001 | 19% |
| **85%** | 15 | 8% | 83 | 25% | <0.001 | **17%** |

p-values obtained using Mantel-Haenszel mean score test controlling for cluster

## II. Study S3B40031

| Days With Satisfactory Control of Urgency At | Placebo-Treated (N=171) | | Lotronex-Treated (N=169) | | p-value * | Therapeutic Gain |
|---|---|---|---|---|---|---|
| **Month 1** | 171 | | 168 | | | |
| 75% | 23 | 13% | 43 | 26% | 0.007 | 13% |
| **85%** | 9 | 5% | 23 | 14% | 0.007 | **9%** |
| **Month 2** | 171 | | 168 | | | |
| 75% | 47 | 27% | 69 | 41% | 0.009 | 13% |
| **85%** | 20 | 12% | 49 | 29% | <0.001 | **17%** |
| **Month 3** | 171 | | 168 | | | |
| 75% | 51 | 30% | 73 | 43% | 0.009 | 13% |
| **85%** | 30 | 18% | 55 | 33% | 0.001 | **15%** |
| **Overall (12 Weeks)** | 171 | | 169 | | | |
| 75% | 28 | 16% | 58 | 34% | <0.001 | 18% |
| **85%** | 11 | 6% | 33 | 20% | <0.001 | **14%** |

* p-values obtained using Mantel-Haenszel mean score test controlling for cluster



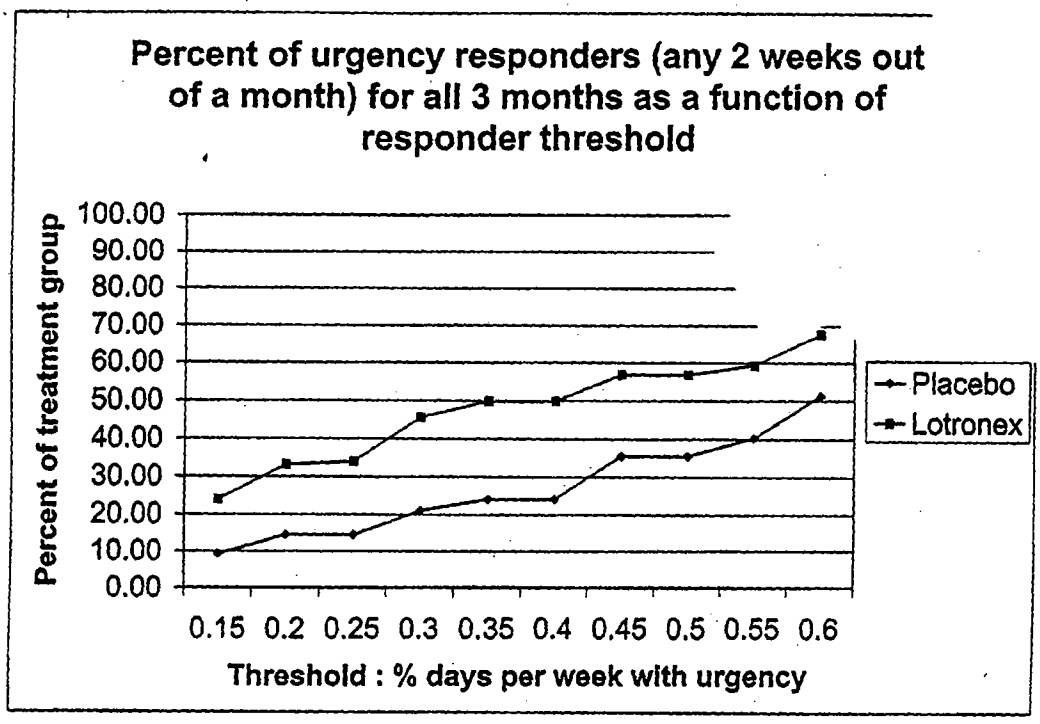




Fig. 1.- Proportion of Urgency Responders in the alosetron RCTs

Evaluations, LOTRONEX® is shown to be more effective than placebo with both approaches but more so when the 2 weeks out of a month approach is used.

## B. QUALITY OF LIFE

- A variety of cultural, social environmental and behavioral factors may influence IBS. Hormonal influences (e.g. menses), diet, psychologic stress and activity level may exacerbate IBS symptoms[9]. This common disorder can be associated with significant disability and health care costs[10]. Psychosocial processes play a role in IBS. They influence illness recognition, use of services and treatments, and response to treatments, pharmacologic and non-pharmacologic. There is considerable interest in exploring how this disorder and its treatment influence health-related quality of life (HRQoL) of patients.

- The sponsor used 3 QoL instruments: A QoL questionnaire specifically for IBS patients (IBSQoL), the SF-36 a questionnaire that produces a profile of eight domain scores[11] and a work-related instrument (work-loss days). For his analysis, Dr. Hoberman chose selected items from the IBSQoL and information about days of lost work due to IBS.

- The results of Dr. Hoberman's analyses of the Social and Work Scales of the IBSQoL in trials 3001 and 3002, the two pivotal studies in NDA 21-107, are summarized, in graphic form, in Figure 2. These data indicate that the Alosetron-treated patients do better than patients on placebo in all the noted aspects of the scales.

  NOTE: "Better" is defined as the change in the percentage of patients who are severely affected at baseline and who then experience marked improvement within 3 months on therapy.

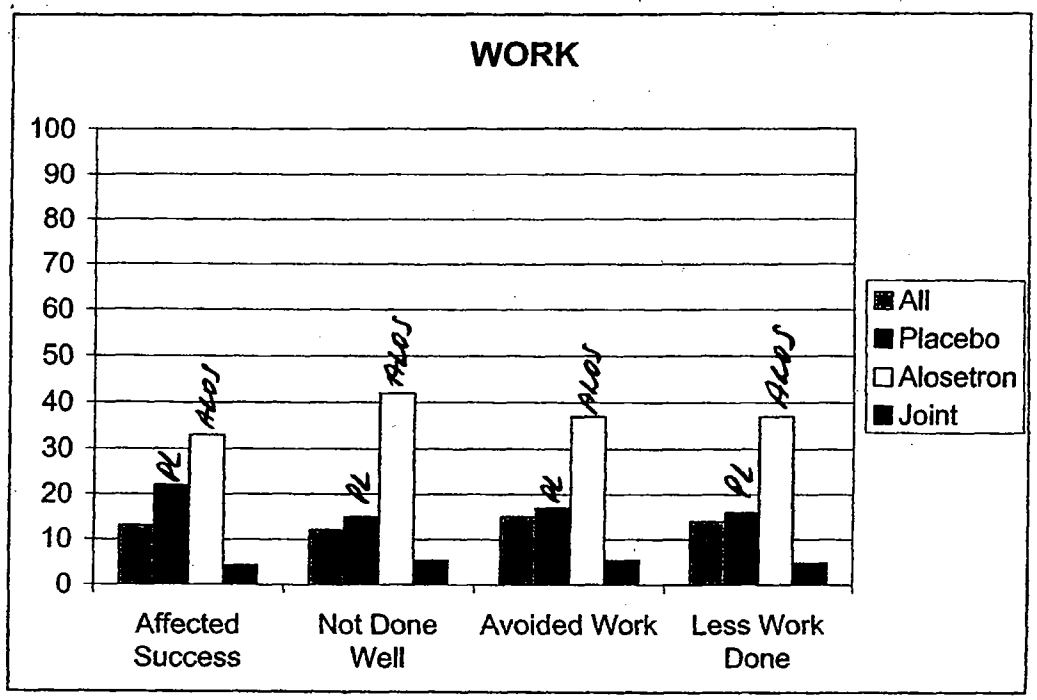
  In terms of the absolute benefit as defined by the percentage of alosetron-treated patients who are severely affected and who experience marked relief, between 10 to 20% can expect to get this margin of benefit on Social scales and approximately 5% on the Work scales (See the 4th bars on each bar chart).

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[9] D.A. Drossman. Irritable Bowel Syndrome.
Gastroenterologist 2: 315-326 (1994).

[10] D.A. Drossman et al. Health Care Status by gastrointestinal diagnosis and abuse history.
Gastroenterology 110: 999-1007 (1996).

[11] These include physical functioning, physical role limitations, emotional role limitations, social, functioning, bodily pain, general mental health, vitality and mental components.



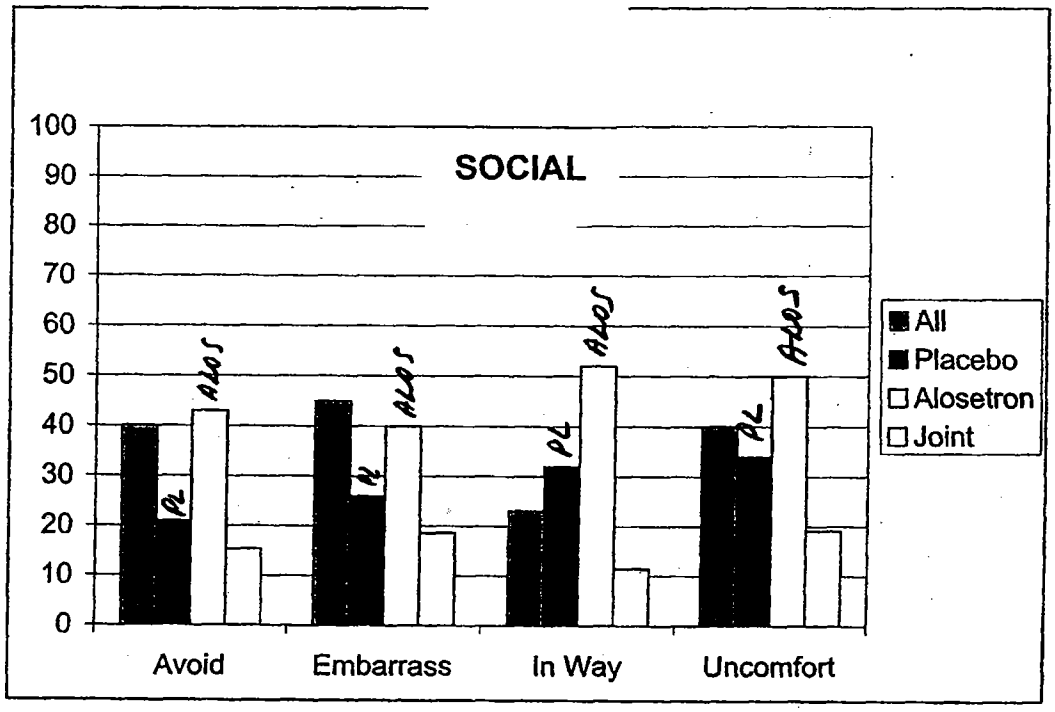




**Fig.2.- Results of IBS-QoL-Social and Work Scales in Pivotal Studies S3B3001 and – 3002, as computer by Dr. David Hoberman (Biometrics).**

Dr. Hoberman notes that the QoL scales appear to indicate a clear benefit compared to placebo. However, in these trials, the results are less impressive when actually counting the number of school or workdays lost as a result of the patient's IBS. Although the full distributions of lost days are statistically different alosetron and placebo, producing before-and-after weekly strata reveals that there is little difference between the groups in terms of the actual number of days lost.

# VIII. APPENDICES

## Appendix 1

The following Table summarizing safety data from 18 PK/PD studies with Lotronex has been formulated in conjunction with Dr. Gallo-Torres, Team Leader, GI drugs. The Table includes a summary of the major adverse events by study, which were reported in the Clinical Pharmacology and Biopharmaceutics section of Lotronex (Alosetron) supplement (NDA 21-107/S-005). Only adverse events in Alosetron treatment arms have been reported in the Table.

Overall, no serious adverse events were reported in the PK/PD studies (18 trials). There were no cases of Ischemic Colitis, Serious Complications of Severe Constipation or Bloody Diarrhea reported. Results from safety evaluation of these PK/PD studies were integrated into the overall safety summary appraisal entitled "The Randomized Clinical Trial Experience."

**Summary of the adverse events in the Clinical Pharmacology and Biopharmaceutics Studies (N 21-107)**

| Study # | N | IC | SCSC | Bloody Diarrhea | Constipation | Adb. Discomfort | Abd. Dist. | N/V | H/D |
|---|---|---|---|---|---|---|---|---|---|
| S3B10942 (SD PK, healthy Koreans) | 24 | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 9 |
| S3B10903 (SD PK in IBS Peds 6-11 yrs) | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | |
| S3B10934 (SD PK in IBS Peds 12-17 yrs) | 21 | 0 | 0 | 0 | IM | 4 (3F, IM) | 0 | 0 | 2 |
| S3B10947 (Mass Balance Study) | 7 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| S3B10935 (DDI w Fluoxetine) | 1 | 0 | 0 | 0 | 1 (1F) | 3 | 0 | 1 | 1 |
| S3B10936 (DDI w Amitriptyline) | 12 | 0 | 0 | 0 | 1 | 2 | 0 | 1 | |
| S3B10937 (DDI Hydrocodone/Paracetamol) | 12 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| S3B10938 (DDI w alprazolam) | 12 | 0 | 0 | 0 | 1 | 2 | 0 | 0 | 0 |
| S3B10939 (DDI w Ibuprofen) | 12 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| S3B10948 (DDI w Ocs) | 17 | 0 | 0 | 0 | 11 | 10 | 0 | 0 | 7 |
| S3B10906 (Effect on Colonic Transit Time) | 30 | 0 | 0 | 0 | 4 | 3 | 0 | 2 | 5 |
| S3BA1006 (Effect on CCK-induced Colonic Motility in IBS pts) | 22 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| S3BB1002 (Effects of MD on 24-h small bowel motility in IBS pts) | 8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| S3B10945 (Effect on Visceral hypersensitivity) | 24 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| S3BA1003 (Effect on Colonic Transit Time w Mebeverine+Alosetron vs. Alosteron in healthy females) | 13 | 0 | 0 | 0 | 18 | 5 | 6 | 0 | 4 |
| S3B10932 (Effect on QT in healthy females) | 20 | 0 | 0 | 0 | 4 (3 @ 1 mg, 1 @ 2 mg) | 3 (1 @ 1, 2 & 4 mg each) | 0 | 3 | 8 |
| S3B10901 (Effect on Serotonin Synthesis Rates) | 23 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| S3BA2002 (PET study of regional brain activity) | 47 | 0 | 0 | 0 | 11 | 0 | 0 | 0 | 0 |

IC= Ischemic Colitis, SCSC = Serious Complications of Severe Constipation, Abd. Dist. = Abdominal Distention, N/V = Nausea/Vomiting, H/D = Headache/Dizziness.

# APPENDIX 2
## Case Summaries for Each of The Patients

## Experiencing Ischemic Colitis

## I. Alosetron-Treated Patients

**Pt. #2829 [S3BA2001]**
**The 1996 Case**

- 33 y-old Caucasian woman
- 22 mg bid alosetron for 2 days, starting 17 Jul 96
- severe abdominal pain, 30 watery stools that day
- nothing found on exam in E.R. Levsin given
- pain worse, peritoneal signs; admitted
- colonic mucosal erosions at 40-80cm
- ISCHEMIC COLITIS diagnosed, withdrawn from study
- gradually recovered over he next 11 weeks

**Pt. #15687 [S3BA 3001]**
**The 1998b Case**

- 41 y-old Caucasian woman
- 1 mg bid alosetron for 54 days, starting 15 Jul 98
- abdominal pain, rectal bleeding; seen in E.R.
- did not respond to hyoscyamine; admitted
- severe segmental colitis involving the distal transverse and descending colon
- biopsy indicated **ISCHEMIC COLITIS**; withdrawn
- gradually recovered over subsequent weeks

**Pt. # 40398 [S3B20023]**

- 41y-old male
- 0.5 mg bid alosetron
- colonoscopy 56 days after an event of BLOODY Diarrhea was first reported
- continued on test medication after this event occurred
- COLONOSCOPY: 4 mm hyperplastic rectal polyp, otherwise normal colonic mucosa, and very small hemorrhoids.
- Biopsy from the rectosigmoid revealed focal fibrosis, consistent with a history of **ISCHEMIC COLITIS** and focal mild active colitis
- The event was categorized as NON-SERIOUS
- Subject exhibited no further symptoms of rectal bleeding or abdominal pain following alosetron cessation

**Pt. # 7195 [S3BA 3002]**
**The 1998a Case**

- 48 y-old Caucasian woman
- 1 mg alosetron, for 39 days, starting 21 Jan 98
- rectal bleeding and crampy abdominal pain
- local doctor prescribed fluid and fiber
- did not respond, pain worse, admitted at 3 a.m.
- colonoscopy showed mucosal sloughing
- **ISCHEMIC COLITIS** not attributed to test medication
- withdrawn, no more episodes of rectal bleeding

**Pt. # 34069 [S3BA30011]**
**The 1999 Case**

- 61 y-old Caucasian woman
- Received amitriptyline, raloxifene and multivitamins concurrently but denied use of estrogens, amphetamines and cocaine.
- 7 days of treatment with 1 mg bid alosetron
  -severe abdominal pain (10/28/99)
  -bloody diarrhea
  -WBC 19,700
- Hospitalized after 8 days of starting test medication
- Test medication discontinued
- CT Scan (10/29/99)
  -Mural thickening entire transverse colon, hepatic flexure
  -Changes were consistent with COLITIS but ISCHEMIC COLITIS was considered unlikely
- Hb 15.5 on admission; ↓ to 10.8 prior to Hospital discharge
- Had protein C deficiency and this may have played a contributory role
- **ISCHEMIC COLITIS** on pathological examination
- Discharged from the Hospital 7 days after admission. The event was considered resolved.

**Pt. # [S3B30031]**

- 64 y-old woman
- History of intermittent rectal bleeding, hyperplastic polyps, angina, emphysema, smoking
- 1 mg bid alosetron
- Concurrent meds.: Flax oil, Nitrospray, and Librium
- 29 days after initiating test med., she developed acute lower abdominal pain and noted repeated passage of small amounts of bright red blood per rectum.
- E.R. but not admitted to the Hospital.
- Test med. D/C
- Hb and WBC count normal
- COLONOSCOPY: dusky area in the splenic flexure consistent with **ISCHEMIC COLITIS.**
- Managed as an outpatient
- Condition considered resolved on a F/U visit 31 days after onset of symptoms.

**Pt. # 32451 [S3B30013]**

- 54 y-old woman
- History of pancolonic diverticulosis ns hemorrhoids
- Concurrent aspirin
- 1 mg bid alosetron for 3 days
- Abdominal discomfort/cramping and bright red rectal bleeding plus bloody diarrhea, nausea and vomiting.
- Test medication discontinued.
- Flexible sigmoidoscopy, done at the clinic, showed hemorrhoids and colitis. The investigator final/postprocedure diagnosis was diverticulosis and colitis which required clinically significant medical intervention.
- Colon biopsy: patchy chronic inflammation with FOCAL ISCHEMIC CHANGES
- Given ciprofloxacin
- Events resolved with 2 weeks

**Pt. # 49203 [S3B30012]**

**Little information available**

- 31 y-old F
- Reported as nonspecific colitis found on biopsy at the time of the early termination colonoscopy.
- Due to an episode of rectal bleeding following an episode of constipation, test med. was permanently D/C and the Pt. was W/D from the trial at which time the colonoscopy was performed.
- The investigator's opinion: nonspecific colitis or **ISCHEMIC COLITIS.**
- No further relevant information available.

**Pt. # 63223 [S3B30020]**

- 55 y-old women
- History of depression, fundoplication hysterectomy, lactose intolerance and **MICROSCOPIC COLITIS**
- 1 mg bid alosetron for 11 weeks
- Concurrent estrogens and loperamide
- Sudden onset of severe, crampy, lower abdominal pain associated with lower abd. Distension
- Frank blood per rectum initially with some solid, then diarrheal stool, and then just blood without any stool
- Treated with meperidine.HCl at the E.R.
- Admitted to Hospital for lower GI bleed (→anemia), abdominal pain/tenderness.
- Sigmoidoscopy: ulceration plus **ISCHEMIC COLITIS** (descending colon-proximal sigmoid colon. No confirmed on biopsy).
- WNL thrombosis panel.
- Negative stool cultures for salmonella, shigella and E-coli
- Drug D/C Pt. W/D from trial
- Event considered resolved 7 days after onset.

**Pt. # 72823 [S3B30020]**

- 64 y-old woman
- 1 mg bid alosetron
- Concurrent thyroxine, zolpidem, lansoprazole, alprazolam, estradiol and prosteroe.
- 1 day after initiating test med., she experienced constipation: treated with bisacodyl.
- Several hours later: cramping and bloody diarrhea
- Sigmoidscopy (at the physician's office): large amount of blood in the sigmoid colon.
- Test med. D/C. Treated with acetaminophen and ciprofloxacin.
- COLONOSCOPY (4 days later): **ISCHEMIC COLITIS**
- Histological features were not absolutely specific for IC
- Thrombosis panel test: WNL
- Event considered **disabling/incapacitating** although she was not hospitalized.
- Event resolved 6 days after onset.

**Pt. # 66556 [S3B30020]**

- 75 y-old woman
- History of diverticulosis and internal hemorrhoids
- 1 mg bid alosetron for 5 months
- Concurrent ramipril, verapamil, multivitamins, alprazolam, fiorinal, psyllium husk, ibuprofen alendronate sodium and acetaminophen
- Went to E.R. for severe lower abdominal crampy pain, nausea vomiting, rectal bleeding, chills and bloody diarrhea.
- Hospitalized, treated with meperidine, promethazine, dextrose + saline; placed on a clear liquid diet.
- Distressed and anxious on admission; abdominal tenderness.
- Liquid bowel movement with frank bleeding
- Test med. D/C
- COLONOSCOPY: edema, multiple areas of ulceration with exudates and hemorrhagic appearance and a few spots of bluish discoloration.
- Biopsy: **ISCHEMIC COLITIS**
- Events resolved 7 days after onset.

**Pt., # 72824 {S3B 30020}**

- 57 y-old woman
- History of severe reflux
- 1 mg bid alosetron
- Concurrent conjugated estrogens, atenolol, lansoprazole and clonazepam.
- Abd. cramping, diarrhea, chills and rectal bleeding ca. 4 days after starting test med.
- Seen in the clinic 3 days for the same complaints + soreness.
- Inadequate sigmoidoscopy (Pt's pain)
- Test med. D/C
- COLONOSCOPY (3 days later): non-specific colitis in the descending and sigmoid colon
- Biopsy: **ISCHEMIC COLITIS**
- Thrombosis panel test: WNL (the pt.'s symptoms had resolved at that time)
- Events considered **disabling/incapacitating** although she was not hospitalized.
- Event considered self-limiting.
- Events resolved within 7 days of onset.

**Pt. # 78134 [S3B30020]**

- 20 y-old woman
- History of Kidney stone and allergy to penicillin; smaller
- 1 mg bi.d alosetron
- Concomitant levonorgestrel/ethinyl estradiol for birth control.
- Following receipt of 4 doses of alosetron (3 days into trial. She developed, nausea, vomiting and severe crampy abdominal pain in the LLQ which she described as worse than her usual pain due to IBS.
- E.R.→diffuse tenderness of the abdomen (no fever, vaginal discharge, signs of dehydration or urinary symptoms).
- Hospitalized; treated with dicyclomine, I.V. fluids and bowel rest. The following day: rectal bleeding and blood diarrhea with mucus. Rectal bleeding resolved one day after onset.
- COLONOSCOPY: diffuse erythema with loss of vasculature and a few shallow ulcerations in descending colon and splenic flexure, with mild acute and chronic inflammation and fibrosis of the lamina propria consistent with **ISCHEMIC COLITIS.**
- Test med. Was D/C
- The IC was resolved with 4 days.
- Pt. Discharged from the hospital on loperamide and hyoscyamine

**Pt. # 80357 [S3B 30020]**

- 51 y-old woman
- History of diverticulosis
- 1mg bid alosetron
- Concurrent meds.: famotidine, hyoscyamine sulfate, alprazolam. Donnatal, Esgic and progesterone.
- 3 weeks after initiating test med. she began complaining of abdominal pain and distress, abdominal spasms and constipation; also anxiety and possible allergic Rx. to anti-inflammatory medication.
- Treated with lactulose, Senokot, and Fleet Phospho-Soda with no relief.
- COLONOSCOPY: multiple diverticula; findings consistent with diverticulosis or **ISCHEMIC COLITIS**
- Hospitalized; test med. D/C.
- Events resolved within 3 weeks of onset of initial symptoms.

**Pt. # 82125 [S3B30020]**

- 61 y-old woman
- History of NSAID use
- Conjugated estrogens and Accuretic
- Began to experience hard stools and straining while taking alosetron but was passing 2 to 3 stools per day.
- 7 days after initiation test med. She took NAPROXEN; developed stomach pain first, then diarrhea, which became bloody several hours later. She also reported abd. cramping.
- At the E.R. she complained of nausea, vomiting and hematochezia .
- COLONSCOPY: severe ulcerations, erythema, and friable tissue of the descending colon and distal and transverse colon consistent with **ISCHEMIC COLITIS.**
- CT of the abdomen and pelvis moderate thickening of the proximal 2/3 of the descending colon extending to above the splenic flexure, ascending colon.
- Admitted to Hospital. Test med. was D/C.
- Although histological feature were most consistent with pseudomembranous colitis, IC was not completely ruled out.
- On the day of discharge, 3 days after admission, she noted no blood in her stool.
- The event was considered resolved ca. 2 weeks after onset.

**Pt. # 69433 [S3B30020]**

- 36 y-old Caucasian woman.
- 1 mg bid alosetron
- Concomitant meds: tiazadone, Xanax, Motrin, clescin T, benzyl peroxide, gas X.
- Co-morbid conditions: asthma, bronchitis, ovarian cysts, arthritic foot, back, acne, depression, anxiety.
- On month 4 after the start of test med. she had severe abd. pain and bloody diarrhea
- E.R.: severe abd. pain, bloody diarrhea; given I.V. fluids.
- COLONSCOPY: segmental colitis and probale **ISCHEMIC COLITIS**
- Test med. D/C; Pt. W/D from trial
- Pt. did not undergo hospitalization or surgical procedure.
- The investigator **did not consider this a SAE.**
- The events resolved 9 days after onset.

| Pt. # 71843 [S3B30020] | Pt. # 65448 [S3B30020][a] |
|---|---|
| • 37 y-old Caucasian woman<br>• Co-morbid Conditions: anxiety<br>• 1 mg bi.d. alosetron<br>• Concomitant meds: Paxil, Imodium<br>• 2.5 months after the start of test med., Pt. experienced sudden onset abd. cramping and diarrhea followed by bloody stools a few hours later.<br>• COLONOSCOPY 2 days later: segmental colitis with patchy erythema, erosions and edema of splenic flexure and mid-descending colon.<br>• Biopsy: non-specific mild abnormalities suggestive of **ISCHEMIC COLITIS**; very mild, focal acute inflammation with focal superficial erosions and minimal focal glandular attenuation.<br>• The Pt. was neither hospitalized nor underwent a surgical procedure.<br>• The event resolved in 4 days. | • 67 y-old woman<br>• Co-morbid Conditions: diverticulosis colelithiasis, hypothyroidism, smoking, colonic polyps.<br>• 1 mg bid alosetron<br>• Concomitant meds.: estrogens<br>• On Day 4 after the start of therapy Pt. was hospitalized because of rectal bleeding, lower abd. pain, hypotension, ventricular tachycardia.<br>• Abd. CT scan: peritonitis, free air and intra abd. fluid.<br>• Reason for hospitalization (duration = 8 weeks): perforation 2.8 cm colon, diverticulitis.<br>• Surgical procedure: sigmoid colon resection, descending colon colostomy.<br>• Developed sepsis, stroke, dysphagia, hemiparesis; life-threatening DIC; cardioversion.<br>• Post-operative: tachycardia required cardioconversion<br>• ICU: peritonitis, septic, methicillin-resistant staph. aureas, abd. wound infection infection, DIC, respiratory distress required intubation, stroke with right-side hemiparesis.<br>• Extended Care Facility: rehabilitation 3 months<br>• Outpatient physical therapy: 5 months.<br>• This event did not resolve. It left permanent sequelae of hemiparesis, colostomy and personality changes.<br><br>[a]The sponsor did not include this patient among the cases of IC, but patient's attorney had specimen of resected colon tissue reviewed by pathologist and claims it demonstrated **ISCHEMIC COLITIS.** |

# APPENDIX 2

## II. Placebo-Treated Patient

Placebo Case
**Pt. # 8245 [S3BA3003]**
27 y-old woman

- Co-morbid conditions: No information
- **Placebo bid**
- Concurrent meds.: No information
- Developed bloody diarrhea after 299 days on test medication.
- FLEXIBLE SIGMOIDOSCOPY: finding interpreted by the endoscopist as representing ISCHEMIC COLITIS
- Diagnosis of IC was not confirmed on biopsy ("lamina propria congestion and edema").

# APPENDIX 3
## Case Summaries for Each of The Patients Experiencing Serious Complications of Severe Constipation

## I. Alosetron-Treated Patients

**Pt. # 65385 [S3B30020]**

- 76 y-old woman
- Co-morbid Conditions: coronary artery disease, diverticular disease, internal hemorrhoids
- 1 mg bid alosetron
- Concomitant meds: paroxitine, calcium,
- 4 months after the start of therapy she was hospitalized because of nausea, vomiting, cramping abd. pain, distention, obstipation
- X-ray: partial small bowel obstruction, increased stool in the rectum and rectosigmoid.
- Pt. did not undergo surgical procedure.
- The reason for hospitalization was partial **small bowel** obstruction. The duration of hospitalization was not specified.
- The event resolved in 11 days. There was no permanent sequelae.

**Pt. # 67694 [S3B30020]**

- 56 y-old woman
- Co-morbid conditions: hypertension, PUD, abd. adhesions, hyperplastic rectosigmoid polyps
- 1 mg bid alosetron
- Concomitant meds.: conjugated estrogens, tolterodine, trazodone, citalopram, tramadol, amlodcipine/benazepril, rofecoxib
- On Day 27 after start of test med., Pt. was hospitalized because of crampy peri-umbilical abdominal pain, nausea, vomiting, lower abdominal pain, distention. Constipation day prior, hypotensive, hemoccult positive gastric fluid, stool hemoccult positive, dehydration, acute renal failure, pancreatitis (amylase 1120)
- X-ray – Multiple air-fluid levels
- Pelvic scan – complex left ovarian cyst
- CT Abd – transmural thickening proximal small bowel and entire left colon
- Upper endosc. – mild gastritis
- Colonoscopy –**fecal impaction**
- The reason for hospitalization was **Toxic MEGACOLON** with diffuse transmural ischemic gangrenous colitis and purulent septicemia. "Stercoraceous obstruction. megacolon and secondary ischemia"
- **The Pt. underwent a surgical procedure: total abdominal colectomy with Brook ileostomy.**
- Duration of hospitalization: 2 weeks
- Sequelae: ileostomy (? Follow-up procedure?)

**Pt. # 80655 [s3B30020]**

- 26 y-old woman
- Co-morbid conditions: hypertension, morbid obesity
- 1 mg bid alosetron
- Concomitant meds.: birth control pills, Lotrel, docusate, sennosides
- On month 4 of therapy, Pt. was hospitalized because of severe crampy lower abd. pain.
- COLONOSCOPY: Large fecal mass (5 X 13 cm on barium enema), erythema and superficial ulcerations distal to fecal mass.
- PATHOLOGY: Ischemic changes; focal mucosal ulceration, crypt loss, fibrosis, vascular ectasia, flattening surface epithelium.
- The reason for hospitalization, which lasted 4 days, was **impaction with secondary ischemia.**
- The Pt. did not undergo surgical procedure.
- The event resolved in 6 days. It did not leave sequelae, as shown on repeat colonoscopy 8 weeks after the event.

**Pt # 83206 [S3B30020]**

- 47 y-old woman
- Co-morbid conditions: personality disorder, somatization disorder.
- 1 mg bid alosetron
- Concomitant meds.: Vicodin, Percocet, Vicoprofen prn for pain
- On week 10 after the start of treatment, the Pt. was hospitalized because of left abdominal pain of 2-week duration.
- CT scan: colon full of stool
- The reason for hospitalization, which lasted 3 days, was **fecal impaction.**
- The Pt. did not undergo surgical procedure.
- The event resolved within 3 days and it did not leave sequelae.

**Pt. # 88034 [S#B30020]**

- 50 y-old woman
- Co-morbid conditions: No info.
- 1 mg bid alosetron
- Concomitant meds.: No info
- 6 weeks after the start of therapy the Pt. was hospitalized with left lower quadrant abdominal discomfort, constipation, and rectal bleeding
- Urinary tract infection –pyuria
- Treated – I.V. fluids, antibiotics
- Rectal bleeding due to hemorrhoids
- The reason for hospitalization, which lasted 3 days, was **constipation**.
- The Pt. did not undergo surgical intervention.
- The event resolved in 3 days and did not leave sequelae.

**Pt. # 87373 [S3B30020]**

- 67 y-old woman
- Co-morbid conditions: hiatal hernia, adenomatous polyps.
- 1 mg bid alosetron
- Concomitant meds.: Estrogens, salmetrol xinofoate, albuterol, loperamide, fexofenadine hydrochloride, atorvastatin, omeprazole, citalopram hydrobromide, antihypertensives
- On month 3 of therapy, the Pt. was hospitalized because of abdominal pain, vomiting, dehydration, and diarrhea
- Abdominal x-ray – mild small bowel ileus and mild hepatomegaly
- Lab – leucocytosis
- Stool tests – negative culture, negative ova and parasites
- Treated I.V. fluids, famotidine, promethazine
- The reason for hospitalization, which lasted 4 days, was **SMALL BOWEL ILEUS.**
- The Pt. did not undergo surgical intervention.
- The event resolved in 4 days and did not leave sequelae. Test med. was restarted upon resolution of the event.

**Pt. # 2330 [S3BB3002]**

- 45 y-old woman
- 4-year history of abdominal complaints but all examinations were normal
- 1mg bid alosetron
- Within 10 days of starting test med. complained of recurrent lower abd. pain.
- Hospitalized.
- Abd. US suggested CDz and suspected stenosis in the terminal ileus.
- W/D from the trial
- Surgery 2 days later:ileal stenosis and **associated ileus** confirmed.
- CDz was pre-existing
- Ileus was considered severe and regarded as resolved post surgery.
- F/U info. notes that the $CD_z$ with ileal stenosis was considered resolved 2 weeks after onset.

**Pt. #2541 [S3BB3002]**

- Co-morbid conditions: No info.
- 1 mg bid alosetron
- Concurrent meds.: No info
- Hospitalized ca. 10 weeks after starting test med. because of moderate abdominal pain.
- Test med. interrupted.
- Symptoms initially considered related to possible acute appendicitis but abd. X-ray showed **CONSTIPATION**; US scan was negative.
- Symptoms resolved spontaneously within 4 days.

**Pt. # 3773 [S3BB3002]**

- 54 y-old woman
- Co-morbid conditions: No info.
- 1 mg bid alosetron
- Concomitant meds.: No info.
- 1 week after starting test med. she developed a **worsening of constipation** and abdominal pain
- She had very hard stools, which had to be **digitally removed.**
- Hospitalized [she had been hospitalized previously with similar symptoms]
- Treated with I.V. metamizole•.Mg and an enema.
- Test med. stopped 2 days after the onset of the event.
- Pt. W/D from the trial.
- Normal hematology + biochem. Tests.
- Discharged from Hospital
- Her condition was resolved one week after onset.

**Pt. # 176167 [S3B30025]**

- 56 y-old woman
- Co-morbid conditions: No info.
- 1 mg bid alosetron
- Concomitant meds. No info.
- considered **disabling** by the investigator.
- 2 weeks after starting test medication, the Pt. reported she was constipated but did not inform the Investigator until one week later.
- Treated with psyllium husk for 10 days, as per protocol.
- 4 weeks after stopping laxative treatment and 8 weeks after initiating test medication, Pt. reported sores in her mouth and feeling unwell. Developed flu-like illness, vomited > 10 times but did not report any bleeding or diarrhea.
- Hospitalized the following day. Silent colon. Intestinal symptoms with vomiting, nausea, abd. cramps and shaking.
- Treated with pethidine, codeine, dicyclomine, dimenhydrinate and I.V. saline.
- Test med. D/C. Pt. W/D from the trial.
- Nil by mouth.
- Abdominal X-ray: severe intestinal distention and **severe intestinal subocclusion**
- Lencocytosis. Started on clear fluids 2 days later and her NG tube was removed.
- Discharged from hospital 2 days later.
- Her condition resolved (within 5 days of onset)

**Pt. # 174139 [S3B30017]**

- 21 y-old woman
- Co-morbid conditions: asthma
- 1 mg bid alosetron
- Concomitant med.: salbutamol, beclomethasone and salmeterol.
- Ca. 2 weeks after starting test med. she experienced lower abd. discomfort with **increasing hardening of her stools and constipation.**
- 2 days later, she noticed the onset of bright red rectal bleeding with discharge of mucus and had been vomiting.
- Flexible sigmoidoscopy performed; biopsies taken.
- Small fissure noted in the anal region.
- One Bx sample=normal. The other revealed mucin depletion and attenuation of the colonic mucosa as well as a few muciphages and superficial microhemorrhages, which were possibly pathological. [No evidence of colitis or IBD]. The pathologist considered that the changes were non-specific but may have represented the site of healed erosion.
- A gastroenterologist considered that the bleeding was most likely from the anal fissure (secondary to the constipation).
- Pt. was not hospitalized. Treated with Proctosedyl.
- Test med. was temporarily interrupted.
- Both the bleeding from the anal fissure and constipation were resolved within 20 days of onset of the constipation.
- The events were considered **disabling** by the investigator.

# APPENDIX 3

## II. Placebo-Treated Patients

**Pt. # 23647 [S3B3006]**

- 71 y-old woman
- Co-morbid conditions: No info.
- **PLACEBO bid**
- Concomitant meds.: No info.
- 15 weeks after initiating test med. Pt. developed abdominal pain and vomiting.
- Test med. Interrupted.
- Went to E.R.
- X-ray: sibileus
- Barium meal: **no passage through the terminal ileum into the colon**
- LABORATORY (2 days later): slightly dilated small
- bowels and an adhesion close to the terminal ileum,
- which was diagnosed as the cause of her symptoms. No other significant findings.
- Left Hospital after 1 day.
- Condition resolved 4 days after onset.
- 10 days later there were no post-operative complications and she recommenced test medication.

**Pt. # 6585 [S3BA3002]**

- 31 y-old woman
- History of endometrioma
- **PLACEBO bid**
- Concomitant meds.: No info.
- Ca. 2 weeks after starting test med. she experienced severe diarrhea, vomiting and abd. pain.
- Hospitalized 6 days later with uncontrollable diarrhea, vomiting and abd. pain. Diagnosis at that time: possible endometriosis, rule out a small bowel obstruction and adhesions.
- Diagnosis of **partial bowel obstruction** made 10 days after admission.
- Test med. D/C at entry into the Hospital.
- W/D from trial.
- Event resolved ca. 6 weeks after onset.

**Pt. # 34911 [S3B30011]**

- 67 y-old women
- Co-morbid conditions: No info. other than sigmoid Diverticulosis.
- **PLACEBO bid**
- Concomitant meds. No info.
- 2 months after initialing test medication she was seen in the E.R. for severe lower abd. cramps/pain, nausea and chills.
- Hospitalized.
- Dehydrated; increased blood pressure; passed 2 blood clots along-with large stool
- X-ray: **"small colon paralyzed"** for a little while.
- Treated with an unspecified I.V. antibiotic.
- Diagnosed with hematochezia secondary to an anorectal source.
- Test med. D/C. Pt. W/D from trial
- Events resolved 3 days after onset.
- Pt. discharged home from the Hospital. Started treatment with hyoscyamine sulfate.

## APPENDIX 4

### 190586 [S3B30033]

- 61 y-old woman
- History of ovarian cysts for which she had salpingooophorectomy
- 1 mg bid alosetron
- Concurrent meds: diclofenac and felodipine
- 3 days after initiating test medication she developed abdominal pain and constipation.
- Test med. D/C 6 days later and the symptoms resolved within 13 days of onset.
- Pt. decided to W/D from study (she received test med. for a total of 10 days)
- A week after W/D from the trial, during the F/U phase, the pt. attended Surgery an outpatient and reported alternating bowel habit. Referred for sigmoidoscopy but this was not done by the time of rerouting.
- 6 weeks after D/C of test med. → E.R. with severe acute abdominal pain and blood in her stools (both started 3 days before E.R.)
- **Emergency laparotomy** with resection of necrotic ileum and division of adhesions.
- Both the acute abd. pain and blood in stool resolved within 10 days. Discharged on the day of resolution.

Final Diagnosis: small bowel ischemia secondary to adhesions from previous surgery.

### Pt. # 174138 {S3B30017]

- 50 y-old woman
- Had history of non-insulin dependent diabetes, hyper cholesterolemia and pethidine allergy.
- 1 mg bid alosetron
- Concurrent medication: pethidine
- 4 days after initiating test med. she developed an acute onset of crampy pain in the left iliac fossa, followed 1 h later by diarrhea with mucus and dark blood containing clots. She vomited twice.
- Admitted to the Hospital for investigation of the rectal bleeding.
- Test med. D/C Pt. treated with paracetamol, metoclopramide, hyoscine and temazapam.
- She had a low grade temperature and her mild abdominal pain although the rectal bleeding had stopped.
- COLONOSCOPY (4 days after the onset of symptoms): patchy discontinued colitis extending from the transverse to the descending colon, with a process (3rd fragment). There was reduced thickening and some loss of crypts, with a mild increase in acute and chronic inflammatory cells within the lamina propria and prominent exocytosis of neutrophils through the attenuated surface epithelium. The pattern was considered by pathologist to be consistent with **NON-SPECIFIC COLITIS.**
- Received further treatment with hydrocortisone, ampicillin, gentamycin, metronidazole, prednisolone enema and prednisone.
- Final diagnosis: **TRANSIENT, PATCHY, NON-SPECIFIC COLITIS.**
- The event was considered resolved after 7 days. She was then discharged from the Hospital.

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/s/

Hugo Gallo Torres
3/7/02 09:41:50 PM
MEDICAL OFFICER

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

sNDA: 21-107
SPONSOR: GlaxoSmithkline (formerly Glaxo Wellcome, Inc)
DRUG: Alosetron Hydrochloride (LOTRONEX™) Tablets
DATE OF ORIGINAL SUBMISSION: 29 June, 1999
DATE OF ORIGINAL APPROVAL: 9 February, 2000
VOLUNTARY WITHDRAWAL FROM THE MARKET: 28 November, 2000
DATE OF sNDA SUBMISSION: 7 December, 2001
INITIATION DATE: 16 MAY 2000
EARLY TERMINATION DATE: 28 NOVEMBER 2000
MEDICAL OFFICER: Marcelo A. Barreiro, MD, MSc
MATERIAL REVIEWED: **S3B30025 – A 24 WEEK MULTICENTER, *RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF* QUALITY OF LIFE (QOL) WITH ALOSETRON 1 MG BD VERSUS PLACEBO IN FEMALES WITH NON-CONSTIPATED IRRITABLE BOWEL SYNDROME (IBS)**

## EXECUTIVE SUMMARY THERE WERE NO CASES OF ISCHEMIC COLITIS (TWO SUSPECTED), SERIOUS COMPLICATIONS OF CONSTIPATION OR GI BLEEDING (ONE SUSPECTED), REPORTED IN 1027 PATIENTS EXPOSED TO ALOSETRON

### SUMMARY OF RESEARCH PROTOCOL

- **DESIGN**: Twenty four week, Phase IIIb study of QOL with alosetron 1mg bd versus placebo in females with non-constipated irritable bowel syndrome. Randomization was 2:1 for alosetron 1 mg bd and placebo bd groups
- **DOUBLE BLIND:** Yes **CONTROLS:** Placebo
- **NUMBER OF SITES:** Two hundred and forty three
- **COUNTRIES:** Nine: Belgium (34), Canada (42), Denmark (21), France (52), Greece
- (20), Norway (12), Spain (37), Sweden (18), UK (37)
- **NUMBER OF PATIENTS:** The study randomized 1548 patients Intent to Treat (ITT) population, of whom 1547 (the Safety Population) took at least one dose of study medication: 1027 on alosetron 1 mg bd and 520 patients on placebo bd. Due to early termination of the study, only 245 patients (16 %) completed the study. Of those who discontinued the study prematurely (1303/1548, 84 %), the majority (nearly 60 %) were as a result of the early termination of the by the sponsor, the proportions distributed equally between the two treatment groups.
- **DIAGNOSIS AND ENTRY CRITERIA:** Female ambulatory out-patients, at least 18 years of age, and with at least 12 weeks' history of non-constipated IBS were

enrolled. IBS was defined as abdominal pain and/or discomfort associated with altered bowel function, and subjects must have reported abdominal pain and/or discomfort on at least seven days during the two-week screening period, in addition to to having met all other inclusion and exclusion criteria, to be eligible for randomization

- **PRIMARY ENDPOINTS: Safety:** 1) The impact of two strategies for the management of constipation: laxative use versus drug holiday on the ability of subjects to continue their participation in the study; 2) the effectiveness of the two strategies for management of constipation and 3) the incidence of AEs and abnormalities in laboratory values. **Efficacy:** Change in two domains of the IBSQOL: food and social functioning
- **OTHER ENDPOINTS:** Changes in the other seven domains of the self-rated IBSQOL over the 24 week treatment period and relief of other symptoms used in IBS clinical trials. **DUE TO THE EARLY TERMINATION OF THE STUDY, EVALUATION OF SAFETY PARAMETERS ONLY WAS PERFORMED.**

**SUMMARY OF SAFETY RESULTS** Safety was evaluated by summarizing treatment-emergent AEs and changes from baseline in laboratory values. The effect of constipation was not analyzed due to the limited amount of data.
Subjects ranged in age from 18 to 92 years (mean 47 years) and >99 % were white.
Twenty percent of the total population used hormonal contraceptives.
In the alosetron group 51 % of subjects had up to 91 days of exposure to study medication, 45 % had 92-175 days exposure, and 4 % had over 175 days of exposure.

- **AEs** Sixty six percent of patients on alosetron (676/1027) and 52 % (269/520) of patients on placebo, reported AEs
  The most common AE was constipation (357 [35 %] on alosetron and 30 [6 %] on placebo), abdominal pain/discomfort (82 [8 %] and 30 [6 %], respectively), headache (77 [7 %] and 34 [7 %], respectively), and musculoskeletal pain (32 [3 %] and 30 [6 %] respectively).
- **SAEs** Eighteen patients (2 %) on alosetron and 14 subjects (3 %) on placebo reported SAEs, of which eight were considered treatment related: possible bowel obstruction, choleretic diarrhea, gastroduodenitis superficialis, supraventricular ectopics. Placebo group: abdominal pain (n=2), congenital anomalies in an infant, rhabdomyolysis.

***Reviewer's Comments:*** *Analysis of the case narratives of these patients prompts the following comments:*
*Subject number 176167 (SAE: Possible bowel obstruction) This 56 y/o/f developed stomatitis with ulceration, nausea, vomiting, abdominal pain, shaking, and a silent abdomen, eight weeks after being on Alosetron 1 mg BID. The patient showed no (systemic) signs of the flu. She was hospitalized and withdrawn from the study. The patient was treated with naso-gastric suction, intravenous saline and, among other medications, codeine and dicyclomine. X-rays demonstrated severe intestinal distention. The patient had an uneventful recovery.*
***This picture is consistent with an ileus, and not with an intestinal obstruction.*** *The ileus was probably caused by Alosetron effect on intestinal motility. Whether or not the intestinal circulation was also compromised is difficult to tell.*

*Subject number 176244 (SAE: Choleretic diarrhea) This 44 y/o/f with history of bowel resection (time, reason, length and site unspecified) developed severe abdominal pain two months after being placed on Alosetron 1 mg BID. She was hospitalized and apparently underwent two endoscopies: the first, a "short colonoscopy" revealed inflammation, the second, a "longer colonoscopy" (interval between them unspecified) was normal. An abdominal ultrasound showed submucosal thickening. Biopsies were reported as normal. Treatment with cholestyramine was started. The patient was discharged from the hospital in a week. The event resolved in approximately four and a half months from onset. The investigator's opinion was that this event was related to Alosetron. This reviewer has difficulty understanding how choleretic diarrhea of four and a half months duration could have developed as consequence of Alosetron administration, unless* ***ischemic colitis****, superimposed on a shorter bowel, further reduced absorptive surface and induced a short bowel syndrome-type of clinical picture.*
*Subject number 177252 (Investigator number incorrectly listed as 85553; correct number is 8553) This 57 y/o/f was suspected to have a descending colon tumor, "severe in nature and considered clinically significant", 10 weeks after being placed on Alosetron 1 mg BID. The study drug was permanently discontinued. Colonoscopy showed no signs of cancer, the event resolved 23 days after onset. Review of CRFs fails to add substancial evidence as to what symptoms prompted the suspicion of colonic neoplasia. Of note, ischemic changes in the colon, can mimic neoplasia, and within a few days (three to five) disappear.*
*Subject number 177280 This 73 y/o/f developed constipation 11 days after receiving Alosetron 1 mg BID and discontinued study medication. One week later developed abdominal pain, worse in the RLQ, diarrhea and severe rectal bleeding. She was hospitalized. Gastroscopy was non-diagnostic. Proctoscopy reveal an anal fissure. The investigator's final opinion was that the cause of the bleeding was the anal fissure.The investigator's initial reporting (see Attachment 1) was "rectal bleeding with abdominal pain", amended to "anal fissure". The cardinal symptom of anal fissure is pain. Exceptionally an anal fissure produces severe bleeding.* ***This reviewer's opinion is that the overall picture, as reported, is most compatible with ischemic colitis, and that the anal fissure was an incidental finding.***
*Subject number 178361 This 47 y/o/f had a syncopal episode 17 days after being on Alosetron 1 mg BID. Atrial fibrillation was diagnosed and treated with atenolol. The patient was discharged from the hospital the day after admission.* ***This reviewer concurs with the investigator's opinion that there was a reasonable possibility of the event being related to study medication.***

- **Deaths:** two patients one in each study group died of causes unrelated to study treatment, according to the investigator's opinion. The death in the Alosetron-treated group is summarized below.

**Protocol Id:** S3B30025
**Investigator number** 84879
**Subject number:** 175731
**Treatment number:** 117
**Case Id:** B0084878A
This 71 year old female received oral alosetron 1mg twice daily for the treatment of irritable bowel syndrome. She had a history of hypertension and oedema of the legs and

concurrent medication included calcium carbonate, bromhexine, buscopan and losartan. Two days after starting study medication the investigator visited the subject at home during the evening. The subject's family reported that she was feeling unwell and was confused. Her blood pressure was 130/80mmHg and the investigator considered that the subject's condition was satisfactory, although she did have a small amount of oedema in her legs. The investigator stated that there were no clinical signs of a possible cardiac arrest. Study medication was not withdrawn, she was given alprazolam and zopiclone and went to bed, but during that night she had a cardiac arrest and died. No autopsy was performed. The investigator considered that the event may have been caused by the subject's concurrent disorders of hypertension and oedema, but there was no reasonable possibility that it may have been caused by study medication.
***Reviewer's Comment:*** *Although it is difficult to ascribe causality in cases like this, this reviewer continues to be concerned about these cases of cardiac arrythmia associated with Alosetron administration.*

- **RELATED TO STUDY DRUG** The most common AEs related to study drug were constipation (353 [34 %] on alosetron and 27 [5 %] on placebo) and abdominal pain discomfort (58 [6 %] on alosetron and 15 [3 %] on placebo).
- **CAUSE OF WITHDRAWAL** A total of 211 (21 %) patients on alosetron and 45 (9 %) on placebo were withdrawn because of of AEs, the most common being constipation (130 [13 %] on alosetron and 6 [1 %] on placebo) and abdominal pain discomfort (40 [4 %] on alosetron and 9 [2%] on placebo)
- **SERIOUS COMPLICATIONS OF CONSTIPATION** None reported
- **ISCHEMIC BOWEL** None reported. Two suspected.
- **UNDIAGNOSED RECTAL BLEEDING** None reported. One suspected to be ischemic colitis.

**CONCLUSIONS FROM THIS STUDY** Safety analysis of these 1027 patients follows a similar pattern of AEs/SAEs as other Alosetron studies. The need for a detailed study of extra-intestinal AEs, in particular cardiac arrythmias and angina pectoris-like chest pains, is reinforced. The 47 y/o/f who developed a syncopal episode as a consequence of a supra-ventricular tachycardia, had no previous history of cardio-vascular disease. The sudden death in the 71 y/o with history of hypertension and leg edema, also leaves some questions unanswered.

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/s/
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Marcelo Barreiro
3/5/02 12:36:46 PM
MEDICAL OFFICER

Hugo Gallo Torres
3/5/02 06:42:21 PM
MEDICAL OFFICER

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

sNDA: 21-107
SPONSOR: GlaxoSmithkline (formerly Glaxo Wellcome, Inc)
DRUG: Alosetron Hydrochloride (LOTRONEX™) Tablets
DATE OF ORIGINAL SUBMISSION: 29 June, 1999
DATE OF ORIGINAL APPROVAL: 9 February, 2000
VOLUNTARY WITHDRAWAL FROM THE MARKET: 28 November, 2000
DATE OF sNDA SUBMISSION: 7 December, 2001
INITIATION DATE: 6 APRIL, 2000
EARLY TERMINATION DATE: 28 NOVEMBER, 2000
MEDICAL OFFICER: Marcelo A. Barreiro, MD, MSc
MATERIAL REVIEWED: **S3B30026 = EIGHT WEEK, MULTICENTER, RANDOMIZED DOUBLE-BLIND TRIAL ON NON-CONSTIPATED PATIENTS WITH IRRITABLE BOWEL SYNDROME TREATED WITH 1 MG ALOSETRON TWICE A DAY COMPARED TO 2 MG ALOSETRON ONCE A DAY**

## EXECUTIVE SUMMARY THERE WERE NO CASES OF ISCHEMIC COLITIS, SERIOUS COMPLICATIONS OF CONSTIPATION OR UNEXPLAINED GI BLEEDING IN 960 PATIENTS EXPOSED TO ALOSETRON

**SUMMARY OF RESEARCH PROTOCOL** The study was conducted in non-constipated IBS female subjects. The one week screening phase was designed to eliminate constipated subjects. Randomization was on a 1:1 bases to either treatment group. Primary and secondary objectives were recorded by the patients in a diary card at daily or weekly intervals, as per protocol.
**Core Study:** Medication (drug or placebo) BID for eight weeks. If a patient experienced adequate relief of her IBS symptoms during two of the four week period, and if after discontinuation of therapy, the symptoms recurred in the same degree as before the start of the study, the patient could be entered into an **extension of the study** on Alosetron 1 mg BID for up to six months. Primary and secondary objectives were recorded weekly on diary cards.

- **DESIGN** Phase IIIb, international, randomized, comparative study of two treatment groups
- **DOUBLE BLIND** comparing Alosetron 1 mg BID with Alosetron 2 mg daily
- **NUMBER OF SITES, COUNTRIES** Subjects were randomized at 239 centers in Germany, 23 centers in Switzerland, and 10 centers in Austria.
- **NUMBER OF PATIENTS** Nine hundred fifty seven patients were randomized and of those, 640 completed the eight weeks treatment phase. Three hundred seventeen patients withdrew prematurely (see Table 1). One hundred and thirty six patients were

entered in the six-month extension phase, but only two completed the extended phase. One hundred and eighteen were withdrawn due to termination of the study (see Table 2).

**Table 1**
**Reasons for Withdrawal from the Study**
**(n=317)**

| REASON FOR WITHDRAWAL | # OF PATIENTS |
|---|---|
| ADVERSE EVENTS | 167 |
| FAILED TO RETURN | 18 |
| LACK OF EFFICACY | 27 |
| EARLY TERMINATION OF STUDY | 83 |
| SUBJECT DID NOT WISH TO CONTINUE | 7 |
| OTHER REASONS | 15 |

**Table 2.**
**Patients Entered in 6-Month Extension Phase**
**(n=136)**

| FATE OF PATIENTS ENTERED | # OF PATIENTS |
|---|---|
| COMPLETED THE PHASE | 2 |
| WITHDRAWN BECAUSE OF LACK OF EFFICACY | 5 |
| ADVERSE EVENTS | 5 |
| DID NOT WISH TO CONTINUE | 1 |
| WITHDRAWN DUE TO OTHER REASONS | 5 |
| WITHDRAWN DUE TO EARLY TERMINATION OF STUDY | 118 |

**SUMMARY OF EFFICACY RESULTS** Due to the early termination of the study only population demographics and safety data were analyzed.

**SUMMARY OF SAFETY RESULTS** Of the 957 subjects randomized in the core study all were white females; 84 % were 18 to 64 years of age and 15.3 % were 65 years or older
The **safety population** consisted of 957 randomized patients and three patients who received Alosetron before randomization, for **a total of 960 patients.**

- **AEs 1) Core Study** 360/960 (37.5 %) reported AEs. Alosetron 1 mg BID: 36.7 % of patients; Alosetron 2 mg daily: 37.9 % The most common organ-system involved was the gastrointestinal system (see Table 3).

**Table 3**
**Gastrointestinal Adverse Events**
**(Reported by more than 10 patients)**

| ADV. EVENT | CORE STUDY | EXTENSION PHASE | TOTAL #(%) |
|---|---|---|---|
| Constipation | 68 | 53 | 123 (12.8 %)* |
| Colic | 7 | 23 | 31** |
| Nausea | 13 | 13 | 26 |
| Abd. pain | 8 | 9 | 17 |
| Diarrhea | 6 | 9 | 15 |
| Gastric pain | 6 | 9 | 15 |

* Two of the patients who received Alosetron prior to randomization, dose unknown
** One patient *ibid* above.

**2) Extension Phase** In the safety population of 136 patients in the extension phase, 39 (28.7 %) patients reported AEs during the treatment phase. Gastrointestinal AEs were the most common, following a pattern similar to the core study patients: constipation (6), colic (2), flatulence (2), diarrhea (2), gastric pain (2).

- **SAEs** No deaths occurred in the study.

1) **Core Study** 9/960 patients experienced SAEs, two of which were drug related. In six of these subjects treatment was discontinued and in two treatment was interrupted. Two SAEs involved the gastrointestinal system, leading to hospitalization: one case of abdominal pain (case 1041) and one case of diverticulitis (case 921).
2) **Extension Phase** 2/136 patients experienced SAEs, both unrelated to drug. There was one case of diverticulitis (case 533) which required an 11 day hospitalization and resolved 28 days after onset. There was one case of incontinence which required interruption of treatment.

- **RELATED TO STUDY DRUG 1) Core Study** 224/960 (23.3 %) reported drug related AEs (DRAEs): Alosetron 1 mg BID group 23.3%; Alosetron 2 mg QD 22.9 %; gastrointestinal DRAEs and their breakdown are summarized in Table 4.

**Table 4**
**Core Study**
**Drug Related Adverse Events**
**Gastrointestinal DRAEs Reported by More than 10 Patients**

| ADV. EVENT | CORE STUDY | EXTENSION PHASE | TOTAL #(%) |
|---|---|---|---|
| Constipation | 68 | 53 | 123(12.8 %)* |
| Colic | 5 | 18 | 24** |
| Nausea | 9 | 9 | 18 |
| Gastric pain | 3 | 8 | 11 |

* Two patients received Alosetron before randomization; dose unknown
** One patient *ibid* above

**2) Extension Phase** 12/136 (8.8 %) reported DRAEs. The only DRAE reported by more than one patient was constipation (6 patients).

- **CAUSE OF WITHDRAWAL 1) Core Study** 167/960 (17.4 %) reported DRAEs leading to withdrawal (WAEs): Alosetron 1 mg BID group was 15.9 %, Alosetron 2 mg QD. Gastrointestinal WAEs were the most common and they are listed in Table 5 below. There were no WAEs in other body systems affecting 10 or more subjects.

**Table 5**
**Gastrointestinal WAEs Reported by More than 10 Patients**

| ADV. EVENT | CORE STUDY | EXTENSION PHASE | TOTAL |
|---|---|---|---|
| Constipation | 49 | 44 | 93 |
| Colic | 4 | 15 | 19 |
| Nausea | 3 | 7 | 10 |
| Gastric Pain | 3 | 7 | 10 |

3) **Extension Phase** 5/136 (3.7 %) patients reported AEs leading to withdrawal. All WAEs were in the gastrointestinal system: constipation (2), colic (2) and diverticulitis.

- **SERIOUS COMPLICATIONS OF CONSTIPATION** None reported.
- **ISCHEMIC BOWEL** None reported
- **UNDIAGNOSED RECTAL BLEEDING** None reported

**CONCLUSIONS FROM THIS STUDY** The safety data of this stuy is, in general terms, similar to that of other Alosetron studies. Review of the narrative summaries and some CRFs fails to reveal any symp tom complex compatible with ischemic bowel or any cases of rectal bleeding.

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Hugo Gallo Torres
3/5/02 07:12:52 PM
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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
**MEDICAL OFFICER'S REVIEW**

sNDA: 21-107
SPONSOR: GlaxoSmithkline (formerly Glaxo Wellcome, Inc)
DRUG: Alosetron Hydrochloride (LOTRONEX™) Tablets
DATE OF ORIGINAL SUBMISSION: 29 June, 1999
DATE OF ORIGINAL APPROVAL: 9 February, 2000
VOLUNTARY WITHDRAWAL FROM THE MARKET: 28 November, 2000
DATE OF sNDA SUBMISSION: 7 December, 2001
INITIATION DATE: 14 NOVEMBER, 2000
EARLY TERMINATION DATE: 28 NOVEMBER, 2000
MEDICAL OFFICER: Marcelo A. Barreiro, MD, MSc
MATERIAL REVIEWED: **S3B30028 – AN INTERNATIONAL, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP 12 WEEK STUDY OF ALOSETRON 1 MG BID IN FEMALE PATIENTS WITH DIARRHEA-PREDOMINANT IRRITABLE BOWEL SYNDROME (IBS-D) WITHIN ASIA PACIFIC**

## EXECUTIVE SUMMARY THERE WERE NO CASES OF ISCHEMIC COLITIS, SERIOUS COMPLICATIONS OF CONSTIPATION OR GI BLEEDING IN TWO CASES TREATED WITH ALOSETRON

**INTRODUCTION AND BACKGROUND** Due to its early termination, only 11 patients were enrolled in the study. Two patients received alosetron.

**SUMMARY OF RESEARCH PROTOCOL**

- **DESIGN** As above. Phase III b study.
- **NUMBER OF SITES** Five sites in Taiwan
- **NUMBER OF PATIENTS** Eleven were randomized, only two to Alosetron

**SUMMARY OF EFFICACY RESULTS** No efficacy studies performed

**SUMMARY OF SAFETY RESULTS** The two subjects on Alosetron were not of childbearing potential. One subject received Alosetron for two days, the other for seven days.

- **AEs** No AEs were reported by the patients on Alosetron. In the placebo group one subject reported mild dizziness, unrelated to therapy
- **SAEs** None reported
- **RELATED TO STUDY DRUG** None reported
- **CAUSE OF WITHDRAWAL** None reported
- **SERIOUS COMPLICATIONS OF CONSTIPATION** None reported

- **ISCHEMIC BOWEL** None reported
- **UNDIAGNOSED RECTAL BLEEDING** None reported

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

sNDA: 21-107
SPONSOR: GlaxoSmithkline (formerly Glaxo Wellcome, Inc)
DRUG: Alosetron Hydrochloride (LOTRONEX™) Tablets
DATE OF ORIGINAL SUBMISSION: 29 June, 1999
DATE OF ORIGINAL APPROVAL: 9 February, 2000
INITIATION DATE: 04 JULY, 2000
VOLUNTARY WITHDRAWAL FROM THE MARKET: 28 November, 2000
DATE OF sNDA SUBMISSION: 7 December, 2001
MEDICAL OFFICER: Marcelo A. Barreiro, MD, MSc
MATERIAL REVIEWED: **S3B30031 – AN EIGHT-WEEK, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, STUDY OF ALOSETRON IN FEMALE SUBJECTS WITH NON-CONSTIPATED IRRITABLE BOWEL SYNDROME WHO SHOW THERAPEUTIC RESPONSE TO ALOSETRON**

**EXECUTIVE SUMMARY 1) THERE WERE NO DEATHS, SAEs, OR PREGNANCIES**
**2) NO CASES OF ISCHEMIC COLITIS,**
**3) SERIOUS COMPLICATIONS OF CONSTIPATION, OR**
**4) UNEXPLAINED RECTAL BLEEDING REPORTED IN 276 IBS PATIENTS**

**SUMMARY OF RESEARCH PROTOCOL** Consenting subjects who met entry criteria received open label Alosetron 1 mg BID for 12 weeks, after which were classified as "responders" or "non-responders". Responders were randomized 1:1 to the two treatment groups: Alosetron 1 mg BID or matching placebo.

- **DESIGN** Multicenter, randomized, comparative (Phase IIIb).
- **DOUBLE BLIND:** Yes **CONTROLS:** Placebo
- **NUMBER OF SITES:** 33 **COUNTRY:** Canada
- **NUMBER OF PATIENTS** At the time of early termination, 278 patients were enrolled in the study, of which 276 entered the open label phase and took at least one tablet of study medication (Safety Population). Of these, 63 patients were randomized: placebo 33, Alosetron 30 (Intent-to-treat Population).Seventy subjects (25 %) withdrew prematurely. At early termination of the study 205 patients were terminated. None of the patients completed the two phases of the study.

**SUMMARY OF EFFICACY RESULTS** No efficacy analysis was performed.

- **SUMMARY OF SAFETY RESULTS** During the open label phase 27/276 (10 %) of patients discontinued prematurely due to AEs, and 10/276 (4 %) reported constipation. None of the subjects on Alosetron in the double-blind phase discontinued prematurely

- **AEs** Constipation was reported in 23 % of the open label patients and 13 % of the double blind phase patients.
- **SAEs** None reported
- **RELATED TO STUDY DRUG** Incomplete data.
- **CAUSE OF WITHDRAWAL** Incomplete data
- **SERIOUS COMPLICATIONS OF CONSTIPATION** None reported
- **ISCHEMIC BOWEL** None reported
- **UNDIAGNOSED RECTAL BLEEDING** None reported

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

sNDA: 21-107
SPONSOR: GlaxoSmithkline (formerly Glaxo Wellcome, Inc)
DRUG: Alosetron Hydrochloride (LOTRONEX™) Tablets
DATE OF ORIGINAL SUBMISSION: 29 June, 1999
DATE OF ORIGINAL APPROVAL: 9 February, 2000
VOLUNTARY WITHDRAWAL FROM THE MARKET: 28 November, 2000
INITIATION DATE: 04 OCTOBER, 2000
DATE OF sNDA SUBMISSION: 7 December, 2001
MEDICAL OFFICER: Marcelo A. Barreiro, MD, MSc
MATERIAL REVIEWED: **S3B30033 - A RANDOMIZED, DOUBLE-BLIND, MULTI-CETER, PHASE IIIb, TO COMPARE ALOSETRON 1 MG BID WITH MEBEVERINE 135 MG TID FOR 12 WEEKS IN THE TREATMENT OF IRRITABLE BOWEL SYNDROME (IBS) IN FEMALE PATIENTS WHOSE PREDOMINANT SYMPTOMS ARE PAIN AND DIARRHEA**

**EXECUTIVE SUMMARY**

**1) THERE WAS ONE CASE OF (TISSUE PROVEN) BOWEL INFARCTION**
**2) THERE WERE TWO CASES OF UNEXPLAINED RECTAL BLEEDING AND ONE CASE OF BLOODY DIARRHEA (ALOSETRON GROUP)**
**3) THERE WERE NO CASES OF SERIOUS COMPLICATIONS OF CONSTIPATION**
**4) THERE WERE TWO SAEs (ANGINA PECTORIS AND BOWEL INFARCTION)**
**5) THERE WERE NO DEATHS, IN A TOTAL OF 94 PATIENTS EXPOSED TO ALOSETRON**

**SUMMARY OF RESEARCH PROTOCOL** Patients who met inclusion/exclusion criteria were randomized to Alosetron 1 mg BID plus placebo, or Mebeverine 135 mg TID for 12 weeks. The discontinuation of the study occurred approximately two months after the first patient had been randomized to treatment with study drug. No subject completed the study.

- **DESIGN** Comparative study.
- **DOUBLE BLIND** Yes **CONTROLS** Mebeverine 135 mg TID
- **NUMBER OF SITES** 66 **COUNTRIES** UK (62 centers) Netherlands (4

centers)

- **NUMBER OF PATIENTS** 181 patients were randomized: 94 to Alosetron and 87 to mebeverine (safety analysis population)

**SUMMARY OF EFFICACY RESULTS** No efficacy analysis was performed

***SUMMARY OF SAFETY RESULTS***

- **AEs** The most common AEs were related to the GI system, with constipation present in 23 patients of the Alosetron group and three patients of the mebeverine group.Nausea was the second most common GI AE present in 5 patients of the Alosetron group only. Rectal bleeding (two patients) and bloody diarrhea (one patient) were listed as AEs without further comments, all in the Alosetron treatment group.
- **SAEs** There was one case of angina pectoris that required hospitalization, and one case of bowel infarction that seemed to be due to adhesions arising from a previous ovarian cystectomy performed on 16 November, 1998. These two cases are summarized below:

Case History 2
Protocol Id: S3B30033
Investigator number 32272
Subject number: 187852
Treatment number: 309
Case Id: B0094359A

This 72-year old female received oral alosetron 1mg twice daily plus placebo once daily for the treatment of Irritable Bowel Syndrome. She had a history of ischaemic heart disease and was concurrently receiving multiple medication for this condition. The subject received study medication for only three days and was then withdrawn from the study due to its premature termination. Twelve days after stopping study medication, in the follow-up phase, the subject developed a severe angina attack while attending a hospital appointment for her eye condition. She was treated with nitroglycerin spray and admitted to the AE department. ECG results confirmed no evidence of myocardial infarction and cardiac enzyme levels were within normal limits. No change in the concurrent medication was made. The event resolved the next day. In the opinion of the investigator, the underlying ischaemic heart disease was cited as a possible cause of the angina and there was no reasonable possibility that the event, which required hospitalisation, may have been caused by the study drug.

Case History 3
Protocol Id: S3B30033
Investigator number 88893
Subject number: 190586
Treatment number: 73
Case Id: B0095990A

This 61-year old female received oral alosetron 1mg twice daily plus placebo daily for the treatment of Irritable Bowel Syndrome. She had a history of ovarian cysts for which she had a salpingooophorectomy. Concurrent medications included diclofenac for knee arthritis and felodipine for hypertension. Three days after initiating study medication, the subject developed abdominal pain and constipation. Study medication was discontinued six days later and the symptoms resolved within 13 days of onset. The subject decided to withdraw from the study at this point. The subject had received study medication for a total of ten days. A week after withdrawing from the study, during the follow-up phase, the subject attended surgery and reported alternating bowel habit. She was referred for sigmoidoscopy (which was not done by the time of reporting). Approximately six weeks after discontinuing study medication, the subject presented to the emergency department with severe acute abdominal pain and blood in her stools. Both symptoms had started three days prior to presenting to the emergency room. Emergency laparotomy was performed on the same day, with resection of necrotic ileum and division of adhesions. Both the acute abdominal pain and blood in stools resolved within ten days and the subject was discharged on the day of resolution. The final diagnosis was small bowel ischemia secondary to adhesions from previous surgery. In the opinion of the investigator, there was no reasonable possibility that the event may have been caused by the study drug.

- **RELATED TO STUDY DRUG** According to the investigator, neither SAE was related to study drug.
- **CAUSE OF WITHDRAWAL** The causes for withdrawal are listed weekly, into the following reasons: 1) due to AEs, 2) consent withdrawn, 3) no stools for >8 days, 4) protocol violation and 5) other. No breakdown of the information is provided.
- **SERIOUS COMPLICATIONS OF CONSTIPATION** None reported
- **ISCHEMIC BOWEL** One case
- **UNDIAGNOSED RECTAL BLEEDING** Three patients: rectal hemorrhage (2) and bloody diarrhea (1).

**CONCLUSIONS FROM THIS STUDY** This reviewer has examined the CRF of the patient who underwent surgery because of acute abdominal pain and blood in the stools and was found to have a segment of ileun with ischemic necrosis that required a resection. The hand written notes are barely legible. Apparently the impression, at the time, was that the episode was caused by adhesions. However, it never says in the record that the patient had a "bowel obstruction" (which would be the usual presentation of bowel necrosis due to adhesions) leading to surgery and the consequent findings. Also of note is the fact that the patient had been on premarin for most of the year 2000.

The case of unstable angina in a 72 year old with previous history of ischemic heart disease is also of interest. Not uncommonly we find patients with cardiovascular AEs in the Alosetron clinical trials. It is not inconceivable that Alosetron may be a factor in those cases, since we now know that there are 5-HT3 receptor sites in the left ventricle and the left anterior descending coronary artery.

**RECOMMENDATIONS FOR REGULATORY ACTION** The Agency should allow this reviewer to allocate time for a review of extra-intestinal manifestations of Alosetron.

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

sNDA: 21-107
SPONSOR: GlaxoSmithkline (formerly Glaxo Wellcome, Inc)
DRUG: Alosetron Hydrochloride (LOTRONEX™) Tablets
DATE OF ORIGINAL SUBMISSION: 29 June, 1999
DATE OF ORIGINAL APPROVAL: 9 February, 2000
VOLUNTARY WITHDRAWAL FROM THE MARKET: 28 November, 2000
DATE OF sNDA SUBMISSION: 7 December, 2001
INITIATION DATE: 17 MAY, 2000
COMPLETION DATE: 01 NOVEMBER, 2000
MEDICAL OFFICER: Marcelo A. Barreiro, MD, MSc
MATERIAL REVIEWED: **1) S3B10945 – A DOUBLE-BLIND, RANDOMIZED, TWO-WAY CROSSOVER STUDY TO DETERMINE THE EFFECT OF ALOSETRON 1 MG BID FOR 14 DAYS VERSUS PLACEBO BID ON VISCERAL HYPERSENSITIVITY FOLLOWING DUODENAL LIPID INFUSION IN FEMALE DIARRHEA-PREDOMINANT IBS (IBS-D) PATIENTS 2) SIMREN M, HAGMAN I ET AL, DUODENAL LIPIDS LOWER COLONIC PERCEPTION THRESHOLDS WITHOUT AFFECTING TONE IN PATIENTS WITH IRRITABLE BOWEL SYNDROME. GASTROENTEROLOGY VOL116 (PART 2) G4707 PAGE 1084**

## EXECUTIVE SUMMARY THERE WERE NO CASES OF ISCHEMIC COLITIS, SERIOUS COMPLICATIONS OF CONSTIPATION OR GI BLEEDING IN 24 SUBJECTS TREATED WITH ALOSETRON TWO WEEKS

**INTRODUCTION AND BACKGROUND** Lipids in the duodenum lower the colonic perception thresholds and change the viscerosomatic referral pattern in IBS patients, which may partly explain their postprandial symptoms.

**SUMMARY OF RESEARCH PROTOCOL**

- **DESIGN** Phase I, double-blind, randomized, two-way cross over study in adult female patients with IBS-D. Subjects were screened for ≤ 14 days prior to start the first Treatment Period. Eligible subjects were randomized to receive either Alosetron 1 mg BID or placebo BID over 15 (±2) days followed by a 14-day washout interval and then the alternate treatment. On the final day of each Treatment Period, subjects underwent barostat distension trials before and after duodenal lipid infusion

- **NUMBER OF SITES** One **COUNTRIES** Sweden
- **NUMBER OF PATIENTS** Twenty four subjects were enrolled. Eight subjects dropped out prematurely (2 due to AEs; 2 due to consent withdrawal; 4 due to other

reasons). Twenty four subjects received at least one dose of study medication and were included in the safety population. Fifteen of these subjects had evaluable pharmacodynamic data in both Treatment Periods and were included in the pharmacodynamic population.

- **DIAGNOSIS AND ENTRY CRITERIA** Female subjects 18 years or older with IBS-D (as defined by Rome II criteria). Appropiate contraceptive criteria were used.

- **PRIMARY ENDPOINT** The change in the pressure perception thresholds following the lipid infusion. "Discomfort" was considered an important endpoint. The change in an endpoint was defined as post-lipid (or during) infusion value minus pre-lipid infusion value
- **SECONDARY ENDPOINTS** Change in relative area of referred discomfort and pain, colonic compliance, colonic tone, phasic events.

**SAFETY EVALUATIONS** Physical examination at screening. Clinical laboratory tests were performed at Screening and at Post-Study. AEs were collected from Screening to Post-Study.

**SUMMARY OF SAFETY RESULTS**

- **AEs**There were two AEs in the Alosetron arm and none in the placebo group. There was a report of a viral ENT infection and a report of constipation related to study drug. Both events were moderate in severity. The viral infection resolved in 13 days, the constipation in eight days
- **SAEs** None reported
- **RELATED TO STUDY DRUG** One case of constipation (see above).
- **CAUSE OF WITHDRAWAL** One case of constipation (see above)
- **SERIOUS COMPLICATIONS OF CONSTIPATION** None reported
- **ISCHEMIC BOWEL** None reported
- **UNDIAGNOSED RECTAL BLEEDING** None reported

**CONCLUSIONS FROM THIS STUDY** In this 14 day study of 24 subjects with IBS-D there were no SAEs. Only two moderate AEs were reported in the Alosetron group. A case of constipation resolved in eight days upon discontinuation of the drug.
The study suggests that Alosetron reduces lipid-induced colonic hypersensitivity in IBS subjects (all parameters). The difference was not statistically significant. 5-HT3 receptors may not be the only mediator, but may be a co-factor or one of a number of individual factors responsible for the exaggerated sensory component of the gastrocolonic response in IBS.

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

sNDA: 21-107
SPONSOR: GlaxoSmithkline (formerly Glaxo Wellcome, Inc)
DRUG: Alosetron Hydrochloride (LOTRONEX™) Tablets
DATE OF ORIGINAL SUBMISSION: 29 June, 1999
DATE OF ORIGINAL APPROVAL: 9 February, 2000
VOLUNTARY WITHDRAWAL FROM THE MARKET: 28 November, 2000
INITIATION DATE: 07 JANUARY, 2000
DATE OF sNDA SUBMISSION: 7 December, 2001
MEDICAL OFFICER: Marcelo A. Barreiro, MD, MSc
MATERIAL REVIEWED: **S3B40032 - AN OBSERVATIONAL STUDY TO ASSESS PREVALENCE, NATURAL HISTORY, AND BURDEN OF ILLNESS OF IRRITABLE BOWEL SYNDROME (IBS) IN CLINICAL PRACTICE AND TO EVALUATE THE IMPACT OF ALOSETRON TREATMENT ON NATURAL HISTORY AND BURDEN OF ILLNESS IN A COHORT OF FEMALES WHOSE PREDOMINANT BOWEL SYMPTOM IS DIARRHEA**

**EXECUTIVE SUMMARY** **1) THERE WERE NO CASES OF ISCHEMIC BOWEL**
**2) THERE WERE NO CASES OF SERIOUS COMPLICATIONS OF CONSTIPATION**
**3) THERE WERE SEVEN CASES OF UNEXPLAINED RECTAL BLEEDING IN A TOTAL OF 633 PATIENTS EXPOSED TO ALOSETRON**

**SUMMARY OF RESEARCH PROTOCOL** Female patients with a confirmed diagnosis of diarrhea-predominant IBS, who successfully completed the 3-month baseline period, were offered the option to participate in an open-label, post-approval, alosetron treatment of 1 mg BID, over a 12 week period. Due to the observational nature and anticipated size of this study, traditional data monitoring measures were not employed. Missing data and clarification of discrepant data were not necessarily sought.

- **DESIGN** Open label, Phase IV.
- **DOUBLE BLIND** No **CONTROLS** No
- **NUMBER OF SITES** 267 enrolled patients **COUNTRIES** USA
- **NUMBER OF PATIENTS** 633 (Intent-to-treat population) patients are used for safety analysis

**SUMMARY OF EFFICACY RESULTS** Due to early termination of the study only descriptive results are available.

**SUMMARY OF SAFETY RESULTS** The Intent-to-Treat Population (n=633) was utilized for safety analyses.
Among 633 patients in the Intent-to-Treat Population with study drug exposure data (566), median exposure was 72 days (range = 1-211 days).

- **AEs**The incidence of all AEs during the 3-month treatment period of the study was 40% (256/633) The most common type of AE during the study involved the GI system (230/633, 36%). Thirty percent (30%, 189/633) experienced constipation during the study. No complications due to constipation were reported. There were no cases of colitis
  Seven (7) patients experienced a total of 7 AEs involving bleeding associated with bowel function during the study: blood in stools (patients 1806201 and 1819065) and rectal hemorrhage/rectal bleeding (patients 1050011, 1590202, 2124201, 2336202, and 2299051). Two cases of rectal hemorrhage/rectal bleeding coincided with abdominal pain. One of these patients also reported constipation concurrently. Two other cases of rectal hemorrhage/rectal bleeding coincided with constipation with no report of abdominal pain. One case of blood in stool coincided with constipation. This reviewer has sought for all seven cases and has been able to identify the CRFs of only three (*1806201, 1819065 and 2124201*) *and concurs with above appraisal.*
- **SAEs.** Less than 1 percent (<1%, 4/621) of patients experienced 4 SAEs during the study. Two subjects experienced SAEs which led to their withdrawal from the study. No case of constipation met the criteria for classification as an SAE during the study.
- **RELATED TO STUDY DRUG** Drug-related AEs (i.e., those AEs judged by the investigator as having a reasonable possibility that the event may have been caused by the study medication) occurred among 36% (229/633) of patients. The most common drug-related AE was constipation.
- **CAUSE OF WITHDRAWAL** Twenty two percent (22%, 139/633) of patients were withdrawn during the course of the study due to AEs. The most commonly occurring AE which led to withdrawal was constipation which was reported by 17% (105/633) of patients.
  Two patients experienced SAEs, which led to their withdrawal from the study (asthma and tachyarrythmia)
  Five of the seven patients with unexplained rectal bleeding were withdrawn from the study (one patient with associated abdominal pain and discomfort and three patients with associated constipation)
- **SERIOUS COMPLICATIONS OF CONSTIPATION** None reported
- **ISCHEMIC BOWEL** None reported
- **UNDIAGNOSED RECTAL BLEEDING** Seven patients, five of which were withdrawn from the study.

**CONCLUSIONS FROM THIS STUDY** The safety profile of this study is similar to that of other Alosetron studies.

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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

# MEDICAL OFFICER'S REVIEW
# CARDIOVASCULAR COMPLICATIONS
# of
# ALOSETRON THERAPY

sNDA: 21-107
SPONSOR: GlaxoSmithkline (formerly Glaxo Wellcome, Inc)
DRUG: Alosetron Hydrochloride (LOTRONEX™) Tablets
DATE OF ORIGINAL SUBMISSION: 29 June, 1999
DATE OF ORIGINAL APPROVAL: 9 February, 2000
VOLUNTARY WITHDRAWAL FROM THE MARKET: 28 November, 2000
DATE OF sNDA SUBMISSION: 7 December, 2001
MEDICAL OFFICER: Marcelo A. Barreiro, MD, MSc
MATERIAL REVIEWED: NINETEEN ALOSETRON CLINICAL TRIALS

**INTRODUCTION AND BACKGROUND** Alosetron is a synthetic product designed to selectively block receptor sites present mostly in the wall of the colon, that are activated by a neurotransmitter, serotonin (5-hydroxytriptamine). These particular receptor sites are called 5 HT3 and they are involved in secretory, motor, sensory and vascular processes. 5 HT3 receptors are also present in the central nervous system, peripheral nervous system, and some parts of the cardiovascular system, like the left ventricle and the left anterior descending coronary artery.

The presence of serotonin was suspected in the 1930's because of its cardiovascular effects. Irwin Page and collaborators at the Cleveland Clinic were able to accomplish the chemical isolation and synthesis of serotonin in 1947. Serotonin produces bradychardia and tachycardia, hypotension and hypertension, vasoconstriction and vasodilatation, in the human and many other animal species. 5 HT3 receptors are involved in different ways in different animal species in all these cardiovascular effects.

Alosetron (Lotronex™) has been proven effective in the management of some symptoms of Irritable Bowel Syndrome predominant diarrhea in females. Because of numerous cases of Ischemic Colitis and others, causing Ischemic Necrosis of the small and large intestine, the sponsor decided to withdraw the drug from the market. While studying those cases, trying to elucidate the pathophysiology of these adverse events (AEs), this reviewer came across cases of **chest pain, arrhythmias, sudden death, TIAs and strokes, syncope and near-syncope and thromboses** in patients who were on study medication in those clinical trials. The question arose as to weather Alosetron couldn't also produce extra-intestinal AEs, in particular, cardiovascular AEs. This is a preliminary review of 19 protocols, part of the supplemental NDA, submitted on 7 December, 2001, selected at random, in which the above listed cardiovascular events were sought for as cause of Serious Adverse Events (SAEs).

**METHODOLOGY** Table 1 provides information on the protocols reviewed and the patiens studied.

**TABLE 1**
**GENERAL DATA**
**(19 protocols)**

| PROTOCOL # | SAFETY POPULATION (#) | ALOSETRON PATIENTS (#) | PLACEBO/ CONTROL (#) |
|---|---|---|---|
| S3B30020 | 2700 | 1817 | 883 |
| S3B30017 | 876 | 876 | — |
| S3B30025 | 1547 | 1027 | 520 |
| S3B30026 | 960 | 960 | — |
| S3B20023 | 663 | 534 | 128 |
| S3B30004 | 60 | 32 | 28 |
| S3B30006 | 710 | 348 | 362 |
| S3B30011 | 801 | 532 | 269 |
| S3B30012 | 2422 | 2422 | — |
| S3B30013 | 560 | 280 | 280 |
| S3B30015 | NO DATA | EARLY | TERMINATION |
| S3B30019 | NO DATA | EARLY | TERMINATION |
| S3B40031 | 492 | 296 | 296 |
| S3BB3001 | 622 | 318 | 304 |
| S3BB3002 | 784 | 402 | 382 |
| S3BA3001 | NO SAFETY | DATA | — |
| S3BA3002 | NO SAFETY | DATA | — |
| S3BA3003 | NO SAFETY | DATA | — |
| S3B20015 | 319 | 239 | 80 |
| TOTAL # | 13,516 | 10,083 | 3,433 |

**Definition of Terms**

- **Chest Pain:** All SAEs listed with that term, or angina, angina pectoris, discomfort, burning. When a patient presented with a "chest pain" and later on the diagnosis became GERD or cholelithiasis, those patients were **not** included
- **Cardiac Arrythmia:** All forms of cardiac arrythmia were included : AF, SVT, PAT, etc. Palpitations were included.
- **Sudden Death:** All patients found dead, or who died suddenly and unexpectedly, after taking at least one tablet of study medicine. Patients who died during the screening phase of the trial were **not** included .
- **TIA and Stroke** An effort was made to document a neurological deficit, an investigator's opinion and **not** to include some cases of severe migraine.
- **Thromboses** These are peripheral thromboses or cases other than those listed under stroke.

- **Syncope and near-syncope (lightheadeness)** Dizziness was **not** counted. Some patients who fainted because of a cardiac arrythmia, were counted twice.

**RESULTS**

A total of 13,516 patients were part of the safety review: 10,083 were enrolled in an Alosetron arm, and 3,433 in a placebo/active control arm.

A total of 66 SAEs met criteria for inclusion in this review: 48 in the Alosetron group, and 18 in the placebo/control group. The difference was not statistically significant (p=0.726). These SAEs are summarized in Table 2.

**TABLE 2**
**SUMMARY OF SAEs**
**(n=13,516 patients)**
**(n=66 SAEs)**

| EVENT | ALOSETRON (n=10,083) | P/C (n=3,433) |
|---|---|---|
| Chest pain | 26 | 10 |
| Cardiac arrythmia | 10 | 4 |
| TIA/Stroke | 4 | 2 |
| Syncope/near-syncope | 6 | 1 |
| Thromboses | 2 | 1 |
| TOTALS | 48 | 18 |

**DISCUSSION** This manual review of some of the research protocols demonstrates a similar incidence of selected cardiovascular SAEs in both, the Alosetron and the placebo/control groups. There were, however, many cases of cardiovascular events that were not judged to be serious, but the patient was withdrawn from the study for reasons other than study drug ("withdrew consent").

The scientific rationale exists to expect more cardiovascular symptomatology in the Alosetron patients than, particularly, in placebo patients.

**CONCLUSION There is no statistically significant difference betweeen the Alosetron and the Placebo/Control-treated patients, with respect to the five cardiovascular SAEs studied, in these 19 research protocols.**

**RECOMMENDATIONS FOR REGULATORY ACTION** This reviewer suggests to request the sponsor information about selected cardiovascular events in all Alosetron studies, including serious and non-serious AEs.

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Marcelo Barreiro
3/5/02 11:59:33 AM
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Hugo Gallo Torres
3/5/02 05:26:56 PM
MEDICAL OFFICER

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

sNDA: 21-107
SPONSOR: GlaxoSmithkline (formerly Glaxo Wellcome, Inc)
DRUG: Alosetron Hydrochloride (LOTRONEX™) Tablets
DATE OF ORIGINAL SUBMISSION: 29 June, 1999
DATE OF ORIGINAL APPROVAL: 9 February, 2000
VOLUNTARY WITHDRAWAL FROM THE MARKET: 28 November, 2000
DATE OF sNDA SUBMISSION: 7 December, 2001
INITIATION DATE: 05 OCTOBER, 1999
COMPLETION DATE: 28 SEPTEMBER, 2000
MEDICAL OFFICER: Marcelo A. Barreiro, MD, MSc
MATERIAL REVIEWED: **S3B30012 - A SIX WEEK TRIAL OF ALOSETRON HYDROCHLORIDE 1 MG TWICE DAILY AS EMPIRICAL THERAPY IN FEMALE SUBJECTS WITH SYMPTOMS OF NON-CONSTIPATED IRRITABLE BOWEL SYNDROME**

**EXECUTIVE SUMMARY** **1) THERE WAS ONE CASE OF ISCHEMIC COLITIS**
**2) THERE WERE THREE ADDITIONAL CASES OF "COLITIS", INSUFFICIENTLY DEFINED**
**3) THERE WERE NO CASES OF SERIOUS COMPLICATIONS OF CONSTIPATION**
**4) THERE WERE 14 CASES OF GI BLEEDING (18 AEs), IN A TOTAL OF 422 PATIENTS EXPOSED TO ALOSETRON**

**SUMMARY OF RESEARCH PROTOCOL** Female patients who met a pre-defined criteria suggestive of non-constipated IBS, underwent a **one week screening phase.** The patients could not have been previously diagnosed with IBS, and alarm signs could not be present. The patients were placed on Alosetron 1 mg BID for six weeks **(treatment phase)** during which appropriate measurements were made. Between weeks six to eight, all subjects underwent a GI assessment by a gastroenterologist. **Responders** were allowed to continue Alosetron therapy for another four months **(follow up phase).**

- **DESIGN** Open-label, multicenter, Phase IIIb
- **DOUBLE BLIND** No **CONTROLS** No
- **NUMBER OF SITES** 91 **COUNTRIES** USA
- **NUMBER OF PATIENTS** The Safety Population comprised subjects in the Intent-to- Treat Population (n=426) who received study drug (n=422).

**SUMMARY OF SAFETY RESULTS**

- **AEs** Across the entire 24-week study, 71 % (300/422) of subjects reported AEs, 50 % involving the GI tract (212/422). Twenty eight percent (120/422) experienced constipation during the study.
- **SAEs** Eight subjects experienced a total of 10 SAEs, including one death of unknown cause.
- **RELATED TO STUDY DRUG** Forty percent (169/422) of AEs were judged to be due to study drug.
- **CAUSE OF WITHDRAWAL** Seventeen percent (70/422) withdrew from the study due to AEs. The majority occurred during the treatment phase. The most common reason for withdrawal was constipation (9 %, 38/422)
- **SERIOUS COMPLICATIONS OF CONSTIPATION** None reported
- **ISCHEMIC BOWEL** An AE of colitis, found on biopsy (mild inflammation) at the time of the scheduled flexible sigmoidoscopy, was reported in a 36-year-old subject (Subject 47343). The subject had been considered a non-responder, and her baseline GI symptoms were attributed to the colitis. In the investigator's opinion, the AE, colitis, was not related to the use of study drug. An AE of chronic active colitis, found on biopsy at the time of the scheduled colonoscopy, was reported in a 49-year-old white subject (Subject 48096). The subject had been considered a responder, and her baseline GI symptoms were attributed to IBS. The reporting of colitis was preceded by two reportings of constipation in the previous week. Due to the colitis, study drug was permanently discontinued and the subject was withdrawn from the study. In the investigator's opinion, the AE, colitis, was of severe intensity and not related to the use of study drug.

  An AE of possible ulcerative colitis, observed at the time of the early termination flexible sigmoidoscopy, was reported in a 58-year-old subject (Subjects 48665). Due to an AE of constipation, study drug was permanently discontinued and the subject was withdrawn from the study at which time the flexible sigmoidoscopy was performed. The subject's responder status could not be determined, and her baseline GI symptoms were attributed to the possible ulcerative colitis. In the investigator's opinion, the AE, possible ulcerative colitis, was not related to the use of study drug. An AE of nonspecific colitis, found on biopsy at the time of the early termination colonoscopy, was reported in a 31-year old subject (Subject 49203). Due to an AE of rectal bleeding following an episode of constipation, study drug was permanently discontinued and the subject was withdrawn from the study at which time the colonoscopy was performed. The subject's responder status could not be determined, and her baseline GI symptoms were attributed to IBS. In the investigator's opinion, the AE, nonspecific colitis or **ischemic colitis**, was related to the use of study drug.
- **UNDIAGNOSED RECTAL BLEEDING** Fourteen subjects experienced a total of 18 AEs involving GI bleeding. None of the events was serious and one led to patient withdrawal from the study

**CONCLUSIONS FROM THIS STUDY** The original endoscopic and pathological reports are not available at the time of this review. The data has been obtained from the

sponsor's synopsis and from painstaking identification of the CRFs. This latter are organized by investigator number, and not numerically, by patient number.
The safety data, in general, follows the same pattern of other clinical trials.

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Marcelo Barreiro
3/5/02 01:13:28 PM
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Hugo Gallo Torres
3/5/02 07:04:54 PM
MEDICAL OFFICER

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

sNDA: 21-107
SPONSOR: GlaxoSmithkline (formerly Glaxo Wellcome, Inc)
DRUG: Alosetron Hydrochloride (LOTRONEX™) Tablets
DATE OF ORIGINAL SUBMISSION: 29 June, 1999
DATE OF ORIGINAL APPROVAL: 9 February, 2000
VOLUNTARY WITHDRAWAL FROM THE MARKET: 28 November, 2000
DATE OF sNDA SUBMISSION: 7 December, 2001
INITIATION DATE: 03 DECEMBER, 1998
COMPLETION DATE: 15 JUNE, 2000
MEDICAL OFFICER: Marcelo A. Barreiro, MD, MSc
MATERIAL REVIEWED: **S3B30006 - A ONE YEAR RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, STUDY OF ALOSETRON 1 MG BID IN FEMALE SUBJECTS WITH IRRITABLE BOWEL SYNDROME (IBS)**

## EXECUTIVE SUMMARY THERE WERE NO CASES OF ISCHEMIC COLITIS, SERIOUS COMPLICATIONS OF CONSTIPATION OR GI BLEEDING, IN 348 PATIENTS EXPOSED TO ALOSETRON FOR UP TO ONE YEAR

### SUMMARY OF RESEARCH PROTOCOL

- **DESIGN** Phase III, multicenter, randomized
- **DOUBLE BLIND** Yes **CONTROLS** Placebo
- **NUMBER OF SITES** 160 **COUNTRIES** USA: 118; Rest of the World (ROW): 28
- **NUMBER OF PATIENTS** The safety population comprised 710 patients: 362 in the Alosetron 1 mg BID group, and 348 in the placebo BID group.

### SUMMARY OF SAFETY RESULTS

- **AEs** Seventy-two percent (261/362) of subjects in the placebo group reported a total of 1058 treatment-emergent AEs. Subjects who received Alosetron reported significantly more AEs ($p<0.001$): 297/348 (85%) subjects reported a total of 1163 AEs. AEs involving the gastrointestinal system, in particular constipation, account for most of this difference in the incidence of AEs ($p<0.001$). There were no other significant differences in the overall incidence of AEs between the placebo and Alosetron treatment groups for other body systems.
- **SAEs** A total of 18/348 (5%) subjects who received Alosetron reported 29 SAEs compared with 15/362 (4%) subjects in the placebo group who reported 20 SAEs. The overall incidence of SAEs among subjects who received Alosetron was not significantly different from the incidence in the placebo group. Within individual

body systems, there were no significant differences in the incidences of SAEs between treatment groups.

In both treatment groups, SAEs occurred mainly in the GI body system. Neither ischemic colitis nor constipation or its sequelae were reported in either treatment group as an SAE. Among subjects who received Alosetron, SAEs reported in the GI body system included nausea (n=2), vomiting (n=2), abdominal discomfort and pain (n=2), dental and gum inflammation (n=1), diarrhea (n=1), and viral gastrointestinal infections (n=1).

- **RELATED TO STUDY DRUG** Among subjects who received Alosetron, 67/348 (19%) were withdrawn from the study due to one or more AEs. A total of 69 AEs associated with study drug withdrawal in 53 subjects were judged by the investigator to be related to the administration of Alosetron. In three subjects, the AEs resolved with sequelae (abnormal liver functions tests; musculoskeletal inflammation; gastrointestinal discomfort and pain) and in three subjects the AEs had not resolved (diarrhea; weight problems; skin rashes). Two subjects were withdrawn as a result of SAEs (musculoskeletal inflammation; dental and gum inflammation). Eleven percent (39/348) of the Alosetron-treated subjects withdrew as the result of constipation. Approximately half of the 39 cases of constipation resulting in withdrawal from the study were mild or moderate in intensity and the other half were severe. In all cases the investigator judged the constipation to be related to the administration of study drug, in all cases the constipation resolved, and in no case was constipation judged by the investigator to be an SAE.

  In comparison, 36/362 (10%) subjects in the placebo group were withdrawn due to one or more AEs. A total of 43 AEs associated with study drug withdrawal in 18 subjects were judged by the investigator to be related to the administration of placebo. In two subjects, two AEs resolved with sequelae (diverticulosis; colitis) and in three subjects five AEs had not resolved (abdominal discomfort and pain, abdominal distension, disorders of defecation; otitis; diarrhea). Five subjects were withdrawn as a result of SAEs (postoperative infections; depressive disorders; primary malignant breast neoplasia; embolisms; abdominal cysts, lumps, and masses), and in one subject the SAE (embolism) was fatal. No placebo-treated subjects were withdrawn due to constipation.

  A total of 50/348 (14%) subjects who received Alosetron reported 72 constipation events that did not result in withdrawal from the study. A total of 85% (61/72) of these events were reported as mild or moderate in intensity, and the remaining nine events (15%) not resulting in withdrawal were reported as severe.

- **CAUSE OF WITHDRAWAL** Among subjects who received Alosetron, 67/348 (19%) were withdrawn from the study due to one or more AEs. A total of 69 AEs associated with study drug withdrawal in 53 subjects were judged by the investigator to be related to the administration of Alosetron. In three subjects, the AEs resolved with sequelae (abnormal liver functions tests; musculoskeletal inflammation; gastrointestinal discomfort and pain) and in three subjects the AEs had not resolved (diarrhea; weight problems; skin rashes). Two subjects were withdrawn as a result of SAEs (musculoskeletal inflammation; dental and guminflammation). Eleven percent (39/348) of the Alosetron-treated subjects withdrew as the result of constipation. Approximately half of the 39 cases of constipation resulting in withdrawal from the

study were mild or moderate in intensity and the other half were severe. In all cases the investigator judged the constipation to be related to the administration of study drug, in all cases the constipation resolved, and in no case was constipation judged by the investigator to be an SAE.

- **SERIOUS COMPLICATIONS OF CONSTIPATION** None reported
- **ISCHEMIC BOWEL** None reported
- **UNDIAGNOSED RECTAL BLEEDING** None reported

**CONCLUSIONS FROM THIS STUDY** This is a very important study in which a substantial number of patients was treated for up to one year, without serious complications of constipation or any symptom suggestive of ischemic colitis.

This study suggests that when Alosetron is administered under the right indications by experienced physicians, it becomes a safe and well tolerated drug, with constipation as an easily controllable main side effect.

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Hugo Gallo Torres
3/5/02 07:02:28 PM
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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
**MEDICAL OFFICER'S REVIEW**

sNDA: 21-107
SPONSOR: GlaxoSmithkline (formerly Glaxo Wellcome, Inc)
DRUG: Alosetron Hydrochloride (LOTRONEX™) Tablets
DATE OF ORIGINAL SUBMISSION: 29 June, 1999
DATE OF ORIGINAL APPROVAL: 9 February, 2000
VOLUNTARY WITHDRAWAL FROM THE MARKET: 28 November, 2000
DATE OF sNDA SUBMISSION: 7 December, 2001
INITIATION DATE: 08 OCTOBER, 1999
COMPLETION DATE: 16 NOVEMBER, 2000
MEDICAL OFFICER: Marcelo A. Barreiro, MD, MSc
MATERIAL REVIEWED: **S3B20023 - A TWELVE WEEK, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, DOSE-RANGING, PHASE II STUDY TO ASSESS THE CLINICAL EFFICACY OF ALOSETRON IN MALE SUBJECTS WITH IRRITABLE BOWEL SYNDROME**

**EXECUTIVE SUMMARY** **1) THERE WAS ONE CASE OF ISCHEMIC COLITIS**
**2) THERE WERE NO CASES OF SERIOUS COMPLICATIONS OF CONSTIPATION**
**3) THERE WERE SEVEN CASES OF GI BLEEDING, IN 534 PATIENTS EXPOSED TO ALOSETRON**

## SUMMARY OF RESEARCH PROTOCOL

**DESIGN** This is a Phase II, multicenter, randomized, parallel group, dose ranging study, designed to evaluate the efficacy, safety and tolerability of varying doses of Alosetron, in adult male subjects with IBS-D.

- **DOUBLE BLIND** Yes **CONTROLS** Placebo
- **NUMBER OF SITES** 186 **COUNTRIES:** Two: USA (163 sites), Canada (23 sites)
- **NUMBER OF PATIENTS** 534

## SUMMARY OF SAFETY RESULTS

- **AEs** With the exception of constipation, the incidences of AEs were generally similar across treatment groups. The incidence of constipation generally increased with increasing alosetron dose. The incidence of constipation among subjects who received alosetron 0.5mg, 1.0mg, or 2.0mg was 9% (12/127), 15% (19/130), and 11% (15/136), respectively. The highest incidence of constipation (21%; 29/140) was noted in those receiving alosetron 4.0mg. The overall incidence of constipation for subjects receiving any dose of alostron was 14% (75/553).

No serious adverse events of constipation occurred. No events of constipation occurred in those receiving placebo.

To evaluate possible events of ischemic colitis, additional information was requested from investigators on **all adverse events of bloody diarrhea or abdominal pain and rectal bleeding** occurring during treatment or follow-up. Seven subjects exhibited non- serious adverse events meeting these criteria (1 exhibited bloody diarrhea alone; 1 exhibited bloody diarrhea and abdominal pain, and 5 exhibited rectal bleeding and abdominal pain) reported within 4 days – 12 weeks of treatment initiation. All affected subjects were on alosetron treatment (0.5-4.0mg po BID). Of these seven subjects, additional evaluation of the rectal bleeding events included colonic endoscopy in 5 subjects and negative stool cultures in 3 subjects. Endoscopy revealed hemorrhoids alone in 4 subjects. The fifth subject (#40398), a 41-year-old male underwent a colonoscopy 56 days after an event of bloody diarrhea was first reported. The subject continued on study medication after this event occurred. The colonoscopy revealed a 4mm hyperplastic rectal polyp, otherwise normal colonic mucosa, and very small hemorrhoids. In this subject, biopsies of the transverse colon were normal, while those from the rectosigmoid revealed focal fibrosis, consistent with a history of ischemic colitis and focal mild active colitis. This subject exhibited no further symptoms of rectal bleeding or abdominal pain following alosetron cessation. Considering that the subject remained on treatment after the initial event and the colonoscopy was not performed for 56 days after the event, 10 days after the conclusion of the study, it is difficult to draw meaningful conclusions on this subject. In the two subjects for whom no endoscopy was performed, one investigator believed hemorrhoids were the most likely etiology of rectal bleeding in one subject (as the subject had a prestudy history of rectal bleeding due to hemorrhoids) and another investigator felt that no further evaluation was needed in the other subject (who reported hard stools with alosetron treatment and a prestudy history of rectal bleeding with passage of stool evaluated with an endoscopy).

In summary, events of rectal bleeding occurred in seven alosetron-treated subjects, with onset at varying times throughout the 12-week treatment period. Of the seven subjects, five subjects exhibited hemorrhoids or a history of hemorrhoids as a possible source of bleeding, one subject's source was undefined, and one subject exhibited evidence **of possible healing ischemic colitis** and focal mild active colitis on colonoscopy performed one month after the event.

- **SAEs** No SAEs were reported among subjects receiving placebo. The overall incidence of SAEs among subjects who received alosetron was <1-4% (2/127, 5/130, 1/136, and 2/140 the 0.5, 1.0mg, 2.0mg, and 4.0mg treatment groups, respectively) in any treatment group.

  Neither ischemic colitis nor constipation or its sequelae were reported in any treatment group as an SAE. One subject who received alosetron 1.0mg, reported SAEs in the GI body system (nausea, vomiting, and diarrhea). No GI body system SAEs were reported in the other alosetron treatment or placebo groups.
- **RELATED TO STUDY DRUG** Thirteen percent (16/128) of subjects in the placebo group reported a total of 34 drug-related AEs. Subjects who received alosetron 0.5, 1, and 4.0mg reported significantly more drug-related AEs than the placebo group ($p<0.05$), with 22-30%reporting drug-related AEs: AEs involving the gastrointestinal

system (mostlyconstipation) account for most of this difference in the incidence of drug-related AEs ($p<0.05$) in the alosetron 0.5, 1.0, and 4.0mg treatment groups. The incidence of constipation attributed to study drug administration was 9-19% among subjects who received alosetron 0.5–4.0mg versus 0 in the placebo group. No significant differences in the incidence of drug-related AEs between the placebo and alosetron treatment groups were found for any other body system. No other drug-related AEs were reported with an incidence exceeding 5% in either treatment group.

- **CAUSE OF WITHDRAWAL** Withdrawal rates due to constipation are proportionate to the constipation incidence rates in any given alosetron group, with the lowest incidence of constipation (9%;12/127) and withdrawal due to constipation (2%; 2/127) in the alosetron 0.5mg group and the highest incidence of constipation (21%; 29/140) and withdrawal rate due to constipation (6%; 8/140) in the alosetron 4.0mg group.
- **SERIOUS COMPLICATIONS OF CONSTIPATION** None reported
- **ISCHEMIC BOWEL** One non-serious AE, reported above
- **UNDIAGNOSED RECTAL BLEEDING** Seven cases reported above, non-serious AEs.

**CONCLUSIONS FROM THIS STUDY** As expected from the pharmacology of this product, increasing the dose, increased the incidence of constipation.
Because the cases of GI bleeding were non-serious, this reviewer has not been able to identify the CRFs, and perform a more detail study of each case.

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MEDICAL OFFICER

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

sNDA: 21-107
SPONSOR: GlaxoSmithkline (formerly Glaxo Wellcome, Inc)
DRUG: Alosetron Hydrochloride (LOTRONEX™) Tablets
DATE OF ORIGINAL SUBMISSION: 29 June, 1999
DATE OF ORIGINAL APPROVAL: 9 February, 2000
VOLUNTARY WITHDRAWAL FROM THE MARKET: 28 November, 2000
DATE OF sNDA SUBMISSION: 7 December, 2001
INITIATION DATE: 24 MARCH, 1999
COMPLETION DATE: 12 JANUARY, 2000
MEDICAL OFFICER: Marcelo A. Barreiro, MD, MSc
MATERIAL REVIEWED: **S3B20015 - A TWELVE WEEK, RANDOMIZED, DOUBLE-BLIND, DOSE-RANGING, PLACEBO-CONTROLLED STUDY OF ALOSETRON IN SUBJECTS WITH NON-ULCER DYSPEPSIA (NUD)**

## EXECUTIVE SUMMARY THERE WERE NO CASES OF ISCHEMIC COLITIS, SERIOUS COMPLICATIONS OF CONSTIPATION OR UNEXPLAINED GI BLEEDING IN 239 PATIENTS EXPOSED TO ALOSETRON

**SUMMARY OF RESEARCH PROTOCOL** Patients of both sexes, with the diagnoses of NUD based on the Rome I criteria, with symptoms for at least six months, were enrolled in the trial. During a two week screening period, baseline levels of symptom severity were established, and an esophagogastroduodenoscopy and a gastric emptying test (USA only) were performed. *H. Pylori* status was determined. Eligible subjects were randomized in a 1:1:1:1 fashion to Alosetron 0.5 mg, 1.0 mg, 2.0 mg, or placebo BID for a 12 week treatment phase, followed by a one week follow up period.

- **DESIGN** Phase II, randomized, parallel group, multinational.
- **DOUBLE BLIND** Yes **CONTROLS** Placebo
- **NUMBER OF SITES** 87 **COUNTRIES** USA (61 sites), Canada (7 sites), Norway (7 sites), South Africa (6 sites), Spain (6 sites)
- **NUMBER OF PATIENTS** Three hundred nineteen patients received at least one dose of study medication (Alosetron n=239; placebo n=80) and constitute the safety analysis population.

**SUMMARY OF SAFETY RESULTS** Subgroup analyses by age, sex, race, hormone use among females, or gastric emptying status revealed no notable differences in the incidence of AEs.

- **AEs** were similar in the Alosetron- and placebo-treated subjects, with the exception of constipation which occurred in 34 %-46 % of subjects receiving Alosetron vs. 13 % in the placebo group.

- **SAEs** There was no significant difference between the Alosetron- and placebo-treated groups
- **RELATED TO STUDY DRUG** Twenty percent (16/80) of subjects in the placebo group reported a total of 20 drug-related AEs. Overall, subjects who received alosetron reported significantly more drug-related AEs ($p<0.001$) than placebo: 116/239 (49%) alosetron-treated subjects reported a total of 174 AEs, and the incidence of drug-related AEs was similar across dose groups. AEs involving the gastrointestinal system (mostly constipation) account for this difference in the incidence of drug-related AEs ($p<0.001$). The incidence of constipation attributed to study drug administration ranged from 33%-45% among subjects who received alosetron versus 11% in the placebo group. The only other common drug-related AE was nausea, which was reported in 5% (4/83) of subjects who received 2mg BID alosetron.
  No significant differences in the incidence of AEs between the placebo and alosetron treatment groups were found for any other body system.
- **CAUSE OF WITHDRAWAL** Among subjects who received alosetron, 27/239 (11%) were withdrawn from the study as the result of one or more AEs. Eight percent (20/239) of subjects withdrew as the result of constipation. The majority of cases of constipation resulting in withdrawal from the study (80%, 16/20) were mild or moderate in intensity, in all cases the investigator judged the constipation to be related to the administration of study drug, in all cases the constipation resolved, and in no case was constipation judged by the investigator to be an SAE.
  In comparison, 5/80 (6%) subjects in the placebo group were withdrawn due to an AE, and only one subject (1/80) was withdrawn due to constipation.
- **SERIOUS COMPLICATIONS OF CONSTIPATION** None reported.
- **ISCHEMIC BOWEL** None reported.
- **UNDIAGNOSED RECTAL BLEEDING** None reported

**CONCLUSIONS FROM THIS STUDY** The safety profile of this study is similar to that of other Alosetron studies. Overall, NUD patients seemed to have good tolerance to Alosetron.

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Marcelo Barreiro
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Hugo Gallo Torres
3/5/02 06:57:32 PM
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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
**MEDICAL OFFICER'S REVIEW**

sNDA: 21-107
SPONSOR: GlaxoSmithkline (formerly Glaxo Wellcome, Inc)
DRUG: Alosetron Hydrochloride (LOTRONEX™) Tablets
DATE OF ORIGINAL SUBMISSION: 29 June, 1999
DATE OF ORIGINAL APPROVAL: 9 February, 2000
*VOLUNTARY WITHDRAWAL FROM THE MARKET*: 28 November, 2000
DATE OF sNDA SUBMISSION: 7 December, 2001
INITIATION DATE: 11 JULY, 2000
COMPLETION DATE: 22 NOVEMBER, 2000
MEDICAL OFFICER: Marcelo A. Barreiro, MD, MSc
MATERIAL REVIEWED: **S3B10948 – AN OPEN-LABEL, WITHIN-SUBJECT STUDY, TO COMPARE THE PHARMACODYNAMICS (PD) AND PHARMACO KINETICS (PK) OF AN ORAL CONTRACEPTIVE CONTAINING LEVONORGESTREL (LN) 100 µG AND ETHINYL ESTRADIOL (EE) 20 µG IN HEALTHY FEMALES SUBJECTS WHEN ADMINISTERED ALONE AND FOLLOWING CO-ADMINISTRATION OF ALOSETRON 1 MG BID ORALLY FOR 28 DAYS**

**EXECUTIVE SUMMARY** 1) **THERE WERE NO DEATHS, SAEs, OR PREGNANCIES**
2) **NO CASES OF ISCHEMIC COLITIS,**
3) **SERIOUS COMPLICATIONS OF CONSTIPATION, OR**
4) **UNEXPLAINED RECTAL BLEEDING REPORTED IN 18 HEALTHY SUBJECTS OBSERVED FOR AN APPROXIMATELY THREE MONTH PERIOD**

**SUMMARY OF RESEARCH PROTOCOL** Eligibility was determined within 28 days of Period 1. Subjects not on OC containing LN and EE were switched to Alesse-21. In Period 1 all subjects received Alesse-21 on Days 1 to 21. In Period 2 subjects received Alosetron 1 mg BID Days 1 to 7 and in Period 3, Alesse-21 daily plus Alosetron 1 mg BID Days 1 to 21. Treatments were on outpatient bases with the exception of Day 21 in Periods 1 and 3, when subjects were admitted to the Clinical Research Unit for PK blood sampling. A post-study visit was conducted at least 30 hours after the last dose of Alosetron in Period 3. Total duration of the study was approximately 3 months: Alesse-21 one tablet daily – Periods 1 and 3, Days 1 to 21 (42 days); Alosetron 1 mg BID – Period 2, Days 1 to 7 and Period 3, Days 1 to 21 (28 days).

Safety: AEs throughout the study. Thrombosis panel on Days 1 and 21 of Periods 1 and 3. Transvaginal ultrasound, clinical laboratory determinations, pregnancy tests, as per protocol.

- **DESIGN** Open label, comparative study (Phase 1).
- **NUMBER OF SITES, COUNTRIES** One. Austin, Texas, USA
- **NUMBER OF PATIENTS** Eighteen enrolled, 17 completed.

**SUMMARY OF PK RESULTS** Alosetron had no statistically significant effect on the PKs of LN and EE.
**SUMMARY OF PD RESULTS** Alosetron did not have any effect on the efficacy of the oral contraceptive.

**SUMMARY OF SAFETY RESULTS** Alosetron had no statistically significant effect on any of the thrombosis variables evaluated either following dosing alone (seven days, Period two), or following 21 days Dosing in combination with an oral contraceptive (Period 3).

- **AEs** Constipation was the most common AE while on Alosetron alone or Alosetron + Alesse-21 (11 subjects), gastrointestinal discomfort and pain were observed in 7 subjects and headaches, on seven subjects. All AEs were mild to moderate in intensity and resolved.
- **SAEs** None reported.
- **RELATED TO STUDY DRUG** Constipation, GI discomfort and pain and headaches.
- **CAUSE OF WITHDRAWAL** None reported.
- **SERIOUS COMPLICATIONS OF CONSTIPATION** None reported
- **ISCHEMIC BOWEL** None reported
- **UNDIAGNOSED RECTAL BLEEDING** None reporte.

**CONCLUSIONS FROM THIS STUDY** This is a very important study , carried out independently by the sponsor (GSK), begins to test the hypothesis formulated by this reviewer in his Alosetron Associated Ischemic Bowel Disease (AAIscBD) Review. The proposed pathogenesis of AAIscBD was that there is a subset of patients (5-8 % of the population), who have a congenital thrombophilia that worsens with the administration of some drugs (like female sex hormones) and on whom Alosetron triggers a mesenteric vascular event. This PK-interaction study, carried out in healthy females, could serve as baseline for other studies performed in females affected with one of the known congenital thrombophilias or with personal or familial history suggestive of a hypercoagulable state.

**RECOMMENDATIONS FOR REGULATORY ACTION** The Agency could propose the sponsor to repeat this same protocol in patients affected with a congenital thrombophilia.

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Marcelo Barreiro
3/5/02 12:28:46 PM
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3/5/02 06:24:51 PM
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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
**MEDICAL OFFICER'S REVIEW**

sNDA: 21-107
SPONSOR: GlaxoSmithkline (formerly Glaxo Wellcome, Inc)
DRUG: Alosetron Hydrochloride (LOTRONEX™) Tablets
DATE OF ORIGINAL SUBMISSION: 29 June, 1999
DATE OF ORIGINAL APPROVAL: 9 February, 2000
VOLUNTARY WITHDRAWAL FROM THE MARKET: 28 November, 2000
INITIATION DATE: 11 JANUARY 2000
DATE OF sNDA SUBMISSION: 7 December, 2001
MEDICAL OFFICER: Marcelo A. Barreiro, MD, MSc
MATERIAL REVIEWED: **S3B30020 - A 24 WEEK RANDOMIZED, OPEN LABEL STUDY OF HEALTH CARE RESOURCE USE, QUALITY OF LIFE, AND PRODUCTIVITY WITH ALOSETRON 1 MG TWICE A DAY VERSUS TRADITIONAL THERAPY IN FEMALES WITH IRRITABLE BOWEL SYNDROME WHOSE PREDOMINANT BOWEL SYMPTOM IS DIARRHEA**

**EXECUTIVE SUMMARY** **1) THERE WERE 10 CASES OF CONFIRMED ISCHEMIC COLITIS (IC) AND TWO ADDITIONAL CASES OF POSSIBLE IC, 2) FOUR CONSTIPATION SAEs, ONE LEADING TO TOTAL COLECTOMY, 3) SIXTY FOUR (4 %) CASES OF GI BLEEDING, 4) ONE DEATH, 5) EIGHTY PATIENTS (4%) REPORTED 146 SAEs, IN A TOTAL OF 1817 PATIENTS EXPOSED TO ALOSETRON**

**SUMMARY OF RESEARCH PROTOCOL**

**DESIGN** This Phase IV study was a randomized, open-label, parallel group, multicenter trial in which female subjects were randomized 2:1 to alosetron or traditional therapy.
**DOUBLE BLIND** No **CONTROLS** No
**NUMBER OF SITES** 486 **COUNTRIES** USA
**NUMBER OF PATIENTS** Enrollment was discontinued when a total of 2706 subjects were randomized to treatment; 67% (1823/2706) to alosetron and 33% (883/2706) to traditional therapy.

**SUMMARY OF SAFETY RESULTS** The safety analysis population (n=2700) included all randomized subjects who received at least one dose of study treatment.

- **AEs** Forty-eight percent (48%, 428/883) of subjects in the traditional therapy group and 72% (1312/1817) of subjects in the alosetron group reported at least one AE during the treatment phase.
  Treatment group effects were similar with regard to the proportion of subjects experiencing AEs for all body systems except the gastrointestinal system. Gastrointestinal AEs were reported for 20% (177/883) of subjects in the traditional therapy group compared with 55% (1004/1817) of subjects in the alosetron group. This difference was primarily due to constipation experienced by 4% of subjects in the traditional therapy group and 37% of subjects in the alosetron group and abdominal or gastrointestinal discomfort and pain which was experienced by 6% of subjects in the traditional therapy group and 15% of subjects in the alosetron group. The most common AEs were defined as those that occurred in >5% of subjects in either treatment group. The most frequently reported AE in the alosetron group was constipation reported by 37% (675/1817) of subjects compared to 4% (33/883) of subjects treated with traditional therapy. **For 4 (<1%) subjects in the alosetron group, constipation met the criteria for serious** (see below under SAEs). On average, subjects who reported constipation in the alosetron group reported an average of 1.3 episodes during the treatment period while subjects treated with traditional therapy reported 1.1 episodes. **The average time to onset of the first episode was 14.5 days for alosetron treated subjects and 36.5 days for subjects treated with traditional therapy.** Subjects who reported constipation were allowed to treat the event as directed by the investigator. Twelve percent (219/1817) of alosetron treated subjects withdrew from the study due to constipation while <1% (5/883) of subjects treated with traditional therapy withdrew for this reason.
  The most commonly reported AE by subjects treated with traditional therapy was abdominal discomfort and pain which occurred in 6% (56/883) of subjects in this group.
  Seven pregnancies were reported during this study, two from the traditional therapy group and five from the alosetron treatment group. Both subjects randomized to traditional therapy gave birth to healthy infants. For the alosetron group, two experienced miscarriage, one had an elective termination of the pregnancy, one gave birth to a healthy infant, and the outcome of the remaining subject was unknown at the time of reporting.
- **SAEs** Five percent (41/883) of the traditional therapy group and 4% (80/1817) of the alosetron group reported 68 and 146 SAEs, respectively, during the study. The nature of SAEs was varied within both treatment groups. One subject in each treatment group experienced a fatal SAE.on 1.3).
  No subjects in the traditional therapy group reported constipation as a SAE. Four SAEs of constipation were reported in 4 subjects (<1%) in the alosetron group. Two cases (83206 and 88034) resolved without complications. For one case (80655), colitis was reported as an event secondary to impaction. The event was considered resolved eight weeks after onset. The fourth report of constipation as an SAE involved a subject (67694) who was subsequently diagnosed with colonic ischemia with toxic megacolon resulting in total colectomy. In addition to these four reports of

constipation as a SAE, one case (87373) of small bowel ileus was reported as a SAE. This event resolved four days after onset and study drug was resumed. **No subjects treated with traditional therapy reported colitis as a SAE while ten subjects in the alosetron treatment group (<1%) reported SAEs of colitis.** Two of these cases were reported as secondary to constipation (80655 and 67694). One case (86475) was reported concurrently with gastritis and was judged unrelated to study drug. One case (80357) was reported concurrently with a diagnosis of diverticulitis and was judged as possibly related to study drug. The remaining six cases (78134, 63223, 66556, 72823,72824, and 82125) were reported in the absence of other gastrointestinal diagnoses. These cases resolved in an average of 7.5 days (range 4-14 days) without complications. Twelve (<1%) alosetron treated subjects reported gastrointestinal discomfort and pain as a SAE. One case (80357) was reported in association with a diagnosis of diverticulitis and possible ischemic colitis and was judged as possibility related to study drug. One case (71146) was reported in association with diverticulitis and was judged as unrelated to study drug. One case (77683) was reported in conjunction with a diagnosis of pancreatitis and was judged as unrelated to study drug. Four cases (63793, 63673, 65414,86953) were reported in conjunction with nausea and/or vomiting and were judged unrelated to study drug. Two cases were reported in conjunction with a diagnosis of constipation. One of these (88034) was judged as possibly related to drug and one (83206) was not. The remaining three cases were reported with no concurrent diagnoses. Two of these (63674 and 66526) were judged to be unrelated to study drug and one (62174) was judged to be possibly related to study drug or possibly related to IBS. Three (<1%) subjects treated with traditional therapy reported gastrointestinal discomfort and pain as a SAE. One (66557) was reported in conjunction with diarrhea and one (73276) in conjunction with nausea. The third case (83657) was reported in the absence of other gastrointestinal symptoms. All were judged as unrelated to study treatment.
**Colitis** was reported as an AE in 13 (<1%) subjects randomized to the alosetron group Ten of these events met the criteria for SAEs. One (74887) of the three non-serious reports of colitis was diagnosed as lymphocytic colitis and was judged as unrelated to study drug. The remaining two (71843 and 69433) non-serious reports of colitis were diagnosed as ischemic colitis and both were judged possibly related to study drug. Both events resolved without complications in three and five days, respectively. There were no reports of colitis in subjects treated with traditional therapy.
None of the SAEs in the traditional therapy group were judged by the investigator as having a reasonable possibility of having been caused by the trial medication while nineteen (12%) SAEs in the alosetron group were judged as possibly drug related Seven (<1%) subjects in the traditional therapy group and 29 (2%) subjects In the alosetron group experienced non-fatal SAEs, which led to their withdrawal from the study.

- **Four percent (64/1817) of subjects in the alosetron treatment group reported an event classified under the group term gastrointestinal hemorrhage**. Less than one percent (4/883) of subjects treated with traditional therapy reported events in this group. Thirty-four of the 64 reports in the alosetron group were judged as possibly

related to study drug. Three events met the criteria for serious. Twenty subjects were withdrawn from the study due to an event in this group.
Three events met the criteria for serious One subject (65443) was diagnosed with diverticulitis and one with ischemic colitis (78134). The remaining serious event (88034) classified as gastrointestinal hemorrhage occurred in conjunction with abdominal pain and constipation in a subject with hemorrhoids. Of the 64 cases in the alosetron treatment group involving events grouped as gastrointestinal hemorrhage, one was associated with peptic ulcer disease and one was associated with anal fissure. Twenty-three cases were reported in subjects who also reported constipation as an adverse event. Nine cases involved subjects who also reported abdominal pain as an adverse event. Five cases of gastrointestinal hemorrhage and pain coincided with reports of constipation. Two subjects reported rectal bleeding in conjunction with a diagnosis of diverticulitis and one in conjunction with ischemic colitis. Two subjects reported rectal bleeding in conjunction with diarrhea. The remaining subjects reported rectal bleeding or bloody stool in the absence of other gastrointestinal diagnoses.
Four subjects treated with traditional therapy reported blood in stool or rectal bleeding. Two of these reports coincided with reports of abdominal pain. None of these reports coincided with reports of constipation.
The death in the Alosetron group is summarized below:
Subject 86477: An 87-year-old female in the alosetron group was hospitalized due to a massive stroke approximately 8 days after starting study drug. Chest x-rays showed perihilar vascular congestion and bilateral pulmonary edema. A carotid sonogram revealed mild bilateral obstructive arteriosclerotic disease. The subject had a history of coronary artery disease, hypertension, non-insulin dependent diabetes mellitus, peptic ulcer disease, and diverticulosis. The subject died 9 days from the onset of the event. The investigator considered the event unrelated to study drug.

- **RELATED TO STUDY DRUG** Two percent (16/883) of subjects in the traditional therapy group and 48% (873/1817) of subjects in the alosetron group experienced drug-related AEs during treatment. This difference was driven by the lower frequency of drug-related gastrointestinal AEs in the traditional therapy group (1%, 10/883) compared with the alosetron group (45%, 821/1817). Specifically, the incidence of drug-related constipation differed between groups: <1% (8/883) in the traditional therapy group versus 36% (648/1817) in the alosetron group. The incidence of gastrointestinal discomfort and pain judged as possibly drug-related also differed between groups: <1% (4/883) in the traditional therapy group versus 11% (191/1817) in the alosetron group. Drug-related AE frequencies were similar between treatments for all other body systems
- **CAUSE OF WITHDRAWAL** Two percent (20/883) of subjects in the traditional therapy group and 21% (380/1817) of subjects in the alosetron group were withdrawn from the study due to AEs. The difference between the two groups can be attributed to the higher percentage of subjects withdrawn due to gastrointestinal AEs in the alosetron group (18%, 326/1817) compared with the traditional therapy group (1%, 12/883). Specifically, subjects were withdrawn from the study due to constipation in 12% (219/1817) of subjects in the alosetron group and in less than 1% (5/883) of subjects in the traditional therapy group

- **SERIOUS COMPLICATIONS OF CONSTIPATION** Four cases of constipation met criteria for SAE. Two had an uneventful recovery. One was associated with colitis. The fourth one evolved into a toxic megacolon and necessitated a total colectomy.
- **ISCHEMIC BOWEL** There were 12 patients with a clinical picture and endoscopic or surgical findings strongly suggestive of ischemic colitis, supported in seven instances by a pathology report. In two cases pathology findings were not stated. In three of these cases a thrombotic panel was performed with negative (normal) results.
- **UNDIAGNOSED RECTAL BLEEDING** This heading covers all reported cases of GI bleeding under different terms: rectal bleeding, hematochezia, blood in the stools, bloody diarrhea, others. The etiology of the bleed was open to question in the majority, in others different etiologies had not been appropiately ruled out. Sixty four cases of GI bleeding were recorded in the Alosetron group of 1817 patients and 4/883in the traditional therapy.

**CONCLUSIONS FROM THIS STUDY** The information in this study was sometimes difficult to interpret, since one patient could be listed in more than one category, or special sub-headings like "Other Significant AEs" were not listed in the main text.
Serious complications of Alosetron therapy leading to hospitalization, transfusion and surgery, continue to be reported.
Of interest, is the fact that several cases of ischemic bowel were interpreted by the investigators as either due to Alosetron therapy, or to the disease treated (IBS). This reviewer has no way to learn how a practicing physician has developed such a controversial theory of ischemic bowel disease.
Constipation as AE seems to be a single occurrence, usually at the begining of therapy, ei, the first two or three weeks. This has been observed in other clinical trials.
Angina pectoris-like chest pains and arrhythmias, continue to be observed in these studies associated with Alosetron administration

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Marcelo Barreiro
3/5/02 01:21:31 PM
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3/5/02 07:10:30 PM
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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
**MEDICAL OFFICER'S REVIEW**

sNDA: 21-107
SPONSOR: GlaxoSmithkline (formerly Glaxo Wellcome, Inc)
DRUG: Alosetron Hydrochloride (LOTRONEX™) Tablets
DATE OF ORIGINAL SUBMISSION: 29 June, 1999
DATE OF ORIGINAL APPROVAL: 9 February, 2000
VOLUNTARY WITHDRAWAL FROM THE MARKET: 28 November, 2000
DATE OF sNDA SUBMISSION: 7 December, 2001
INITIATION DATE: 15 MAY, 2000
MEDICAL OFFICER: Marcelo A. Barreiro, MD, MSc
MATERIAL REVIEWED: **S3B30017 - A MULTICENTER STUDY TO DETERMINE THE EFFICACY AND SAFETY OF ALOSETRON 2 MG BID IN FEMALE SUBJECTS WITH DIARRHEA-PREDOMINANT IRRITABLE BOWEL SYNDROME (IBD-D) WHO DO NOT RESPOND TO TREATMENT WITH ALOSETRON 1 MG BID**

**EXECUTIVE SUMMARY** **1) THERE WERE NO CASES OF ISCHEMIC COLITIS**
**2) THERE WAS ONE CASE OF CONSTIPATION THAT WAS A SAE**
**3) THERE WERE TWO CASES OF RECTAL BLEEDING OF UNCLEAR ETIOLOGY**
**IN A TOTAL OF 876 PATIENTS EXPOSED TO ALOSETRON**

**SUMMARY OF RESEARCH PROTOCOL** This study consisted of eight weeks of open-label treatment with Alosetron 1 mg BID, followed by 12 weeks of randomized, double-blind parallel group treatment with Alosetron 1 mg BID or 2 mg BID in subjects who did not respond to the open-label treatment.

- **DESIGN** Randomized, parallel, comparative, Phase IIIb
- **DOUBLE BLIND** Yes **CONTROLS** Alosetron 1mg BID vs 2 mg BID
- **NUMBER OF SITES** 57 **COUNTRIES** Eight: Australia (10), France (10), Germany (11), Hungary (7), Iceland (2), Italy (4), Netherlands (8), New Zealand (5).
- **NUMBER OF PATIENTS** Eight hundred and seventy six patients took at least one tablet of medication (Safety Population). Only 380 patients completed the open label phase. Of these, 106 were randomized, 53 to each treatment arm, and 36 subjects completed the randomized treatment, 18 in each arm.

**SUMMARY OF EFFICACY RESULTS** Efficacy data was not analyzed

**SUMMARY OF SAFETY RESULTS** No statistical analysis of AEs was planned.

- **AEs** 504/876 (58 %) of patients reported AEs overall and they were similar for each treatment group. The most common were constipation (228, 26 %), abdominal pain/discomfort (80, 9 %), headcache (60, 7%), nausea (44,5 %) and diarrhea (39, 4 %)
- **SAEs** Twelve patients reported 14 SAEs, of which four were treatment related (anal fissure bleeding, colitis, constipation and hyperventilation). This reviewer has not been able to find information on the constipation case in the data provided. Details in four cases that this reviewer considers relevant (bloody diarrhea, rectal bleeding, right subclavian vein thrombosis and aggravation of hypertension with angina pectoris-like chest pain) are provided below:

Protocol Id: S3B30017
Investigator number 51781
Subject number: 174138
Treatment number: OPEN
Case Id: B0087718A
This 50 year old female received oral alosetron 1mg twice daily in the open label phase of a study for the treatment of irritable bowel syndrome. She had a history of non-insulin dependent diabetes, hypercholesterolemia and a pethidine allergy and was concurrently receiving fluvastatin. Four days after initiating study medication the subject developed an acute onset of crampy pain in the left iliac fossa, followed one hour later by diarrhoea with mucous and dark blood containing clots. She vomited twice. She was admitted to hospital for investigation of the bleeding per rectum. Study medication was discontinued and the subject was treated with paracetamol, metoclopramide, hyoscine and temazepam. She had a low grade temperature and her mild abdominal pain persisted, although the rectal bleeding had stopped. A colonoscopy, which was carried out four days after the onset of symptoms, revealed patchy discontinuous colitis extending from the transverse to the descending colon, with a few diverticula. Biopsies taken from two of three fragments of colonic mucosa were normal and the third fragment indicated an inflammatory process. There was reduced thickening and some loss of crypts, with a mild increase in acute and chronic inflammatory cells within the lamina propria and prominent exocytosis of neutrophils through the attenuated surface epithelium. The pattern was considered by the pathologist to be consistent with non-specific colitis. The subject received further treatment with hydrocortisone, ampicillin, gentamycin, metronidazole, prednisolone enema and prednisone. The final diagnosis was transient, patchy, non-specific colitis. The event was considered resolved after 7 days and she was discharged from hospital. The investigator considered that there was a reasonable possibility that the transient, patchy, non-specific colitis may have been related to study medication.

Protocol Id: S3B30017
Investigator number 51781
Subject number: 174139
Treatment number: OPEN
Case Id: B0088386A
This 21 year old female received open-label oral alosetron 1mg twice daily for the treatment of irritable bowel syndrome. She had a history of asthma for which she was concurrently taking salbutamol, beclomethasone and salmeterol, and was known to be allergic to penicillin. Approximately two weeks after initiating study medication, the subject experienced lower abdominal discomfort with increasing hardening of her stools and constipation. Two days later, she noticed the onset of bright red per rectal bleeding with discharge of mucous and had been vomiting. A flexible sigmoidoscopy was performed which was normal and biopsies were taken. A small fissure was noted in the anal region. One biopsy sample appeared normal and the other revealed mucin depletion and attenuation of the colonic mucosa as well as a few muciphages and superficial microhaemorrages, which were possibly pathological. There was no evidence of colitis or idiopathic inflammatory bowel disease. The pathologist considered that the changes were non-specific but may have represented the site of a healed erosion. A gastroenterologist considered that the bleeding was most likely from the anal fissure, which was secondary to the constipation. The subject, who was not hospitalised, was treated with Proctosedyl and study medication was temporarily interrupted. Both the bleeding from the anal fissure and constipation were resolved within 20 days of onset of the constipation. The investigator considered that there was reasonable possibility that the events, which were considered disabling, may have been caused by study medication.

Protocol Id: S3B30017
Investigator number 86567
Subject number: 174920
Treatment number: OPEN
Case Id: B0092231A
This 42 year old female received open-label oral alosetron 1mg twice daily for the treatment of irritable bowel syndrome. She had a history of hypertension.
Approximately eight weeks after initiating study medication, the subject was hospitalised with chest pain, extremely high blood pressure of 220/120mmHg (normal range < 135/85mmHg) and numbness in the left arm. The subject had experienced severe worsening of hypertension and developed severe angina pectoris. The subject was treated with nitrogycerin, urapidil, normodipin and lisinopril. At onset of the events, echocardiography demonstrated slight disturbances in wall-movement. Enzyme values were normal. ECG recordings showed slight ST-depression in the AVL-lead. Both events, which required hospitalisation, were resolved within seven days. Study medication was discontinued a day after resolution of the serious events. In the opinion of the investigator, both events were attributed to the concurrent disorder of hypertension and there was no reasonable possibility that the worsening of hypertension and angina pectoris may have been caused by the study medication.

Protocol Id: S3B30017
Investigator number 86084
Subject number: 175044
Treatment number: 11542
Case Id: B0088539A
This 53 year old female received oral alosetron 1mg twice daily for the treatment of irritable bowel syndrome. She had previously received open label alosetron 1mg twice daily for eight weeks. She had a history of thoracic outlet syndrome to her right arm and was hospitalised for elective surgery for this indication. Study medication was temporarily stopped a day before the operation (18 days after starting randomised study medication) . One day after the operation, the subject developed a moderately severe thrombus in the arterial bloodstream to her right arm. A diagnosis of right subclavian vein thrombosis was confirmed. She was treated with heparin for seven days. She had numbness and pallor in her right arm. She also developed dyspnoea, raising the fear of embolus to her lungs. The numbness, pallor and dyspnoea resolved within two days. She was continued on an oral anticoagulant, nicoumalone, and was discharged from hospital within nine days of onset of the event. The right subclavian vein thrombosis resolved the next day. Study drug was not restarted and permanently discontinued. In the opinion of the investigator, the subclavian vein thrombosis, which prolonged hospitalisation, was possibly due to the subject's underlying thoracic outlet syndrome and the surgery, and there was no reasonable possibility that the event may have been caused by study medication.

- **RELATED TO STUDY DRUG** Four SAEs were considered drug-related.
- **CAUSE OF WITHDRAWAL** 162 (18 %) were withdrawn due to AEs, the most common being constipation (91, 10 %) and abdominal pain/discomfort(35, 4 %)
- **SERIOUS COMPLICATIONS OF CONSTIPATION** One SAE was due to constipation. Details not available.
- **ISCHEMIC BOWEL** None reported
- **UNDIAGNOSED RECTAL BLEEDING** Two cases (subjects #174138 and 174139 detailed above) have an overall clinical picture compatible with ischemic colitis although the biopsy did not confirm it in one, and a colonoscopy was not performed in the other. :

**CONCLUSIONS FROM THIS STUDY** The first of the four cases summarized above has a clinical picture compatible with a mild, transient ischemic colitis, where the pathological diagnosis not always confirms the clinical suspicion.
The second case lends itself to the same consideration, the anal fissure being incidental.
The third and fourth cases could be interpreted as extra-intestinal manifestations of Alosetron. Similar cases have been observed in other Alosetron clinical trials.
The SAE due to constipation is not reported in detail anywhere this reviewer can find it.

**RECOMMENDATIONS FOR REGULATORY ACTION** Review the Alosetron data from the point of view of extra-intestinal manifestations of Alosetron effect (cardio vascular, dermatological, other)

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Marcelo Barreiro
3/5/02 12:16:48 PM
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3/5/02 05:49:03 PM
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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
**MEDICAL OFFICER'S REVIEW**

sNDA: 21-107
SPONSOR: GlaxoSmithkline (formerly Glaxo Wellcome, Inc)
DRUG: Alosetron Hydrochloride (LOTRONEX™) Tablets
DATE OF ORIGINAL SUBMISSION: 29 June, 1999
DATE OF ORIGINAL APPROVAL: 9 February, 2000
INITIATION DATE: 20 OCTOBER, 1999
VOLUNTARY WITHDRAWAL FROM THE MARKET: 28 November, 2000
DATE OF sNDA SUBMISSION: 7 December, 2001
MEDICAL OFFICER: Marcelo A. Barreiro, MD, MSc
MATERIAL REVIEWED: **S3B30013 - A 12-WEEK, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ALOSETRON IN FEMALE SUBJECTS WITH ALTERNATING DIARRHEA/CONSTIPATION IRRITABLE BOWEL SYNDROME**

**EXECUTIVE SUMMARY** **1) THERE WAS ONE CASE OF ISCHEMIC COLITIS,**
**2) THERE WAS ONE CASE OF DRUG-RELATED COLITIS,**
**3) THERE WERE NO CASES OF SERIOUS COMPLICATIONS OF CONSTIPATION AND**
**4) THERE WERE 10 CASES OF GI BLEEDING IN 280 PATIENTS EXPOSED TO ALOSETRON**

**SUMMARY OF RESEARCH PROTOCOL**

- **DESIGN** This was a Phase III, randomized, multicenter study in female patients who met Rome I criteria for IBS alternating diarrhea with constipation (IBS-A).
- **DOUBLE BLIND** Yes **CONTROLS** Placebo
- **NUMBER OF SITES** 164 **COUNTRIES** Two: USA (149), Canada (15)
- **NUMBER OF PATIENTS** Eligible patients received Alosetron 1 mg BID (280 patients) or identical placebo BID (281 patients), for 12 weeks.

**SUMMARY OF SAFETY RESULTS**

- **AEs** Fifty-two percent (146/280) of subjects in the placebo group reported a total of 344 treatment-emergent AEs compared with 169/280 (60%) of subjects reporting a total of 434 AEs in the Alosetron group. AEs involving the gastrointestinal system, in particular constipation, account for the difference in the incidence of AEs (p=0.050). There were no other significant differences in the overall incidence of AEs between the placebo and Alosetron treatment groups for other body systems.

- **SAEs** A total of 8/280 (3%) subjects who received Alosetron reported 12 SAEs compared with 5/280 (2%) subjects in the placebo group who reported 6 SAEs. The overall incidence of SAEs among subjects who received Alosetron was not significantly different from the incidence in the placebo group. Within individual body systems, there were no significant differences in the incidences of SAEs between treatment groups.
  In both treatment groups, SAEs occurred mainly in the GI body system
  Neither constipation nor its sequelae was reported in either treatment group as an SAE. In the Alosetron group, SAEs reported in the GI body system included abdominal discomfort and pain (n=1), colitis (n=2), appendicitis (n=1), diverticulosis (n=1) and gastrointestinal hemorrhage (n=1).
  In the Alosetron treatment group, four subjects were withdrawn due to the occurrence of one or more SAEs (abdominal discomfort and pain/pain; benign neurological neoplasia; colitis; colitis/diverticulosis). Four SAEs were judged by the investigator to be drug related (myalgias; pain; colitis[2]). In one subject the SAE resolved with sequelae (benign neurological neoplasia); all other SAEs resolved.
- **RELATED TO STUDY DRUG** Fourteen percent (40/280) of subjects in the placebo group reported a total of 58 drug-related AEs. Subjects who received Alosetron reported significantly more drug-related AEs ($p<0.001$): 83/280 (30%) subjects reported a total of 158 AEs.
  AEs involving the gastrointestinal system (mostly constipation) account for this difference in the incidence of drug-related AEs ($p<0.001$). The incidence of constipation attributed to study drug administration was 16% among subjects who received Alosetron versus 4% in the placebo group. The incidence of abdominal discomfort and pain attributed to study drug administration was 5% among subjects who received Alosetron versus <1% in the placebo group. No other drug-related AEs were reported with an incidence =5% in either treatment group.
- **CAUSE OF WITHDRAWAL** Among subjects who received Alosetron, 34/280 (12%) were withdrawn from the study due to one or more AEs. A total of 47 AEs associated with study drug withdrawal in 24 subjects were judged by the investigator to be related to the administration of Alosetron. In one subject, the AEs resolved without sequelae (migraines) and in three subjects the AEs had not resolved (vomiting; abdominal discomfort and pain; positive fecal occult blood; musculoskeletal pain). Four subjects were withdrawn as a result of one or more SAEs (abdominal discomfort and pain/pain; benign neurological neoplasia; colitis; colitis/diverticulosis). Six percent (18/280) of the Alosetron-treated subjects withdrew as the result of constipation and in all cases the investigator judged the constipation to be related to the administration of study drug, in all cases the constipation resolved, and in no case did the constipation meet the definition of an SAE. In comparison, 17/280 (6%) subjects in the placebo group were withdrawn due to one or more AEs. A total of 18 AEs associated with study drug withdrawal in 16 subjects were judged by the investigator to be related to the administration of placebo. In two subjects, two AEs resolved without sequelae (diverticulosis; colitis) and in two subjects three AEs had not resolved [abdominal distension; gastrointestinal discomfort and pain (in two different subjects)]. One subject was withdrawn as a result of a SAE (abdominal

discomfort and pain). Two placebo-treated subjects were withdrawn due to constipation.

- **SERIOUS COMPLICATIONS OF CONSTIPATION** There were no cases of serious complications of constipation.
- **ISCHEMIC BOWEL** There was one SAE of ischemic colitis (subject # 32451).
- **UNDIAGNOSED RECTAL BLEEDING** Events of rectal bleeding occurred in 10 Alosetron-treated subjects and 2 subjects receiving placebo, with onset at varying times throughout the 12 week treatment period. Of the Alosetron-treated subjects, 4 subjects exhibited hemorrhoids or a history of hemorrhoids as a possible source of bleeding. Two subjects' source was undefined. One subject had diverticulosis. Two subjects were reported to have non-specific colitis: **one with histopathologic evidence of focal ischemia and inflammation, (# 32451),** the other, (subject # 28960) endoscopically diagnosed as ischemic colitis, the investigator amended his diagnosis to non-specific colitis related to Alosetron, in view of the path report (see Attachment). One subject reported proctitis. In those receiving placebo, one subject exhibited diverticulosis, while the other, with a reportedly normal endoscopy, exhibited histopathologic evidence of non-specific and possibly "drug-induced" colitis.

**CONCLUSIONS FROM THIS STUDY** The pattern of AEs in this study is similar to that of other clinical trials. Constipation continues to be a frequent AE in the Alosetron-treated group, but easily manageable with simple measures. Cases of GI bleeding continue to be reported by the sponsor. Many of them are not considered serious, and are not appropriately investigated by colonoscopy with biopsies. The subject numbers are not listed, and they become impossible to identify. Simple explanations of causality are offered, most revolving around different forms of anal-canal disease. This reviewer believes, on intuitive bases, that are mild forms of ischemic colitis that resolve spontaneously, since they are present, nearly always, in the Alosetron-treated group.

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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
**SUMMARY OF SAFETY REVIEW**
(16 RANDOMIZED CLINICAL TRIALS)

sNDA: 21-107
SPONSOR: GlaxoSmithkline (formerly Glaxo Wellcome, Inc)
DRUG: Alosetron Hydrochloride (LOTRONEX™) Tablets
DATE OF ORIGINAL SUBMISSION: 29 June, 1999
DATE OF ORIGINAL APPROVAL: 9 February, 2000
VOLUNTARY WITHDRAWAL FROM THE MARKET: 28 November, 2000
DATE OF sNDA SUBMISSION: 7 December, 2001
MEDICAL OFFICER: Marcelo A. Barreiro, MD, MSc

**INTRODUCTION AND BACKGROUND** Alosetron (Lotronex™) was approved for sale in the United States on 9 February, 2000. Its only indication was for the management of abdominal pain and discomfort in female patients with Irritable Bowel predominant diarrhea (IBS-D). Because of serious complications of constipation (which had not been observed during the clinical trials) and cases of intestinal necrosis leading to massive bowel resection, and in some cases death, the sponsor decided to voluntarily withdraw the drug from the market on 28 November, 2000. Since then, both the sponsor and the Agency have been considering the reintroduction of Alosetron in the market under more restricted circumstances, and as part of a Risk Management Plan. The Agency requested all available information world-wide from the 40 Randomized Clinical Trials (RCTs) in progress up until 28 November, 2000, when they were all terminated. The sponsor complied in the form of a supplemental NDA, filed on 7 December, 2001.

The sixteen protocols subject of this review are part of the sNDA, and were assigned to this reviewer by the Medical Team Leader, Hugo Gallo-Torres, MD, PhD. The review was limited to the Safety Population of these studies, with special attention to cases of Ischemic Bowel Disease ("Ischemic Colitis"), serious complications of constipation, and GI bleeding (hematochezia, bloody diarrhea) of poorly documented etiology or unknown source. Drs. S Kress and E. Kaminskas reviewed the other 26 research protocols included in the sNDA.

The findings of this review are summarized in the Master Table below.

**MASTER TABLE**
**SUMMARY OF FINDINGS**
**IN**
**SIXTEEN RCTs PART OF sNDA 21-107**

| PROTOCOL # | # PTS. | # IC PTS. | # SCOC PTS. | # GI BLEED |
|---|---|---|---|---|
| S3B1048 | 18 | 0 | 0 | 0 |
| S3B10945 | 24 | 0 | 0 | 0 |
| S3B10947 | 7 | 0 | 0 | 0 |
| S3B10948 | 18 | 0 | 0 | 0 |
| S3B20015 | 239 | 0 | 0 | 0 |
| S3B20023 | 534 | 1 | 0 | 7 |
| S3B30006 | 348 | 0 | 0 | 0 |
| S3B30012 | 422 | 1(3*) | 0 | 14 |
| S3B30013 | 280 | 1(1+) | 0 | 10 |
| S3B30017 | 876 | 0 | 1 | 2 |
| S3B30020 | 1817 | 10 | 4 | 64 |
| S3B30025 | 1027 | 0(2**) | 1 | 0(1**) |
| S3B30026 | 960 | 0 | 0 | 0 |
| S3B30031 | 276 | 0 | 0 | 0 |
| S3B30033 | 94 | 0 | 0 | 3 |
| S3B40032 | 633 | 0 | 0 | 7 |
| TOTALS | 7573 | 13(6***) | 6 | 107 (1) |

- Three cases of undefined "Colitis". Original records not available.

** Suspected

+ One case of drug-related colitis

*** Above, combined

**SUMMARY** Eleven of these 16 clinical trials were terminated prematurely on 28 November, 2000 when the sponsor voluntarily decided to withdraw the drug from the market. In those trials, the data, both in form and content, is sometimes difficult to obtain and interpret.

There is, nevertheless, a pool of 7573 patients that provide abundant safety information.

- Thirteen cases of Ischemic Colitis were observed in these 7573 patients. They all subsided without sequelae. One case of toxic megacolon was preceded by constipation, and it required a total colectomy (S3B30020, subject # 67694). It is difficult, in retrospect, with limited information, to establish causality. Constipation, in any of its forms, does not lead to toxic megacolon
- Other cases were observed in association with different clinical pictures, and, in retrospect it is impossible to determine causality or what role, if any at all, the ischemic features of the bowel had in the overall picture (S3B30033, subject # 190586).

- The cases of constipation are less, numerically, and the severity also seem to be less, suggesting that prevention of complications of constipation is within reach.
- The cases of GI bleeding are of concern, since simplistic explanations as to the etiology (hemorrhoids, anal fissure, diverticulitis) may hide additional cases of AAIscBD.
- The same applies to the six cases of "colitis", or "non-specific colitis", always in the Alosetron treated group, that do not quite make criteria for ischemic bowel. But, regardless of etiology, they all seemed to do well, and resolved with little or no treatment.
- Not infrequently, cases of severe cardiac arrythmia, sudden death, angina pectoris-like pain and heart failure, are reported associated with Alosetron administration. This fact, to this reviewer's knowledge, has never been addressed with due scientific rigor, to demonstrate whether it is a statistical phenomenon or secondary to Alosetron effect.

**RECOMMENDATIONS FOR REGULATORY ACTION**

1. This reviewer recommends (and volunteers for) an in-depth review of all available data for extra-intestinal manifestations of Alosetron effect.
2. For the purpose of the RMP, all cases of rectal bleeding in patients on treatment with Alosetron should be considered as due to ischemic colitis, unless proven otherwise by appropriate studies (endoscopy, histology, radiology).
3. The focus of the Risk Management Plan should be the identification of factors that make patients prone to Ischemic Bowel Disease, particularly the forms that lead to transfusion, surgery and death, present in the post-marketing data, and to their prevention, early diagnosis and treatment.

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

| | |
|---|---|
| **NDA:** | **21-107 SE8-05** |
| **Applicant:** | **GlaxoSmithKline** |
| **Drug:** | **LOTRONEX (alosetron)** |
| **Pharmacological Category:** | **5HT-3 Receptor antagonist** |
| **Drug Study:** | **A 24 Week Randomized, Open Label Study of Health Care Resource Use, Quality of Life and Productivity With Alosetron 1 mg Twice Daily Versus Traditional Therapy in Females with Irritable Bowel Syndrome whose Predominant Bowel Symptom is Diarrhea** |
| **Study Administration:** | **Pharmaceutical Research Associates International** |
| **Material Reviewed:** | **Safety Review of Clinical Reports for Protocol S3B30020 (Phase IIIb Study) Initiation; Jan. 11, 2000 Early Termination: Nov. 28, 2000** |
| **Reviewer:** | **Scheldon Kress, M.D.** |

## Executive Summary

Protocol S3B30020 was a 24 Week Randomized, Open Label Study of Health Care Resource Use, Quality of Life and Productivity With Alosetron 1 mg Twice Daily Versus Traditional Therapy in Females with Irritable Bowel Syndrome whose Predominant Bowel Symptom was Diarrhea. Enrollment was discontinued when a total of 2706 subjects were randomized to treatment; 67% (1823/2706) to alosetron and 33% (883/2706) to traditional therapy. Fifty-three percent (53%, 1435/2706) of randomized subjects completed the study. The percentage of subjects who completed the study was substantially impacted by the sponsor's decision to terminate the study prematurely.

Sixty four percent (1435/2256) of subjects in the evaluable population (EP) completed the study and 36% (821/2256) withdrew prematurely. Twenty six percent (594/2256) of the EP withdrew voluntarily prior to study termination and 10% (227/2256) withdrew due to termination of the study after completing at least 20 weeks of treatment. The reasons for premature discontinuation from the study were: adverse events (11%), consent withdrawn (5%), lost to follow-up (4%), protocol violation (2%), screen failure (<1 %), lack of efficacy (2%), and "other" reasons (12%).

The safety analysis population included all randomized patients who received at least one dose of study treatment. Nearly all patients reported use of concurrent medications, the most common of which were grouped as anti-depressants (30% specifically SSRIs), NSAIDs (31%), and estrogens (30%).

A summary of the safety data provided in this protocol follows:

- The incidence of drug related AEs, especially constipation (<1% for traditional therapy and 36% for alosetron treated subjects), was higher among the alosetron treated patients compared with traditional therapy. From within the alosetron-treated group, 18% withdrew due to gastrointestinal AEs and 12% withdrew due to constipation as the AE (consistent with the previously observed withdrawal rate of one-third of constipated patients).

- Gastrointestinal AEs were more common among alosetron-treated patients than among Traditional-therapy patients. This was primarily due to the incidence of constipation in the alosetron group (4% with traditional therapy versus 37% with alosetron)

- Gastrointestinal SAEs were the most commonly reported in both treatment groups. A SAE of severe constipation was reported in 6 patients randomized to alosetron and none of the traditional therapy patients. One of these patients developed toxic megacolon, fulminant secondary ischemic colitis, and septicemia and required a total colectomy and ileostomy. Ischemic colitis occurred as SAEs in 10 alosetron-treated patients and none of the patients treated with traditional therapy. One of the patients with ischemic colitis developed a colonic perforation, peritonitis, and sepsis and required a sigmoid resection and colostomy.

**Executive Summary (continued)**

- In this study, ischemic colitis was a frequently occurring SAE (1:180 patient exposures), but was generally mild, reversible, and self-limited. However, the SAEs associated with severe constipation occurred less frequently (1:302 patient exposures), but always required hospitalization. One patient with each of these two SAEs required surgical intervention. No study-related deaths were reported.

In summary, from among the 1817 alosetron-treated patients in this planned 24 week study, 16 patients (approximate incidence of 1:114, 0.9%) collectively experienced SAEs of ischemic colitis and serious complication of severe constipation

6 patients experienced serious complications of severe constipation (@ 1/300)

- 6 patients required hospitalization
- 5 patients resolved with conservative treatment
- 2 patients developed small bowel dysfunction (1 patient an ileus and 1 a partial obstruction)
- 1 patient with toxic megacolon developed fulminant secondary ischemic colitis with septicemia and required a total colectomy and ileostomy

10 patients experienced ischemic colitis (@ 1/180)

- Diagnosis was established via colonoscopy in 9 patients and via pathological examination in 8 patients
- 6 patients required hospitalization
- 9 patients resolved with conservative treatment
- 1 patient developed a secondary perforation with peritonitis and sepsis, and required a sigmoid resection and colostomy. She subsequently suffered a stroke.

Similar to the occurrence of these SAEs observed during the post-marketing distribution of alosetron, ischemic colitis cases occurred more frequently than did cases of serious complications of constipation. However, the smaller number of cases of serious complications of constipation were associated with a greater frequency of hospitalization and surgery. No deaths among alosetron-treated patients in this study could be attributed to the usage of alosetron.

While based on small numbers of cases, the incidence of these SAEs appear to occur sporadically throughout the duration of the study. If any pattern can be suggested from these data, it would be that vulnerability for ischemic colitis is highest at the onset of therapy. Six of the ten cases of ischemic colitis associated with alosetron therapy for 24 weeks occurred within the first 3 weeks of therapy.

Data remain insufficient to determine any definite risk factors that would be useful in reducing the incidence of ischemic colitis. Reduction of the risk of complications from severe constipation, will continue to depend on the earliest recognition of constipation.

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## I. Introduction To Safety Review

Protocol S3B30020 was a 24 Week Randomized, Open Label Study of Health Care Resource Use, Quality of Life and Productivity With Alosetron 1 mg Twice Daily Versus Traditional Therapy in Females with Irritable Bowel Syndrome whose Predominant Bowel Symptom was Diarrhea. Traditional therapy was the comparator, defined as any therapy deemed appropriate by the investigator to treat the symptoms of IBS, excluding alosetron or any other 5-HT3 antagonist.

Enrollment was discontinued when a total of 2706 subjects were randomized to treatment; 67% (1823/2706) to alosetron and 33% (883/2706) to traditional therapy. Fifty-three percent (53%, 1435/2706) of randomized subjects completed the study. The percentage of subjects who completed the study was substantially impacted by the sponsor's decision to terminate the study prematurely. The safety analysis population included all randomized patients who received at least one dose of study treatment. Nearly all patients reported use of concurrent medications, the most common of which were grouped as anti-depressants (30% specifically SSRIs), NSAIDs (31%), and estrogens (30%). Use of concurrent medications was similar for both groups of patients. While meticulous recording of the concomitant prescribed and OTC medications were made, no comparisons are available for those patients with and without AEs and SAEs.

## II. Safety Review

### 1. Adverse Events

Sixty four percent (1435/2256) of subjects in the evaluable population (EP) completed the study and 36% (821/2256) withdrew prematurely. Twenty six percent (594/2256) of the EP withdrew voluntarily prior to study termination and 10% (227/2256) withdrew due to termination of the study after completing at least 20 weeks of treatment. The reasons for premature discontinuation from the study were: adverse events (11%), consent withdrawn (5%), lost to follow-up (4%), protocol violation (2%), screen failure (<1 %), lack of efficacy (2%), and "other" reasons (12%). Subjects who discontinued due to study termination make up the majority of the "other" category.

During treatment, 48% (428/883) of patients treated with traditional therapy and 72% (1312/1817) of alosetron-treated patients reported at least one adverse event. Gastrointestinal AEs were reported for 20% (177/883) of patients in the traditional therapy group compared with 55% (1004/1817) of patients in the alosetron group. This difference was driven by events involving the gastrointestinal system, specifically, constipation (4%, traditional therapy; 37%, alosetron) and gastrointestinal pain and discomfort (6%, traditional therapy; 15% alosetron), as demonstrated in Table 1. The proportion of patients reporting other events was similar between the two treatment groups. Events judged by the investigator as possibly related to study drug were reported for 2% of patients treated with traditional therapy and 48% of alosetron-treated patients. Again, this difference was driven by the difference in the number of patients who reported constipation judged to be drug related (<1% traditional therapy; 36% alosetron) and gastrointestinal pain and discomfort (<1% traditional therapy; 11% alosetron).

Frequency of most adverse events and drug related AEs were similar in age and race subgroups. In the alosetron-treated group, constipation was reported as an AE in 41% of patients > 65 years of age and in 37% of patients < 65 years of age, while traditionally-treated patients at all ages reported constipation orted as an AE in 4% of patients Clinical chemistry and hematology values were similar between treatment groups.

**Table 1**
**Most Commonly Reported Adverse Events During Treatment**
**Safety Population, Protocol S3B30020**

| | Traditional Therapy n/883 (%) | Alosetron 1 mg BID n/1817 (%) |
|---|---|---|
| **Gastrointestinal** | 177 (20) | 1004 (55) |
| **Constipation** | 33 (4) | 675 (37) |
| **Gastrointestinal discomfort and pain** | 56 (6) | 276 (15) |
| **Diarrhea** | 34 (4) | 129 (7) |
| **Nausea** | 36 (3) | 123 (7) |
| **Ear, Nose & Throat** | | |
| **Ear, Nose & Throat infections** | 44 (5) | 90 (5) |
| **Neurology** | | |
| **Headaches** | 26 (3) | 98 (5) |

Source data: Sponsor's Table S1

Events meeting the criteria for serious adverse events were reported for 5% (41/883) of patients treated with traditional therapy and 4% (80/1817) of alosetron treated patients. Two deaths were reported during the study. One alosetron treated patient died following a massive stroke and one traditional therapy-treated patient died from coronary artery disease and congestive heart failure. The reporting investigators judged both events to be unrelated to the study treatment.

Gastrointestinal SAEs were the most commonly reported in both treatment groups. SAEs associated with constipation were reported in 6 patients randomized to alosetron and in none of the traditional therapy patients. Ischemic colitis was reported as a SAE in 10 alosetron-treated patients and in none of the patients treated with traditional therapy.

Seven pregnancies were reported during the study, five in alosetron treated patients and two in patients treated with traditional therapy. Both patients randomized to traditional therapy gave birth to healthy infants. For the alosetron group, two patients experienced miscarriage, one underwent an elective termination of the pregnancy, one gave birth to a healthy infant, and the outcome of the remaining patient was unknown at the time of reporting

## 2. Serious Adverse Events

A serious adverse event (SAE) was any AE occurring at any dose that resulted in any of the following outcomes:

1) death
2) life-threatening AE
3) inpatient hospitalization or prolongation of existing hospitalization
4) disability/incapacity
5) congenital anomaly in the offspring of a subject who received drug
6) important medical events that may not have resulted in death, been life-threatening, or required hospitalization may have been considered SAEs when, based upon appropriate medical judgement, they may have jeopardized the subject and may have required medical or surgical intervention to prevent one of the outcomes listed in this definition.

During the study, 5% (41/883) of the traditional therapy group and 4% (80/1817) of the alosetron group reported 68 and 146 SAEs, respectively. The nature of SAEs varied within both treatment groups. There were no reports of SAEs of ischemic colitis or severe constipation among patients in the traditional-therapy-treated patients.

No patients in the traditional therapy group reported constipation as a SAE. SAEs associated with constipation were reported in 6 patients (0.3%) in the alosetron group. Five cases resolved without complications. For one case (80655), colitis was reported as an event secondary to impaction. The event was considered resolved 6 days after onset. The sixth report of constipation as an SAE involved a patient (67694) who was subsequently diagnosed with toxic megacolon and colonic ischemia and required a total colectomy and ileostomy.

Included in these six reports of constipation as SAEs, were two cases of small bowel dysfunction: one case (87373) of small bowel ileus resolved four days after onset and study drug was resumed and one case (65385) of partial small bowel obstruction.

No patient treated with traditional therapy reported colitis as a SAE while ten patients in the alosetron treatment group (0.6%) reported SAEs of colitis . Two additional cases were reported as secondary to severe constipation (80655 and 67694). One case (86475) was reported concurrently with gastritis and was judged unrelated to study drug. One case (80357) was reported concurrently with a diagnosis of diverticulitis and was judged as possibly related to study drug. Nine cases resolved spontaneously in an average of 7.5 days (range 4 to 14 days) without complications. A tenth case (65443) developed a colonic perforation with peritonitis and sepsis during the study and was reported to OPDRA as demonstrating pathologic confirmation of ischemic colitis upon examination by an out-of-study pathologist. One (74887) of the non-serious reports of colitis was diagnosed as lymphocylic colitis and was judged as unrelated to study drug.

Twelve (<1%) alosetron-treated patients reported gastrointestinal discomfort and pain as a SAE. One case (80357) was reported in association with a diagnosis of diverticulitis and possible ischemic colitis and was judged as possibility related to study drug. One case (71146) was reported in association with diverticulitis and was judged as unrelated to study drug. One case (77683) was reported in conjunction with a diagnosis of pancreatitis and was judged as unrelated to study drug. Four cases (63793, 63673, 65414, 86953) were reported in conjunction with nausea and/or vomiting and were judged unrelated to study drug. Two cases were reported in conjunction with a diagnosis of constipation. One of these (88034) was judged as possibly related to drug and one (83206) was not by the investigator. The remaining three cases were reported with no concurrent diagnoses. Two of these (63674 and 66526) were judged to be unrelated to study drug and one (62174) was judged to be possibility related to study drug or possibly related to IBS. Three (<1 %) patients treated with traditional therapy reported gastrointestinal discomfort and pain as a SAE. One (66557) was reported in conjunction with diarrhea and one (73276) in conjunction with nausea. The third case (83657) was reported in the absence of other gastrointestinal symptoms. All were judged as unrelated to study treatment.

None of the SAEs in the traditional therapy group were judged by the investigator as having a reasonable possibility of having been caused by the trial medication while nineteen (12%) SAEs in the alosetron group were judged as possibly drug related. Seven (<1%) patients in the traditional therapy group and 29 (2%) patients in the alosetron group experienced non-fatal SAEs, which led to their withdrawal from the study. Two patients in the alosetron group reported SAEs during the non-treatment phase.

Among the 121 patients with SAEs in this study, gastrointestinal disorders predominated, (36/1817, 2% in the alosetron-treatment group and 13/883, 1% in the traditional-treatment group). Gastrointestinal SAEs included isolated instances of abdominal cancers, pancreatitis, gastroenteritis, gastritis, hematemesis, vomiting, diarrhea, and dehydration. Five patients developed appendicitis and required surgery, 2 in the traditional therapy group and 3 in the alosetron-treated group. Six patients developed cholecystitis, most associated with calculi, and required surgery, 5 in the alosetron-treated group and 1 in the traditional therapy group. Three patients were discovered to have common bile duct stones which required removal, 2 in the alosetron-treated group and 1 in the traditional therapy group. One patient in the alosetron-treatment group developed biliary dyskinesia.

The significance of this increased frequency of occurrence of gall bladder-biliary tract SAEs among alosetron-treated patients, if any exists, remains to be determined. Summary of gall bladder-biliary tract SAEs observed during the study are shown in Table 2.

**Table 2**
**Gall Bladder-Biliary Tract SAEs in Protocol S3B30020**

| Gall Bladder-Biliary Tract SAEs | Patient # | Alosetron -Treated | Traditional -Treated |
|---|---|---|---|
| Cholecystitis with surgery | 62543 | X | |
| Cholecystitis with surgery | 63793 | X | |
| Cholecystitis with surgery | 74234 | X | |
| Cholecystitis with surgery | 75648 | X | |
| Cholecystitis with surgery | 82006 | X | |
| Cholecystitis with surgery | 83863 | | X |
| Common bile duct stone removal | 79515 | X | |
| Common bile duct stone removal | 82675 | X | |
| Common bile duct stone removal | 84254 | | X |
| Biliary dyskinesia | 63309 | X | |
| TOTALS | | 8 | 2 |
| | | 8/1823<br>0.4% | 2/883<br>0.2% |

Source of data: Medical reviewer's tables

Summaries of alosetron-treated patients who experienced SAEs during the study are shown in Table 3 (Serious Complications of Severe Constipation) and Table 4 (Ischemic Colitis).

**Table 3**

**Summary of Patients with Serious Complications of Severe Constipation Associated with Alosetron Usage In Protocol S3B30020**

| Patient Number | Age | Wt. | Onset on Therapy | SAE | Hospita-lization | Surgical Procedure | Outcome |
|---|---|---|---|---|---|---|---|
| 65385 | 77 | 119 | Month 4 | Partial small bowel obstruction | Yes | None | Resolved in 11 days |
| 67694 | 56 | 129 | Day 27 | Toxic megacolon, fulminant secondary ischemic colitis, septicemia | yes | Total colectomy, ileostomy | Ileostomy, |
| 80655 | 26 | 351 | Month 4 | Impaction, secondary ischemic colitis | Yes | None | Resolved in 6 days |
| 83206 | 48 | N/A | Week 10 | Obstipation with impaction | Yes | None | Resolved in 3 days |
| 87373 | 67 | 247 | Month 3 | Small bowel ileus | Yes | None | Resolved in 4 days |
| 88034 | 50 | 165 | Week 6 | Abdominal pain and constipation | Yes | None | Resolved in 3 days |
| **TOTAL Patients 6** (6/1817, 0.3%) @1/300 | | | | | | | |

Source of data: Medical reviewer's tables

**Table 4**

**Summary of Patients with Ischemic Colitis Associated with Alosetron Usage In Protocol S3B30020**

| Patient Number | Age | Wt. | Onset on Therapy | SAE | Hospita-lization | Surgical Procedure | Outcome |
|---|---|---|---|---|---|---|---|
| 63223 | 55 | 160 | Week 11 | Ischemic colitis | Yes | None | Resolved in 7 days |
| * 65443 | 67 | 168 | Day 4 | Perforation colon secondary to ischemic colitis*, peritonitis, sepsis, stroke, | yes | Sigmoid resection, colostomy | Hospital 8 weeks Colostomy hemiparesis, personality change |
| 66556 | 75 | 195 | Month 5 | Ischemic colitis | Yes | None | Resolved in 7 days |
| 69433 | 37 | 120 | Month 4 | Ischemic colitis | No | No | Resolved in 4 days |
| 71843 | 37 | 222 | Month 2.5 | Ischemic colitis | No | No | Resolved in 4 days |
| 72823 | 64 | 146 | Day 2 | Ischemic colitis | No | None | Resolved in 6 days |
| 72824 | 57 | 139 | Day 4 | Ischemic colitis | No | None | Resolved in 7 days |
| 78134 | 20 | 134 | Day 3 | Ischemic colitis | Yes | None | Resolved in 4 days |
| 80357 | 51 | 182 | Week 3 | Ischemic colitis | Yes | None | Resolved |
| 82125 | 61 | 180 | Day 7 | Ischemic colitis | Yes | None | Resolved in 2 weeks |
| **Total Patients 10** (10/1817, 0.55%) @ 1/180 | | | | | | | |

Source of data: Medical reviewer's tables

* Sponsor did not include this patient among the cases with ischemic colitis, but patient's attorney had specimen of resected colon tissue reviewed by pathologist and claims it demonstrated ischemic colitis.

In summary, from among the 1817 alosetron-treated patients in this study 16 patients (approximate incidence of 1:114, 0.9%) experienced SAEs of ischemic colitis and serious complication of severe constipation

6 patients experienced serious complications of severe constipation (@ 1/300)

- 6 patients required hospitalization
- 5 patients required discontinuation of treatment with alosetron
- 5 patients resolved with conservative treatment
- 2 patients developed small bowel dysfunction (1 patient an ileus and 1 patient a partial obstruction)
- 1 patient with small bowel ileus, treatment with alosetron was temporarily interrupted and then restarted
- 1 patient with toxic megacolon developed fulminant secondary ischemic colitis with septicemia and required a total colectomy and ileostomy

10 patients experienced ischemic colitis (@ 1/180)

- Diagnosis was established via colonoscopy in 9 patients and via pathological examination in 8 patients
- 10 patients required discontinuation of treatment with alosetron
- 9 patients resolved with conservative treatment
- 6 patients required hospitalization
- 1 patient developed a secondary perforation with peritonitis and sepsis, and required a sigmoid resection and colostomy. She subsequently suffered a stroke.

### 3. Adverse Events Leading to Discontinuation of Study Drug and/or Study Withdrawal

Two percent (20/883) of patients in the traditional therapy group and 21% (380/1817) of patients in the alosetron group were withdrawn from the study due to AEs. The difference between the two groups can be attributed to the higher percentage of patients withdrawn due to gastrointestinal AEs in the alosetron group (18%, 326/1817) compared with the traditional therapy group (1%, 12/883). Specifically, patients were withdrawn from the study due to constipation in 12% (219/1817) of patients in the alosetron group and in less than 1% (5/883) of patients in the traditional therapy group.

### Adverse Events Involving Bleeding Associated with Bowel Function

Four percent (64/1817) of patients in the alosetron treatment group reported an event classified under the group term gastrointestinal hemorrhage. Less than one percent (4/883) of patients treated with traditional therapy reported events in this group. Of the 64 cases in the alosetron-treatment group involving events grouped as gastrointestinal hemorrhage:

- 34 reports of gastrointestinal hemorrhage in the alosetron-treated group were judged as "reasonably related to study drug"
- 23 cases were reported in patients who also reported constipation as an adverse event.
- 20 alosetron-treated patients were withdrawn from the study due to gastrointestinal hemorrhage
- 9 cases involved patients who also reported abdominal pain as an adverse event
- 5 cases of gastrointestinal hemorrhage and pain coincided with reports of constipation
- 3 patients met the criteria for serious adverse events
- 2 patients reported rectal bleeding in conjunction with a diagnosis of diverticulitis
- **2 patients reported rectal bleeding in conjunction with diarrhea.**
- 1 patient (65443) was diagnosed with diverticulitis
- 1 patient was diagnosed with ischemic colitis (78134).
- 1 patient with a serious event (88034) classified as gastrointestinal hemorrhage occurred in conjunction with abdominal pain and constipation in a subject with hemorrhoids
- 1 case was associated with peptic ulcer disease
- 1 case was associated with anal fissure
- The remaining subjects reported rectal bleeding or bloody stool in the absence of other gastrointestinal diagnoses.
- 1 patient in conjunction with ischemic colitis

Due to the lack of detailed clinical data and/or classification criteria, definitive assessment of severity and alosetron-causality of each of these cases of rectal bleeding remains impractical. Examples of these deficiencies were presented. In those two patients who experienced rectal bleeding in conjunction with diarrhea,, neither the possibility of mild ischemic colitis nor the possibility that alosetron contributed to these adverse events can be excluded

Four subjects treated with traditional therapy reported blood in stool or rectal bleeding. Two of these reports coincided with reports of abdominal pain. None of these reports coincided with reports of constipation.

**5. Deaths**

One patient in each treatment group experienced a fatal SAE. Summaries of the two deaths that occurred during the study follows:

Patient 86477: An 87-year-old female in the alosetron group was hospitalized due to a massive stroke approximately 8 days after starting study drug. Chest x-rays showed perihilar vascular congestion and bilateral pulmonary edema. A carotid sonogram revealed mild bilateral obstructive arteriosclerotic disease. The subject had a history of coronary artery disease, hypertension, non-insulin dependent diabetes mellitus, peptic

ulcer disease, and diverticulosis. The subject died 9 days from the onset of the event. The investigator considered the event unrelated to study drug.

Patient 87082: A 76-year-old female in the traditional therapy group experienced cardiac arrest after 9 weeks of treatment. The subject was pronounced dead upon arrival at the hospital. The subject had a history of arteriosclerotic heart disease and congestive heart failure. An autopsy was not performed. The investigator considered the event unrelated to study related treatment of Vitamin C and Magnesium Sulfate.

### 6. Pregnancies

Seven pregnancies occurred during the study, five in the alosetron group and two in the traditional therapy group:

Patient 69315: A 30-year-old female in the alosetron group discovered she was pregnant approximately 19 weeks after the initiation of study medication. Study drug was discontinued. Four days following discontinuation of study drug, the patient developed vaginal bleeding and miscarried.

Patient 74443: A 33-year-old female in the alosetron treatment group discovered she was pregnant approximately five and one half months after initiating treatment. The patient denied being pregnant and stated she continued to menstruate. She refused a follow-up pregnancy test and reported that she had false pregnancy tests in the past with an IUD as her method of birth control. Study drug was discontinued. The confirmation of the potentially false positive pregnancy test was unavailable at time of reporting.

Patient 77001: A 32-year-old female in the alosetron group was withdrawn from the study due to non-compliance, weight gain, and constipation. She subsequently reported that she had discontinued birth control pills during the study and received study treatment for approximately three weeks without contraception. She became pregnant. The patient had a miscarriage approximately six weeks after discontinuing the study.

Patient 78678: A 28-year-old female in the alosetron treatment group discovered she was pregnant approximately one month after study initiation. She was withdrawn from the study. The father of the fetus had a history of cocaine abuse. The patient gave birth to a healthy female infant.

Patient 87705: A 41-year-old female in the alosetron group discovered she was pregnant two weeks after discontinuing alosetron. Approximately two weeks later, she underwent elective termination of the pregnancy without complications.

Patient 77773: A 29-year-old female received traditional therapy (oral hyoscyamine) and discovered she was pregnant five months after initiating treatment. Traditional therapy was discontinued. The patient gave birth to a healthy male infant.

Patient 80774: A 25-year-old female in the traditional therapy group discovered she was pregnant approximately 10 weeks after starting study medication of omeprazole 40 mg daily and Metamucil twice daily. Both omeprazole and Metamucil had been discontinued four weeks prior. She was withdrawn from the study. The patient gave birth to a healthy female infant.

### 7. Clinical Laboratory Evaluations

No clinically significant hematologic, clinical chemistry, or laboratory abnormalities were noted during the study.

## III. Safety Summary and Conclusions

In this 24 week randomized, open label study of alosetron 1 mg BID daily versus traditional therapy in females with IBS, 1817 patients whose predominant bowel symptom was diarrhea, were exposed to alosetron. Sixty four percent (1435/2256) of patients in the evaluable population (EP) completed the study and 36% (821/2256) withdrew prematurely. Twenty six percent (594/2256) of the EP withdrew voluntarily prior to study termination and 10% (227/2256) withdrew due to termination of the study after completing at least 20 weeks of treatment.

During treatment, 48% (428/883) of patients treated with traditional therapy and 72% (1312/1817) of alosetron-treated patients reported at least one adverse event. Gastrointestinal AEs were reported for 20% (177/883) of patients in the traditional therapy group compared with 55% (1004/1817) of patients in the alosetron group. This difference was driven by events involving the gastrointestinal system, specifically, constipation (4%, traditional therapy; 37%, alosetron) and gastrointestinal pain and discomfort (6%, traditional therapy; 15% alosetron). The proportion of patients reporting other events was similar between the two treatment groups. Events judged by the investigator as possibly related to study drug were reported for 2% of patients treated with traditional therapy and 48% of alosetron-treated patients. Again, this difference was driven by the difference in the number of patients who reported constipation judged to be drug related (<1% traditional therapy; 36% alosetron) and gastrointestinal pain and discomfort (<1% traditional therapy; 11% alosetron).

During the study, 5% (41/883) of the traditional therapy group and 4% (80/1817) of the alosetron group reported 68 and 146 SAEs, respectively. There were no reports of SAEs of ischemic colitis or severe constipation among patients in the traditional-therapy-treated patients.

SAEs associated with constipation were reported in 6 patients (<1%) in the alosetron group. All cases required hospitalization and five cases resolved with conservative management. The sixth report of constipation as an SAE involved a patient (67694) who was subsequently diagnosed with toxic megacolon and secondary colonic ischemia and required a total colectomy and ileostomy.

Ten patients in the alosetron treatment group (<1%) reported SAEs of ischemic colitis . Six cases required hospitalization and nine cases resolved spontaneously in an average of 7.5 days (range 4 to 14 days) without complications. A tenth case (65443) developed a colonic perforation with peritonitis and sepsis during the study and was reported to OPDRA as demonstrating pathologic confirmation of ischemic colitis upon examination by an out-of-study pathologist.

The SAEs ischemic colitis and serious complications of severe constipation have taken on special interest to the Agency because of their frequency and morbidity during the post-marketing use of this drug. A summary of the incidence and treatments required for management of these SAEs occurring within Study S3B30020 appears in Table 5.

**Table 5**

**Summary of Patients with Ischemic Colitis and Serious Complications of Constipation Associated with Alosetron Usage In Protocol S3B30020**

| Treatment / Outcome Required For SAEs | Serious Complications of Severe Constipation | Ischemic Colitis | Totals Alosetron-Treated Patients n = 1817 | |
|---|---|---|---|---|
| | n= 6 | n=10 | These SAEs n=16 | TOTAL 16 (0.9%) |
| Treatment without Hospitalization | 0 | 4 (40%) | 4 (25%) | |
| Hospitalization | 6 (100%) | 6 (60%) | 12 (75%) | 12 (0.7%) |
| Surgery | 1 (17%) | 1 (10%) | 2 (12.5%) | 2 (0.1%) |
| Deaths | 0 | 0 | 0 | |

Medical Reviewer's Table

**Based on the data shown in Table 5 for this 24 week study, almost one per hundred ( 0.9%) patients developed one or the other of the two SAEs of special interest to the Agency. Almost one per hundred (0.7%) patients required hospitalization for treatment of their SAEs and approximately one per thousand (0.1%) patients required a major surgical procedure for their IBS treatment-related SAE.**

Similar to the occurrence of these SAEs observed during the post-marketing distribution of alosetron, ischemic colitis cases occurred more frequently than did cases of serious complications of constipation. However, the smaller number of cases of serious complications of constipation have been associated with a greater frequency of hospitalization and surgery. Blood transfusions are not mentioned in any of these case reports. However, some patients were certainly sick enough that transfusions may have been administered. No deaths among alosetron-treated patients could be attributed to the usage of alosetron in this study.

Whereas, the incidence of the SAEs of special interest, ischemic colitis and serious complications of severe constipation, occurred at a higher frequency in this longer study (24 rather than the 12 weeks duration for most other studies), an attempt was made to analyze the onset of these SAEs and search for possible contributory risk factors. Figure 1 shows the onset of cases of serious complications of severe constipation and Figure 2 shows the onset of cases of ischemic colitis by weeks of alosetron therapy.

**Figure 1**

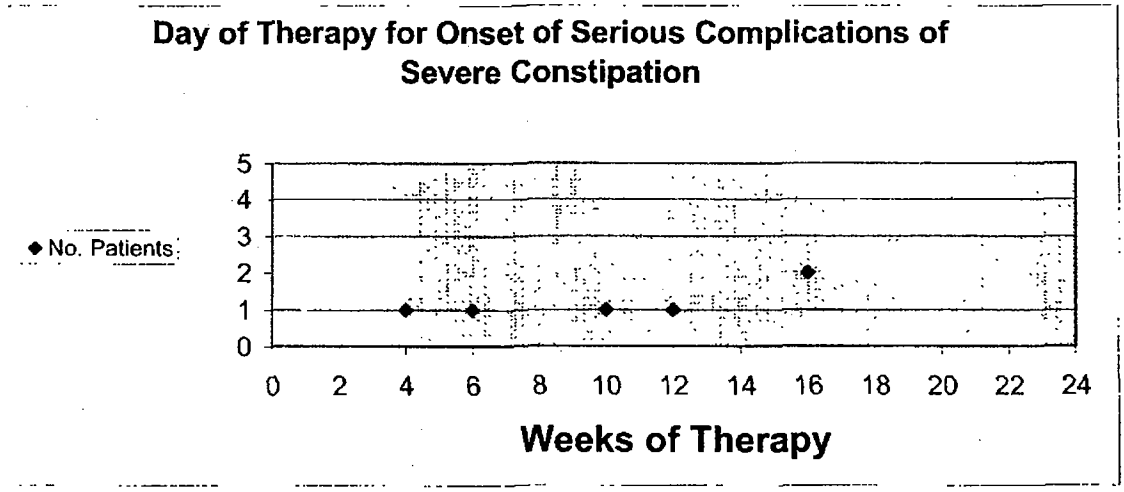
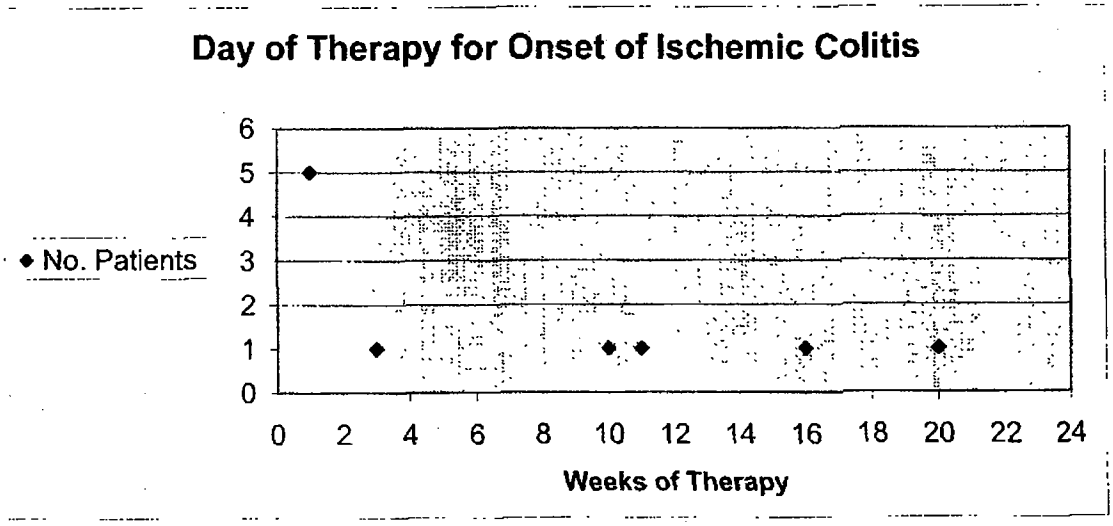


**Figure 2**




While based on small numbers of cases, the incidence of these SAEs appear to occur sporadically throughout the duration of the study. If any pattern can be suggested from these data, it would be that vulnerability for ischemic colitis is highest at the onset of therapy. Six of the ten cases of ischemic colitis associated with alosetron therapy for 24 weeks occurred within the first 3 weeks of therapy. In contrast, severe constipation took time to develop.

Table 6 reviews the concomitant medications taken by the patients with serious complications of severe constipation, Table 7 reviews the concomitant medications taken by the patients with ischemic colitis in this protocol, and Table 8 summarizes the most frequently occurring concomitant medications.

## Table 6

### Concomitant Medications Taken by the Patients with Serious Complications of Severe Constipation* In Protocol S3B30020

| | | |
|---|---|---|
| Antidepresssants | | 4 |
| | Paroxitine | 1 |
| | trazodone | 1 |
| | citalopram | 2 |
| Estrogens | | 3 |
| | Estrogens conjugated | 1 |
| | Birth control pills | 1 |
| | estrogens | 1 |
| $\beta_2$– agonists | | 2 |
| | Salmetrol xinofoate | 1 |
| | albuterol | 1 |
| Antihypertensives | | 3 |
| | Amlodopine/benazepril | 1 |
| | Lotrel | 1 |
| | Unspecified | 1 |
| NSAID | | 2 |
| | rofecoxib | 1 |
| | vicoprofen | 1 |
| Opioids | | 5 |
| | vicodin | 1 |
| | percocet | 1 |
| | vicoprofen | 1 |
| | loperamide | 1 |
| | tramadol | 1 |

- Medical Reviewer's Table

Table includes only those groups of drugs with more than a single listing.

## Table 7

### Concomitant Medications Taken by the Patients with Ischemic Colitis * In Protocol S3B30020

| | | |
|---|---|---|
| Antidepresssants | | 2 |
| | Paroxitine | 1 |
| | trazodone | 1 |
| Estrogens | | 6 |
| | Estrogens conjugated | 2 |
| | Birth control pills | 1 |
| | estrogens | 3 |
| Progesterone | | 1 |
| Antihypertensives | | 5 |
| | Unspecified | 2 |
| | Verapamil | 1 |
| | Altace | 1 |
| | atenolol | 1 |
| NSAID | | 3 |
| | ibuprophen | 2 |
| | naproxin | 1 |
| Opioids | | 2 |
| | loperamide | 2 |
| Barbiturate +salicylate | | 2 |
| Benzodiaxepine | | 4 |
| | alprazolam | 3 |
| | clonazepam | 1 |
| Lipid lowering | | 2 |
| | fluvastatin | 1 |
| | simvastatin | 1 |
| Proton pump inhibitors | | 2 |
| | lansoprazole | 2 |

* Medical Reviewer's Table
Table includes only those groups of drugs with more than a single listing.

Over the treatment period, both groups of patients were taking a mean total of 9 OTC and prescription medications, averaging 5 each week. The mean total number of prescription medications taken by both groups of patients was 6, and OTC medications taken by the alosetron-treated group of patients was 2.6 and by the traditional-treated group of patients was 2.9. Those groups of drugs most often taken by alosetron-treated patients with the two special interest SAEs in this protocol are shown in Table 8.

**Table 8**

**Most Common Groups of Drugs Taken by Patients in Association with Ischemic Colitis and Serious Complications of Severe Constipation in Protocol S3B30020**

| Most Common Groups of Drugs | Ischemic Colitis | Serious Complications of Severe Constipation |
|---|---|---|
| # 1 | Estrogens | Opioids |
| # 2 | Antihypertensives | Antidepressants |
| # 3 | Benzodiaxepines | Estrogens |
| # 4 | NSAIDs | Antihypertensives |

While the absolute numbers are small, drugs that contribute to constipation would be expected to be most commonly associated with complications of severe constipation. The role of concomitant drugs to contribute to the development of ischemic colitis remains speculative. However, drugs from these groups remain high on the suspect list for contributing to the development of ischemic colitis.

**In summary:**

1. Gastrointestinal AEs were more common among alosetron-treated patients than among traditional-therapy patients. This was primarily due to the incidence of constipation in the alosetron group (4% with traditional therapy versus 37% with alosetron)

2. The incidence of drug related AEs, especially constipation (<1% for traditional therapy and 36% for alosetron treated subjects), was higher among the alosetron treated patients compared with traditional therapy. From within the alosetron-treated group, 18% withdrew due to gastrointestinal AEs and 12% withdrew due to constipation as the AE (consistent with the previously observed withdrawal rate of one-third of constipated patients).

3. Gastrointestinal SAEs were the most commonly reported in both treatment groups. A SAE of serious constipation was reported in 6 patients randomized to alosetron and none of the traditional therapy patients. One constipated patient developed toxic megacolon, fulminant secondary ischemic colitis, and septicemia and required a total colectomy and ileostomy. Primary ischemic colitis was reported as an SAE in 10 alosetron-treated patients and none of the patients treated with traditional therapy. In one patient the ischemic colitis resulted in perforation, peritonitis, and sepsis and required a sigmoid resection and colostomy.

4. In this study, ischemic colitis was a frequently occurring SAE (1:180 patient exposures), but was generally mild, reversible ,and self-limited. However, the SAE associated with severe constipation occurred less frequently (1:302 patient exposures), but usually required hospitalization. One patient with each of these two SAEs required surgical intervention. No study-related deaths were reported.

5. Seven pregnancies were reported during this study, two from the traditional-therapy group and five from the alosetron-treatment group. Both subjects randomized to traditional therapy gave birth to healthy infants. For the alosetron group, two experienced miscarriage, one had an elective termination of the pregnancy, one gave birth to a healthy infant, and the outcome of the remaining patient was unknown at the time of reporting.

5. Clinical chemistry and hematology values were similar between treatment groups.

6. No comparisons are available of the concomitant prescribed and OTC medications taken by those patients with and without AEs and SAEs. Thus, data remains insufficient to arrive at definite risk factors that would be useful in reducing the incidence of ischemic colitis. Reduction of the risk of complications from severe constipation, will continue to depend on the earliest recognition of constipation.

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**Scheldon Kress, M.D.**

**February 5, 2002**

## IV. APPENDIX
## Case Summaries of Alosetron-Associated Serious Adverse Events in Table Format

Case summaries of alosetron-treated patients who experienced SAEs during the study follow.

### 1. Serious Complications of Severe Constipation Associated with Alosetron Usage In Protocol S3B30020

<table>
<tr><td colspan="2">Patient # 65385<br>Protocol # S3B30020</td><td>Sex<br>F</td><td>Age<br>77</td><td>Weight<br>119</td></tr>
<tr><td colspan="3">History<br><br>Hospitalized - Nausea, vomiting, crampy abdominal pain, distention, obstipation<br>X-ray – partial small bowel obstruction, increased stool rectum & rectosigmoid</td><td colspan="2">SAE<br><br>Partial small bowel obstruction<br><br>Onset Day of Therapy<br>Month 4<br><br>Alosetron Causality Assessment<br><br>Probable</td></tr>
<tr><td>Reason for Hospitalization<br><br>Partial small bowel obstruction</td><td>Surgical Procedure<br><br>0</td><td colspan="3">Duration of Hospitalization<br><br>N/A</td></tr>
<tr><td>Co-Morbid Conditions<br><br>Coronary artery disease, diverticular disease, internal hemorrhoids</td><td>Concomitant Medications<br><br>Paroxitine, calcium</td><td colspan="3">Outcome<br><br>Resolved in 11 days<br><br>Death ☐</td></tr>
<tr><td colspan="5">Permanent Sequelae<br><br>None</td></tr>
</table>

| Patient # 67694<br>Protocol # S3B30020 | Sex<br>F | Age<br>56 | Weight<br>129 |
|---|---|---|---|

**History**

Hospitalized - Crampy peri-umbilical abdominal pain, nausea , vomiting, lower abdominal pain, distention, constipation day prior, hypotensive, hemaccult positive gastric fluid, stool hemaccult positive, dehydration, acute renal failure, pancreatitis (amylase 1120)
X-ray – Multiple air-fluid levels
Pelvic scan – complex left ovarian cyst
CT Abd – transmural thickening proximal small bowel and entire left colon
Upper endosc. – mild gastritis
Colonoscopy – fecal impaction

**SAE**

Toxic megacolon
Diffuse ischemic fulminant colitis, purulent peritonitis, septicemia

"Stercoraceous obstruction, megacolon and secondary ischemia"

**Onset Day of Therapy**

Day 27

**Alosetron Causality Assessment**

Probable

**Reason for Hospitalization**

Toxic megacolon with diffuse transmural ischemic gangrenous colitis and purulent septicemia

"Stercoraceous obstruction, megacolon and secondary ischemia"

**Surgical Procedure**

Total abdominal colectomy with Brook ileostomy

**Duration of Hospitalization**

2 weeks

**Co-Morbid Conditions**

Hypertension, peptic ulcer disease, abdominal adhesions, hyperplastic rectosigmoid polyps

**Concomitant Medications**

Conjugated estrogens, tolterodine, trazodone, citalopram, tramadol, amlodipine/benazepril, rofecoxib

**Outcome**

ileostomy
? Follow-up procedure

**Death** ☐

**Permanent Sequelae**

ileostomy
? Follow-up procedure

| Patient # 80655<br>Protocol # S3B30020 | Sex<br>F | Age<br>26 | Weight<br>351 |
|---|---|---|---|

**History**

Severe crampy lower abdominal pain
Colonoscopy – Large fecal mass (5 X 13 cm on barium enema), erythema and superficial ulcerations distal to fecal mass
Pathology – Ischemic changes – focal mucosal ulceration, crypt loss, fibrosis, vascular ectasia, flattening of surface epithelium

**SAE**

Impaction with secondary ischemic colitis

**Onset Day of Therapy**

Month 4

**Alosetron Causality Assessment**

Probable

| Reason for Hospitalization | Surgical Procedure | Duration of Hospitalization |
|---|---|---|
| Impaction with secondary ischemic colitis | 0 | 4 days |

| Co-Morbid Conditions | Concomitant Medications | Outcome |
|---|---|---|
| Hypertension, morbid obesity, | Birth control pills, Lotrel, docusate, sennosides | Resolved 6 days<br><br>Death ☐ |

**Permanent Sequelae**

None (repeat colonoscopy at 8 weeks)

| Patient # 83206<br>Protocol # S3B30020 | Sex<br>F | Age<br>48 | Weight<br>NA |
|---|---|---|---|
| **History**<br><br>Left abdominal pain of 2 weeks duration<br>CT Scan – colon full of stool | | | **SAE**<br><br>Obstipation with impaction |
| | | | **Onset Day of Therapy**<br>Week 10 |
| | | | **Alosetron Causality Assessment**<br><br>Possible<br>(narcotics) |
| **Reason for Hospitalization**<br><br>Fecal impaction | **Surgical Procedure**<br><br>0 | | **Duration of Hospitalization**<br><br>3 days |
| **Co-Morbid Conditions**<br><br>Personality disorder<br>Somatization disorder | **Concomitant Medications**<br><br>Vicodin, Percocet, Vicoprofen prn pain | | **Outcome**<br><br>Resolved in 3 days<br><br>**Death** ☐ |
| **Permanent Sequelae**<br><br>None | | | |

| Patient # 87373<br>Protocol # S3B30020 | Sex<br>F | Age<br>67 | Weight<br>247 |
|---|---|---|---|

**History**

Abdominal pain, vomiting, dehydration, and diarrhea
Hospitalized
Abdominal x-ray – mild small bowel ileus and mild hepatomegaly
Lab – leucocytosis
Stool tests – negative culture, negative ova and parasites
Treated IV fluids, famotidine, promthazine

**SAE**

Small bowel ileus

**Onset Day of Therapy**

3 months

**Alosetron Causality Assessment**

Possibly

| Reason for Hospitalization | Surgical Procedure | Duration of Hospitalization |
|---|---|---|
| Small bowel ileus | 0 | 4 days |

| Co-Morbid Conditions | Concomitant Medications | Outcome |
|---|---|---|
| Hiatal hernia, adenomatous polyps | Estrogens, salmetrol xinofoate, albuterol, loperamide, fexofenadine hydrochloride, atorvastatin, omeprazole, citalopram hydrobromide, antihypertensives | Resolved in 4 days<br><br>Death ☐ |

**Permanent Sequelae**

None (study drug restarted upon resolution of the event)

| Patient # 88034<br>Protocol # S3B30020 | Sex<br>F | Age<br>50 | Weight<br>165 |
|---|---|---|---|

**History**

Hospitalized with left lower quadrant abdominal discomfort, constipation, and rectal bleeding
Urinary tract infection – pyuria
Treated - IV fluids, antibiotics
Rectal bleeding due to hemorrhoids

**SAE**

Constipation

**Onset Day of Therapy**

6 weeks

**Alosetron Causality Assessment**

Probable

| Reason for Hospitalization | Surgical Procedure | Duration of Hospitalization |
|---|---|---|
| Abdominal pain and constipation | 0 | 3 days |

| Co-Morbid Conditions | Concomitant Medications | Outcome |
|---|---|---|
| ? | ? | Resolved 3 days<br>Death ☐ |

**Permanent Sequelae**

None

## 2. Serious Complications of Ischemic Colitis Associated with Alosetron Usage In Protocol S3B30020

| Patient # 63223<br>Protocol # S3B30020 | Sex<br>F | Age<br>55 | Weight<br>160 |
|---|---|---|---|
| **History**<br><br>Severe , crampy, lower abdominal pain, bloody diarrhea, lower gastrointestinal bleeding, anemia<br>Sigmoidoscopy – ulceration, inflammation, distal descending colon, small hemorrhoids | | | **SAE**<br><br>Ischemic colitis<br><br>**Onset Day of Therapy**<br>Week 11<br><br>**Alosetron Causality Assessment**<br><br>Probable |
| **Reason for Hospitalization**<br><br>abdominal pain, bloody diarrhea, lower gastrointestinal bleeding, anemia | **Surgical Procedure**<br><br>0 | | **Duration of Hospitalization** |
| **Co-Morbid Conditions**<br><br>Depression, lactose intolerance, microscopic colitis, hysterectomy<br><br>Status post:<br>Hysterectomy, fundoplication | **Concomitant Medications**<br><br>Conjugated estrogens, loperamide | | **Outcome**<br><br>Resolved in 7 days<br><br>**Death** ☐ |
| **Permanent Sequelae**<br><br>**None** | | | |

| Patient # 65443 * Protocol # S3B30020 | Sex F | Age 67 | Weight 168 |
|---|---|---|---|

**History**

Hospitalized – rectal bleeding, lower abdominal pain, hypotension, ventricular tachycardia,
Abdominal CT scan – free air and intra-abdominal fluid, Peritonitis, sepsis, Stroke, dysphagia, hemiparesis, Cardioversion, Lifethreatening disseminated intravascular coagulation

Post operative – Tachycardia required cardioversion
ICU – peritonitis, septic, methicillin resistant staphalococcus aureas abdominal wound infection, disseminated intravascular coagulation, respiratory distress required intubation, stroke with right-sided hemiparesis,
Extended care facility- rehabilitation 3 months
Out subject physical therapy – 5 months

**SAE**

Ischemic colitis *

**Onset Day of Therapy**

Day 4

**Alosetron Causality Assessment**

Probable

**Reason for Hospitalization**

Perforation 2.8cm colon, diverticulitis

**Surgical Procedure**

Sigmoid colon resection, descending colon colostomy

**Duration of Hospitalization**

8 weeks

**Co-Morbid Conditions**

Chronic diarrhea, diverticulosis, spastic colon, cholelithiasis, hypothyroidism, smoking, colonic polyps

**Concomitant Medications**

Estrogens

**Outcome**

Permanent sequelae

**Death** ☐

**Permanent Sequelae**

Hemiparesis, colostomy, personality changes

* Sponsor did not include this patient among the cases with ischemic colitis, but patient's attorney had specimen of resected colon tissue reviewed by pathologist and claims it demonstrated ischemic colitis.

| Patient # 66556<br>Protocol # S3B30020 | Sex<br>F | Age<br>75 | Weight<br>195 |
|---|---|---|---|

**History**

Hospitalized – crampy lower abdominal pain, nausea, vomiting, rectal bleeding, bloody diarrhea, fever, chills
Colonoscopy – ischemia, submucosal hemorrhages, acute and chronic inflammation, ulceration, bluish discoloration descending colon
Colon biopsy – ischemic colitis

**SAE**

Ischemic colitis

**Onset Day of Therapy**
Month 5

**Alosetron Causality Assessment**

Probable

| Reason for Hospitalization | Surgical Procedure | Duration of Hospitalization |
|---|---|---|
| crampy lower abdominal pain, nausea, vomiting, rectal bleeding, bloody diarrhea, fever, chills | 0 | N/A |

| Co-Morbid Conditions | Concomitant Medications | Outcome |
|---|---|---|
| Diverticulosis, internal hemorrhoids | Ramipril, fiorinal, verapamil, psyllium, alpazolam, ibuprofen, alendronate, acetaminophen | Resolved in 7 days<br>Death ☐ |

**Permanent Sequelae**

None

| **Patient #** 69433<br>**Protocol #** S3B30020 | **Sex**<br>F | **Age**<br>37 | **Weight**<br>120 |
|---|---|---|---|

**History**

Evaluated in ER –
severe abdominal crampy pain & bloody diarrhea
Given intravenous fluids
Colonoscopy – segmental colitis
Probable ischemic colitis
Biopsy – patchy superficial ulceration and mucosal hemorrhage left colon
Cultures – normal

**SAE**

Ischemic colitis

**Onset Day of Therapy**
Month 4

**Alosetron Causality Assessment**

Probable

| **Reason for Hospitalization** | **Surgical Procedure** | **Duration of Hospitalization** |
|---|---|---|
| None | None | None |

| **Co-Morbid Conditions** | **Concomitant Medications** | **Outcome** |
|---|---|---|
| Asthmatic bronchitis<br>Ovarian cyst<br>Arthritis, foot, bach<br>Acne<br>Depression<br>Anxiety | Trazadone<br>Xanax<br>Motrin<br>Cleocin T<br>Benzyl peroxide<br>Gas X | Resolved in 4 days<br>**Death** ☐ |

**Permanent Sequelae**
Resolved in 4 days

| **Patient #** 71843<br>**Protocol #** S3B30020 | **Sex**<br>F | **Age**<br>37 | **Weight**<br>222 |
|---|---|---|---|

**History**

Sudden onset abdominal cramping and diarrhea followed by blood in stool a few hours later

Colonoscopy 2 days later – segmental colitis with patchy erythema, erosions, and edema of splenic flexure and mid-descending colon

Biopsies – non-specific mild abnormalities suggestive of ischemic colitis
very mild, focal acute inflammation with focal superficial erosion and minimal focal glandular attenuation
Cultures - normal

**SAE**

Ischemic coliitis

**Onset Day of Therapy**

2.5 months

**Alosetron Causality Assessment**

Probable

| **Reason for Hospitalization** | **Surgical Procedure** | **Duration of Hospitalization** |
|---|---|---|
| None | None | |

| **Co-Morbid Conditions** | **Concomitant Medications** | **Outcome** |
|---|---|---|
| Anxiety | Paxil<br>Imodium | Resolved 4 days<br><br>**Death** ☐ |

**Permanent Sequelae**

Resolved in 4 days

| Patient # 72823<br>Protocol # S3B30020 | Sex<br>F | Age<br>64 | Weight<br>146 |
|---|---|---|---|

**History**

Constipation followed by cramps and bloody diarrhea
Sigmoidoscopy – large amount of blood
too uncomfortable to complete
Colonoscopy – ischemic colitis transverse colon, scattered non-specific colitis
Colon biopsies – ulcerated , inflamed, ischemic changes colorectal mucosa

**SAE**

Ischemic colitis

**Onset Day of Therapy**

Day 2

**Alosetron Causality Assessment**

Probable

| Reason for Hospitalization | Surgical Procedure | Duration of Hospitalization |
|---|---|---|
| 0 | 0 | 0 |

**Co-Morbid Conditions**

**Concomitant Medications**

Estradiol, thyroxine, zolpidem, prasterone, lansoprazole, alprazolam,

**Outcome**

Resolved in 6 days

**Death** ☐

**Permanent Sequelae**

None

| Patient # 72824<br>Protocol # S3B30020 | Sex<br>F | Age<br>57 | Weight<br>139 |
|---|---|---|---|

**History**

Abdominal cramping, diarrhea, chills, rectal bleeding
Colonoscopy - Non-specific colitis descending and sigmoid colon
Pathology – ischemic colitis
focal fibrosis, ischemic degenerative glandular changes

**SAE**

Ischemic colitis

**Onset Day of Therapy**
Day 4

**Alosetron Causality Assessment**

Probable

| Reason for Hospitalization | Surgical Procedure | Duration of Hospitalization |
|---|---|---|
| 0 | 0 | 0 |

| Co-Morbid Conditions | Concomitant Medications | Outcome |
|---|---|---|
| Severe reflux | Estrogen, atenolol, lansoprazole, cloazepam | Resolved 7 days<br><br>Death ☐ |

**Permanent Sequelae**

None

| Patient # 78134<br>Protocol # S3B30020 | Sex<br>F | Age<br>20 | Weight<br>134 |
|---|---|---|---|

**History**

Nausea, vomiting, severe crampy LLQ abdominal pain, rectal bleeding, bloody diarrhea with mucous
Colonoscopy – diffuse erythema, loss vasculature, shallow ulcerations splenic flexure and descending colon
Pathology – ischemic colitis
atrophic colonic mucosa, acute and chronic inflammation, fibrosis lamina propria

**SAE**

Ischemic colitis

**Onset Day of Therapy**

Day 3

**Alosetron Causality Assessment**

Probable

| Reason for Hospitalization | Surgical Procedure | Duration of Hospitalization |
|---|---|---|
| Severe crampy LLQ abdominal pain, rectal bleeding | 0 | 4 days |

| Co-Morbid Conditions | Concomitant Medications | Outcome |
|---|---|---|
| Kidney stones,<br>penicillin allergy,<br>cigarette smoker | Birth control pills | Resolved 4 days<br><br>Death ☐ |

**Permanent Sequelae**

None

| Patient # 80357<br>Protocol # S3B30020 | Sex<br>F | Age<br>51 | Weight<br>182 |
|---|---|---|---|
| **History**<br><br>Abdominal pain, spasms and constipation<br>Colonoscopy – edema, erythema and ulcerations sigmoid colon consistent with ischemic colitis or diverticulitis (?) | | | **SAE**<br><br>Ischemic colitis<br><br>**Onset Day of Therapy**<br>Week 3<br><br>**Alosetron Causality Assessment**<br><br>Probable |
| **Reason for Hospitalization**<br><br>Abdominal pain, spasms and constipation | **Surgical Procedure**<br><br>0 | | **Duration of Hospitalization**<br><br>? |
| **Co-Morbid Conditions**<br><br>Diverticulosis | **Concomitant Medications**<br><br>Progesterone, famotidine, esgic, hyoscyamine, alprazolam, donnatal | | **Outcome**<br><br>Resolved<br><br>**Death** ☐ |
| **Permanent Sequelae**<br><br>None | | | |

| Patient # 82125<br>Protocol # S3B30020 | Sex<br>F | Age<br>61 | Weight<br>180 |
|---|---|---|---|

**History**

Crampy abdominal pain, bloody diarrhea, nausea, vomiting, light headed
Preceded by constipation and rock-hard stools
CT Scan – Moderate thickening ascending and proximal 2/3 descending. Suspected fluid collection superior right rectal fossa
Colonoscopy – Ischemic colitis - severe ulcerations, erythema, friable tissue distal transverse and descending colon
Pathology – Ischemic colitis (or pseudomembranous colitis) – fibrinopurulent exudate, epithelial debris, coagulative necrosis, bacterial colonization

**SAE**

Ischemic colitis

**Onset Day of Therapy**

Day 7

**Alosetron Causality Assessment**

Probable

| Reason for Hospitalization | Surgical Procedure | Duration of Hospitalization |
|---|---|---|
| Crampy abdominal pain, bloody diarrhea, nausea, vomiting, light headed | 0 | 3 days |

| Co-Morbid Conditions | Concomitant Medications | Outcome |
|---|---|---|
| Hypertension | Estrogen, Accuretic<br>Naproxen (Day 7 for lower extremity pain) (diarrhea-prone with NSAID use) | Resolved in 2 weeks<br><br>Death ☐ |

**Permanent Sequelae**

None

### 3. Case Summary of Single Alosetron-Associated Death in Table Format

**Single Death Occurring in Association with Alosetron Treatment In Protocol S3B30020**

<table>
<tr><td colspan="2">Patient # 86477<br>Protocol # S3B30020</td><td>Sex<br>F</td><td>Age<br>87</td><td>Weight</td></tr>
<tr><td colspan="3">History<br><br>Hospitalized – intensive care unit with massive stroke<br>Chest X-ray – pulmonary edema<br>Carotid sonogram – mild bilateral obstructive arteriosclerotic disease<br>Death</td><td colspan="2">SAE<br><br>Massive stroke<br><br>Onset Day of Therapy<br>Day 8<br><br>Alosetron Causality Assessment<br><br>Insufficient evidence</td></tr>
<tr><td colspan="2">Reason for Hospitalization<br><br>Stroke</td><td>Surgical Procedure<br><br>0</td><td colspan="2">Duration of Hospitalization<br><br>9 days</td></tr>
<tr><td colspan="2">Co-Morbid Conditions<br><br>Coronary artery disease,<br>hypertension,<br>Non-insulin dependent diabetes mellitus,<br>Peptic ulcer disease,<br>colonic diverticulosis</td><td>Concomitant Medications<br><br>Lisnopril,<br>glipizide,<br>Librax,<br>fluvastatin,<br>retinol palmitate,<br>simvastatin,<br>furosimide</td><td colspan="2">Outcome<br><br>Death [X]</td></tr>
<tr><td colspan="5">Permanent Sequelae<br>Death</td></tr>
</table>

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

/s/
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Scheldon Kress
2/6/02 02:25:37 PM
MEDICAL OFFICER

Hugo Gallo Torres
2/8/02 01:07:45 PM
MEDICAL OFFICER

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER REVIEW

sNDA: 21-107
SPONSOR: Glaxo SmithKline, Inc.
DRUG: Alosetron Hydrochloride (LOTRONEX™) Tablets
DATE OF ORIGINAL SUBMISSION: 29 June, 1999
DATE OF ORIGINAL APPROVAL: 9 February, 2000
VOLUNTARY WITHDRAWAL FROM THE MARKET: 28 November, 2000
DATE OF sNDA SUBMISSION: 7 December, 2001
MEDICAL OFFICER: Marcelo A. Barreiro, MD, MSc
MATERIAL REVIEWED: 1) Protocol S3BB3002: A Multicentre, Randomized, Double-Blind Comparison of Alosetron 1 mg BD against Trimebutine 200 mg TDS for 12 Weeks in the Treatment of Female Patients with Irritable Bowel Syndrome
2) Protocol S3B30006: A One Year Randomized, Double-Blind, Placebo-Controlled Study of Alosetron 1 mg BID in Female Subjects with Irritable Bowel Syndrome

1) CLINICAL REVIEW OF S3BB3002: A MULTICENTRE, RANDOMIZED, DOUBLE-BLIND COMPARISON OF ALOSETRON 1 MG BD AGAINST TRIMEBUTINE 200 MG TDS FOR 12 WEEKS IN THE TREATMENT OF FEMALE PATIENTS WITH IRRITABLE BOWEL SYNDROME.

**Summary of Patients with Ischemic Colitis**
**Occurring in Association with Alosetron Usage in Clinical Studies**

| No | Study No S3B | Patient No | Age | Time to Onset (days) | Hospitalization | Surgical Procedure | Transfusion | Outcome |
|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**Summary of Patients with Serious Complications of Severe Constipation Occurring in Association with Alosetron Usage in Clinical Studies**

| No | Study No S3B | Patient No | Age | Time to Onset (days) | Hospitalization | Surgical Procedure | Transfusion | Outcome |
|---|---|---|---|---|---|---|---|---|
| | BB 3002 | 03773 | 30 | 3 DAYS | NO | DIG. DISIMPACTION | NO | UNEV ENTF. |

**Summary of Patients with Mesenteric Vasculopathy Occurring in Association with Alosetron Usage in Clinical Studies**

| No | Study No S3B | Patient No | Age | Time to Onset (days) | Hospitalization | Surgical Procedure | Transfusion | Outcome |
|---|---|---|---|---|---|---|---|---|
| 0 | B3002 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**Summary of Patients with Miscellaneous SAEs* Occurring in Association with Alosetron Usage in Clinical Studies**

| No | Study No S3B | Patient No | Age | Time to Onset (days) | Hospitalization | Surgical Procedure | Transfusion | Outcome |
|---|---|---|---|---|---|---|---|---|
| 1 | B3002 | 02956 | 30 | 3 | YES-MVA | NO | NO | UNEV ENTF. |
| 2 | B3002 | 02541 | 29 | 70 | YES-ABD PAIN | NO | NO | UNEV ENTF |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 3 | B3002 | 03384 | 52 | 5 | YES-CA BREAST | BREAST BIOPSY | NO | UNKN. |
| 4 | B3002 | 02330 | 45 | 10 | YES-CROHN'S | YES-UNKNOWN | UNKN | UNKN |
| 5 | B3002 | 27655 | 20 | 28 | YES-ABD. PAIN | LAPAROSCOPY=ENDOMETRIOSIS | UNKN | UNKN |
| 6 | B3002 | 01474 | 53 | 42 | YES-SYNCOPE | NO | UNKN | UNKN |
| 7 | B3002 | 03231 | 55 | 77 | APPENDICITIS | YES-UNKN | UNKN | UNKN |
| Total Patients in Study # BB3002 = SEVEN Lotronex-treated patients = SEVEN Placebo-treated patients = 0 | | | | | | | | |

**Summary of Patients with Rectal Bleeding, Bloody Stools and Diarrhea with Abdominal/GI Pain*Occurring in Association with Alosetron Usage in Clinical Studies**

| No | Study No S3B | Patient No | Age | Time to Onset (days) | Concomitant Medications | Adverse Event | | Outcome |
|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

## EXECUTIVE SUMMARY

Alosetron is a synthetic product designed to selectively block receptor sites present mostly in the wall of the colon that are activated by a neurotransmitter, serotonin (5-hydroxytriptamine). This particular receptor sites are called 5 HT3 and they are involved in secretory, motor, sensory and vascular process. 5 HT3 receptors are also present in the central nervous system, peripheral nervous system, and some parts of the cardiovascular system. Increased sensitivity of this receptor sites may account for some of the symptoms reported in what is called Irritable Bowel Syndrome, in which usually female patients complain of abdominal pain or discomfort, abnormal bowel habits, bloating, urgency and feeling of incomplete elimination after a bowel movement. There is preliminary evidence that blocking this 5 HT3 receptor sites with drugs like alosetron (a 5 HT3 antagonist) will relieve some of these symptoms.

S3BB3002 is a clinical trial that was carried out in 125 sites in Canada, Mexico and Europe. The objectives of this study were: 1) to compare the two treatment groups with respect to adequate relief of IBS pain and discomfort and 2) to compare the tolerability of the two treatments with respect to safety and tolerance. Probably to satisfy foreign

(mostly european) regulatory agencies, the sponsor used trimebutine maleate, a visceral analgesic and anti-spasmodic, as an active comparator (control), rather than using placebo. This creates some methodological problems, which are discussed in more detail in the narrative below. To date, there is no evidence provided by large, well controlled, clinical trials that trimebutine is effective in the symptomatic treatment of IBS. Yet, trimebutine has been used for the last 30 years by most physicians abroad, and has become an accepted form of treatment of IBS, with a satisfactory safety profile.
Alosetron was approved for sale in the US market on 9 February 2000, but had to be withdrawn by the manufacturer on 28 November, 2000 because of serious adverse events (AE) of ischemic bowel disease and constipation, leading to perforation, strictures, surgeries and death. Since then, the possibility of reintroducing alosetron in the market under more restricted conditions, as part of a risk management plan, has been entertained. S3BB3002 is part of a supplemental New Drug Application submitted by GSK on 7 December 2001, to that end.
Alosetron 1mg bd or trimebutine 200 mg tds, was given in a double-blind fashion (neither the doctor or the patient knows what treatment is being given) to 784 female patients who met the Rome II diagnostic criteria for non-constipated IBS. Fifty one percent (402/784) received alosetron, and 49 % (382/784) received trimebutine.
The primary efficacy endpoint was adequate relief of IBS pain and discomfort.
Secondary endpoints included measurements of the proportion of pain/discomfort-free days each month, urgency, firmness/liquidity of the stools, number of bowel movements per day, psychological evaluations (SCL-90R), quality of life (IBSQOL, SF 36), resource utilization.
Safety was measured by recording of AEs or abnormalities in laboratory examinations. Everyone who had taken at least one tablet of test medication was included in the safety analysis.

**The results can be summarized as follows:**

**Efficacy**

1) For the most part, alosetron failed to prove its superiority over trimebutine. Analysis of the primary endpoint data revealed no statistical significant difference between alosetron 42 % and trimebutine 37 % of adequate relief responders (ARR).
2) IBS predominant diarrhea (IBS-D) patients seemed to benefit more from alosetron, whereas IBS alternators (those who seem to alternate constipation with diarrhea) (IBS-A) benefited more from trimebutine.
3) When the IBS-D subgroup of ARR was analyzed weekly, there was a statistically significant difference in favor of alosetron in seven of the 12 weeks of treatment.
4) There was also a statistically significant difference in favor of alosetron in the firming of the stools in the IBS-D patients.

**Safety**

5) There were no episodes of ischemic bowel disease or severe complications of constipation in either of the two experimental groups.
6) There was no difference in the proportion of AEs between alosetron-treated patients (61 %, 247/402) an trimebutine-treated patients (60 %, 229/382).
7) Constipation was significantly more frequently reported (20 %) in the alosetron group

than in the trimebutine group (7 %). This is in part due to the way constipation was defined and measured. Most of the patients reporting "constipation" were still having one bowel movement a day.

**Conclusion:** The data obtained from S3BB3002 fail to prove alosetron superior to the control trimebutine maleate, other than for a few secondary endpoints. Alosetron demonstrated to be fairly well tolerated by this group of non-constipated IBS female patients at doses of 1 mg bd, orally, for a 12 week period. There were no overt instances of ischemic bowel disease. There were no reported cases of rectal bleeding.

**Recommendations for regulatory action:**

1) The information of this review will be integrated with the reviews of the rest of the sNDA and a final report will be issued.
2) CRFs and original records of some selected patients will be requested from the sponsor.

## I – INTRODUCTION AND BACKGROUND INFORMATION

This review is addressed to the management of DGICDP, ODE III and CDER. The Executive Summary is addressed to the same audience and the lay public.
The reader is familiar with the drug, Alosetron (A), the condition under treatment, Irritable Bowel Syndrome (IBS), and its methodology of study.
The sponsor provides a brief introduction summarizing what IBS, A, serotonin and 5-HT3 receptors are, which was probably written sometime in 1997-1998 since this study was initiated on 14 May 1998. Some of the statements (and omissions) are of interest in view of subsequent events.
**"IBS affects ... depression and anxiety ... "** The references provided [1, 2] do not support that statement. Further, mood alterations are an integral part of IBS, and severe forms of IBS are characterized by an aggravation of the mood changes[3], rather than a worsening of the gastrointestinal (GI) symptoms (ei worse and worse bloating).

**"Serotonin or 5-hydroxytryptamine (5-HT) is an important transmitter in the central and peripheral nervous systems and particularly in the gastrointestinal tract, where it is involved in secretory, motor and sensory processes. It may therefore be expected that excess of 5-HT, or an increased sensitivity to 5-HT within the gastrointestinal tract, would cause abnormal activation of 5-HT receptors in the gut resulting in abdominal pain, abnormal perception of sensory stimuli and increased gut motility. Of the fourteen or more identified 5-HT receptor subtypes, the 5-HT3 receptor appears to be of particular importance in these functions. 5-HT3 receptor antagonists have been shown to (have) visceral analgesic properties to increase colonic transit times and to be effective in animal models of visceral pain "**
This summary omits important vascular effects of this compound. The presence of serotonin was suspected in the 1930's, and ultimately its chemical isolation and synthesis accomplished in 1947[4] because of its cardiovascular effects. Serotonin produces bradychardia and tachycardia, hypotension and hypertension, vasoconstriction and

vasodilatation, in the human and many other animal species. 5 HT3 receptors are involved in different ways in different animal species in all these cardiovascular effects[5,6] One is tempted to speculate that this focus on the effect on visceral motility and sensitivity, made the sponsor underestimate the effects of alosetron, a 5 HT3 antagonist, on the intestinal circulation and not anticipate potential side effects leading to ischemic bowel disease.

Trimebutine maleate has been available for over 30 years and has been in use in many countries for the management of the IBS at doses between 300mg/day and 600mg/day.Trimebutine is a non-selective opioid agonist with activity at μ, δ and opiate receptors and is believed to act as a mild antispasmodic and visceral analgesic There is little evidence in the literature that trimebutine is an effective symptomatic treatment for IBS. Nevertheless, it is an accepted form of management of these patients by physicians overseas.

A number of studies have investigated trimebutine using dosage regimens of 200mg/day to 200mg qds. These studies, however, have diverse and often small study populations, variable (often short) treatment period and a variety of endpoints. Of these, one double-blind placebo controlled study reports evidence supporting of the efficacy of trimebutine. Ghidini et al have reported that the percentage of patients free from abdominal pain after 60 days treatment was 53% with trimebutine 100mg tds, compared with 30% with placebo, and a "normal" bowel habit was reported by 57% and 23% of patients, respectively. Trimebutine 200 mg tds was used in this study as an active control. Trimebutine is not available in the US market.

## II – STUDY OBJECTIVES

### Primary Objectives

1) To compare the two treatment groups (alosetron 1mg bd and trimebutine 200mg tds with respect to proportion of patients who report adequate relief from their abdominal pain and discomfort.
2) To compare the safety and tolerability of the two treatments.

### Secondary Objectives

To compare the two treatment groups with respect to proportion of patients reporting at least 50% of abdominal pain and discomfort-free days.

### Other Objectives

To compare the two treatment groups with respect to changes in the proportion of pain and discomfort-free days experienced by subjects (added in Data Analysis Plan prior to unblinding).

To compare the two treatment groups with respect to changes in mean severity scores for abdominal pain and discomfort.

To compare the two treatment groups with respect to self-ratings of the following gastrointestinal symptoms:

1) stool frequency
2) stool consistency

3) sense of incomplete evacuation
4) sense of urgency
5) bloating.

To compare the two treatment groups in terms of changes in SCL-90R® scores (where translations are available).

To compare the two treatment groups in terms of changes in quality of life scores and productivity (resource utilization) (where translations are available).

## III – STUDY DESIGN

This randomized, double-blind, parallel group, multicentre study was conducted to compare efficacy, safety, health-related QOL, and resource utilization measures of alosetron 1mg bd versus trimebutine 200mg tds therapy in female subjects with IBS. The study was designed for the enrolment of 700 adult ambulatory female outpatients at approximately 125 sites in Europe, Canada and Mexico.

Subjects who reported symptoms fulfilling the Rome Criteria for IBS for a period of at least 6 months participated in a 2-week Screening Phase to confirm the presence of active IBS symptoms. Each subject recorded her abdominal pain and discomfort and other lower GI symptoms daily via a touch-tone telephone data entry system At the end of the 2-week Screening Phase, each subject meeting the pain and discomfort severity and stool consistency entry criteria (see ) was randomized to treatment with alosetron 1mg bd versus trimebutine 200mg tds for 12 weeks. During the 12-week Treatment Phase, subjects continued to record abdominal pain anddiscomfort and other lower GI symptoms daily via a touch-tone telephone data entrysystem. During the 4-week Follow-up Phase, subjects continued to record theirabdominal symptoms until they received a Follow-up Telephone Contact.

### Control Group(s)

An "active" control (trimebutine 200mg tds) group was included in the study for comparison with the alosetron treatment group. No placebo control group was used.

### Study Design Issues

Subjects with IBS may be sub-classified according to their bowel function history i.e. those with diarrhea-predominant IBS, those who alternate between diarrhea and constipation and those who are constipation predominant. As constipation is a common side effect of all 5-HT3 antagonists and as the Phase II studies have shown alosetron was only effective in non-constipated subjects, this study was designed to include diarrhea-predominant subjects or subjects with alternating bowel patterns.

As a result of the known constipating effects of alosetron, in the event that subjects experienced no stool for four consecutive days during the study, they were to follow the procedure outlined below:

Subject reports 4 consecutive days of no stool

↓

Discontinues study drug for up to 4 days. Constipation recorded as an adverse event. Study drug interrupted.

↓
Stool returns. Subject restarts study drug

↓
Stool absent for 8 consecutive days. Subject withdrawn

## IV – STUDY POPULATION

### A – Inclusion Criteria

Female subjects who were not constipated at the time of randomization were included in the study. The rationale for the inclusion of female subjects was based on results from two Phase II studies which showed alosetron to have preferential efficacy in females. Due to the unknown risks of alosetron on the fetus, pregnant or lactating females, and females at risk of pregnancy were not included. The inclusion criteria selected ensured that subjects chosen were from a homogenous population of true IBS sufferers without other underlying morbidities which could otherwise explain their symptoms.
A subject was eligible for inclusion in the study if all of the following inclusion criteria were met.
Subjects must have:

1) signed and dated an informed consent form
2) been female
   a) of non-childbearing potential (i.e., physiologically incapable of becoming pregnant, including any female who is pre-menarchal or post-menopausal); or,
   b) of child-bearing potential, had a negative pregnancy test (serum) at screen, and was, or agreed to comply with one of the following precautions:

- complete abstinence from intercourse from 2 weeks prior to administration of the study drug, throughout the study and for a minimum of one week after the last dose of study drug; or,
- female sterilisation; or,
- sterilisation of male partner; or,
- implants of levonorgestrel; or,
- injectable progestogen; or,
- oral contraceptive (combined or progestogen only); or,
- any intrauterine device (IUD) with published data showing that the lowest expected failure rate was less than 1% per year.

3) been at least 18 years of age
4) been an ambulatory outpatient
5) had normal results from the following tests according to the subject's age:
   - for subjects less than 50 years of age, flexible sigmoidoscopy (using a flexible sidmoidoscope of 60cm) after the onset of IBS symptoms and within 5 years of the randomization visit.
   - for subjects 50 years and older, either an air contrast (double contrast) barium enema plus a flexible sigmoidoscopy or a full colonoscopy (using a scope of >180cm or hospital standard, visualising the caecum), after the onset of IBS symptoms and within 5 years of the randomization visit.

For subjects who required the above procedures, these tests were to be performed after the subject was determined to be eligible for the Treatment Phase. In order to ensure that the above tests did not interfere with symptom assessment, they were performed in a 7-day window between the Screening and Treatment Phases. The tests were performed on the first four days of the 7-day window to allow 3 days for the subject to recuperate. By the seventh day, if the results of the tests were determined to be normal, the subject was randomized and dispensed study drug. Subjects began taking study medication by the evening of the seventh day.

**6. To be included in the 2-week Screening Phase subjects must have satisfied the Rome diagnostic criteria for IBS, as follows:**

experienced at least 6 months of abdominal pain and discomfort which was 1)relieved with defecation, 2) and/or associated with a change in stool frequency, 3)and/or associated with a change in stool consistency (at least one had to be present).and had at least a 6-month history of two or more of the following being present 25% of the time which, for the purpose of the study, was defined as at least two days per week 1) altered stool frequency (defined as >3 bowel movements/day or <3 bowel movements per week), 2) altered stool form (lumpy/hard or loose/watery), 3) altered stool passage (straining, urgency, or feeling of incomplete evacuation), 4) passage of mucus, and/or 5) bloating or feeling of abdominal distention.

To be included in the Phase 12-week Treatment subjects must have satisfied the following criteria during the 2-week Screening Phase:

have recorded the presence of abdominal pain and discomfort with an overall average pain and discomfort severity score between 1.0 and 3.3. Pain and discomfort severity was rated as 0 = no pain, 1 = mild, 2 = moderate, 3 = intense, and 4 = severe. For purposes of analysis, "no pain" was assigned a score of zero. Subjects recorded their maximum daily abdominal pain and discomfort severity and their GI functions using a touch-tone telephone electronic data entry system

have documented an average stool consistency score of =2.5. Stool consistency was rated as 1 = very hard, 2 = hard, 3 = formed, 4 = loose, and 5 = watery. For the purposes of analysis, no stool was assigned a score of zero.

have recorded at least 12 days of daily self-assessments.

The investigator was informed of the subjects' eligibility to continue into the Treatment Phase of the study by the touch-tone electronic data entry system.

**B – Exclusion Criteria**

A subject was not eligible for inclusion in this study if any of the following criteria

1) If, in the opinion of the examining physician, an unstable cardiovascular, renal, hepatic, pulmonary, endocrine, metabolic, hematological, or gastrointestinal condition was present.
2) Evidence of a biochemical or structural abnormality of the digestive tract; these conditions included (but were not limited to):
   - current evidence or history of inflammatory bowel disease (Crohn's disease or ulcerative colitis)
   - current evidence of diverticulitis, erosive esophagitis, symptomatic gastro-

esophageal reflux disease (not controlled by a stable dose of medication), duodenal ulcer, gastric ulcer, gastroparesis, gastrointestinal malignancy, gastrointestinal obstruction, carcinoid syndrome, pancreatitis, symptomatic cholelithiasis, amyloidosis, ileus

- history of gastrointestinal surgery (exceptions: appendectomy, cholecystectomy, benign polypectomy, and repair of hiatus hernia)
- a history or current evidence of laxative abuse (in the clinical judgement of the physician).

3) A major psychiatric disorder (DSM-III-R or DSM-IV) within the last two years that required hospitalization or involved an attempted suicide, including major depression or psychoses. Other subjects with a major psychiatric disorder (DSM-III-R or DSM-IV) within the last two years, had to be on a stable dose of medication for at least six months prior to the Screening Visit.
4) A history of alcohol or substance abuse within the past two years.
5) Hepatic dysfunction (alanine transaminase [ALT, SGPT] or aspartate transaminase[AST, SGOT] > 2.5 times the upper limit of normal).
6) Abnormal thyroid stimulating hormone (TSH). (If a test had not been done within the previous 12 months, it had to be completed by the day of randomization.)
7) Renal impairment (serum creatinine >20mol/L).
8) Any evidence of or treatment of malignancy (other than localized basal cell, squamous cell skin cancer or localized cancer in situ that had been resected) within the previous five years.

   Subjects meeting the above mentioned criteria were excluded from the population for safety reasons and to avoid confounding efficacy results.

9) Use of a research drug or participation in a research study, within 30 days of the screening phase.
10) Use of any concurrent prohibited medications. (Subjects could not take prohibited medications at least seven days prior to entering the screening phase and were to remain off these medications for the duration of the study). A non-exhaustive list of these medications included:
    - antibiotics (more than a 14-day course of therapy). except macrolide antibiotics which were prohibited for any duration of dosing
    - anticholinergics (dicyclomine, hyoscyamine, physostigmine, pyridostigmine, tacrine)
- cholestyramine
- cholinomimetic agents (bethanechol, propantheline, anticholinergics [see above])
- codeine and codeine containing analgesics
- colchicine
- enemas (including corticosteroids, 5-acetylsalicylic acid [5-ASA] preparations)
    - GI preparations (antacids which contain aluminium and/or magnesium, antidiarrheal agents, antinausea agents [benzquinamide, trimethobenzamide, prochlorperazine, promethazine, hydroxyzine], antispasmodic agents [e.g. Donnatal®, Librax, dicyclomine, propantheline], 5-ASA preparations, bismuth compounds, laxatives, prokinetic agents [cisapride, metoclopramide], stool softeners, sulfasalazine)
- agents indicated for IBS

- iron supplements
  laxatives* (docusate, enemas, stimulant laxatives including phenolphthalein, bisacodyl, milk of magnesia, mineral oil, magnesium citrate all other laxatives if used more than once per week)
- morphine and morphine containing analgesics
- all other narcotics
- tramadol
- theophylline
- warfarin
  nonsteroidal anti-inflammatory drugs (if used more than 3 days per week. Aspirin 325mg per day was allowed).
- all other analgesics (if used more than 3 days per week)
- anti-parkinson's agents (e.g. levodopa, deprenyl)
- antipsychotics
- isoniazid
- rifampicin
- anticonvulsants used in seizure disorders
- peppermint oil
- leuprolide
- stimulants and amphetamine-like drugs
- other 5-HT3 antagonists

The above drugs were excluded/prohibited to avoid any interference with the assessment of efficacy, or for safety reasons.

11) A pregnant woman.

12) A woman breastfeeding an infant(s).Pregnant or lactating women were excluded from the study as any risks to the fetus wereunknown.

13) Inability or unwillingness to follow directions, or unable to understand how to use thetouch-tone telephone electronic data entry system.

Subjects had to be able to comply with study requirements to maximize the results of the study . They also had to be able to use a touch-tone telephone diary system because key efficacy data were collected by this method.

* Laxatives which needed to be given as a preparation for the required flexible sigmoidoscopy/colonoscopy test were not excluded as a preparation for these tests

**C– Premature Treatment and/or Study Discontinuation**

A subject could be withdrawn from the study at any time at either the investigator's or the subject's discretion or due to absence of stool for eight consecutive days. Reasons for discontinuing participation in the study were recorded on the summary page in the CaseReport Form (CRF). Subjects discontinued from the study at any time received appropriate treatment by their physician without prejudice.

**D – Treatment Administration**

Each subject was randomized to receive either alosetron 1mg bd po for 12 weeks or trimebutine 200mg tds po for 12 weeks. The dose of alosetron was chosen on the basis of results from an earlier dose-ranging study (S3BA2001) in which 1mg bd was shown to be

the lowest effective dose. The adult dosage of trimebutine varies between 100-200mgtds; thus the highest dose of 200mg tds was chosen for comparison.
Subjects were instructed to take one capsule before breakfast, one capsule before lunch, and one capsule before the evening meal. If the subject skipped any meals, the dose was to be taken at 08:00 hours, 13.00 hours, and 20.00 hours as appropriate. For subjects who worked unusual hours, e.g. night shifts, medication was to be taken before the subject's scheduled breakfast, lunch or evening meal

**E – Treatment Compliance**
At the Randomization Visit and Weeks 4 and 8, medication was dispensed to the subjects.Subjects were instructed to return all unused medication at the next scheduled visit. At Weeks 4, 8 and 12 the amount of study medication returned was recorded in the subjects'medical notes, and compliance documented in the CRF. Reconciliation was to the level of a treatment foil, i.e. 15 tablets. Subjects who consumed less than 80% of the intended dose of study drug were considered non-compliant. If a subject did not return the study drug, compliance for that period was defined as missing. For the purpose of defining protocol violators, where compliance data were missing, subjects were assumed to have been non-compliant.

**F – Concurrent Therapy**
All concomitant medication used by the subjects at study entry were recorded at the Screening Visit. The names of prescription and non-prescription drugs used by each subject were recorded in the subject's CRF; this information was updated at each visit. Medications which were prohibited during the study are listed in Section III-B-10.
The following medications were permitted during the study provided the subject had received stable doses of the drug for 30 days prior to the Screening Visit.
antianginals (calcium channel blockers, nitrates)
antidepressants
antihypercholesterolemics (except cholestyramine)
antihyperglycemics (oral sulfonylureas)
antihypertensives (β-blockers, α-blockers)
anxiolytics
bulking agents
pancreatic enzymes
thyroid replacement therapy (e.g. levothyroxine)
None of these medications, at a stable dose, was considered to have the potential to affect the study endpoints (either efficacy or safety).

**IV – MEASUREMENTS AND EVALUATIONS**
**A – Efficacy Measures**
1 –Primary Efficacy Measure
The primary endpoint was adequate relief of IBS pain and discomfort
In consultation with a panel of International IBS experts, the endpoint of adequate relief of IBS pain and discomfort was derived in order to represent a subject assessment that was clear and clinically meaningful.

The panel concluded that a new IBS therapeutic agent should provide adequate relief of IBS pain and discomfort for at least half of the time that it was assessed.
Adequate relief of IBS pain and discomfort
Subjects made weekly reports during the Treatment Phase, via the touch-tone telephone electronic data entry system, regarding adequate relief of IBS pain and discomfort. All subjects received full training on the use of this data entry system at the Screening and Randomization Visits, and their eligibility was assessed during the 2-week Screening Phase It was recommended that subjects telephone at the same time each day, and preferably in the evening. Subjects were asked the following question:
In the past seven days, have you had adequate relief of your IBS pain and discomfort? [Yes/No]
The touch-tone telephone system first asked this question on Day 8 after Randomization, and every seventh day during the Treatment and Follow-up Phases of the study (i.e. days 8, 15, 22,....., 112). If the subject failed to respond to the question on the first day that it was asked, the system continued to ask the question for two further days until the question was answered. If the question had not been answered by the third day, the result for that week was recorded as missing.
Female subjects sometimes report an exacerbation of their IBS symptoms at menses. There is some evidence that rectal sensitivity in female IBS subjects changes with the menstrual cycle, suggesting that subjects with IBS respond differently to fluctuations in sex hormones compared with normal individuals As a supportive analysis to the primary efficacy endpoint, the effect of menstruation on the weekly adequate relief of abdominal pain and discomfort was also assessed. Subjects supplied the start and stop dates of their last menses during the Treatment and Follow-up Phases.

2 Secondary Efficacy Measure (s)

a) Proportion of pain and/or discomfort-free days at each month

Subjects recorded maximum daily abdominal pain and/or discomfort severity, during the Screening, Treatment and Follow-up Phases, using the touch-tone telephone electronic data entry system. Subjects were asked about their abdominal pain and discomfort as follows:

- Did you experience abdominal pain and/or discomfort today? [Yes/No] If yes, rate your maximum pain and discomfort severity, using the following scale:

Mild = 1, Moderate = 2, Intense = 3, Severe = 4
For the purposes of analysis and for calculating daily mean scores of abdominal pain and/or discomfort severity, no pain and/or discomfort was assigned a score of zero.
**A subject was classified as a monthly responder** if she reported at least 50% pain and discomfort-free days in months with at least 14 recorded daily pain measurements. The proportion of monthly responders was calculated at Months 1, 2 and 3. Month 1 included all data collected in the interval between the treatment start date and the Week 4 visit date, inclusive. Month 2 included all data collected after the date of the Week 4 visit date, up to and including the Week 8 visit date. Month 3 included all data collected after the date of the Week 8 visit date, up to and including the Week 12 visit date.

b)Subject self-rating of pain and discomfort

Subjects recorded maximum daily abdominal pain and/or discomfort severity, during the Screening, Treatment and Follow-up Phases.

The mean severity score was calculated for baseline (14-day Screening Phase) and Months 1, 2 and 3.

c) Lower GI symptoms
Subjects recorded the following daily GI symptoms during the Screening, Treatment and Follow-up Phases, using the touch-tone telephone electronic data entry system:

- How many times did you pass stool today? (Provide number of times.)

If the answer to the above question was zero, the following two questions were omitted.

- Please rate your stool consistency today:

1 = very hard, 2 = hard, 3 = formed, 4 = loose, 5 = watery

For the purposes of analysis, "no stool" was assigned a score of zero.

- With passage of stool, did you experience a sense of incomplete evacuation today? [Yes/No]
- Have you felt or experienced a sense of urgency today? [Yes/No]
- Did you have bloating today? [Yes/No]

d) SCL-90R ® (where translations were available)

The SCL-90R ® consists of 90 questions that reflect psychological symptoms in terms ofnine primary symptom dimensions (somatization, obsessive-compulsiveness, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism) and three global indices of psychological distress (global severity index (GSI), positive symptom distress index (PSDI) and positive symptom total (PST).

Following the collection of AE information at the Randomization and Week 12 (or Final) Visits, subjects were given SCL-90R ® questionnaires which they completed without assistance. SCL-90R ® information was not recorded in the adverse events section of the CRF. The responses indicated how much the subject was distressed by each symptom during the previous seven days, as follows

0 = not at all, 1 = a little bit, 2 = moderately, 3 = quite a bit, 4 = extremely

e) Health Outcomes Measures (where translations were available)

Subjects completed health-related quality of life (QOL) and productivity (resource utilization) assessments at the Randomization and Week 12 (or Final) Visit. Two questionnaires were used to measure health-related QOL outcomes: the disease-specific Irritable Bowel Syndrome Quality of Life (IBSQOL), to assess changes in IBS specific health-related quality of life (HRQOL), and the generic health-related QOL questionnaire: Short Form-36 (SF-36), to assess changes in general health-related quality of life. For productivity (resource utilization), subjects were asked about the number of days they were unable to attend and number of days cutback on work/college/school or main activity and their level of productivity when they had to work with their IBS symptoms.

- The IBSQOL is a 30-item questionnaire that has been developed to measure 9 domains found to be relevant to subjects with IBS:
- Emotional health (feelings of frustration, anger, dissatisfaction)
- Mental health (psychological well-being: feeling upset, nervous, worried)

- Sleep (difficulty initiating and maintaining sleep)
- Energy (emotional and physical tiredness, or fatigue)
- Physical functioning (restrictions or reductions in physical activity)
- Food (appetite and dietary limitations)
- Social functioning (interference with social activities)
- Role-physical (limitations carrying out work or main activity)
- Sexual relations (interference with sexual activities and satisfaction).

The IBSQOL has been shown to be valid, reliable and responsive to change in a clinical trial population

The SF-36 is one of the most widely used generic quality of life questionnaires. It is a 36 item general health-related QOL instrument, focusing on seven health concept scales, a general health indicator scale (General health perception), and a health transition item which tracks a subject's perception of change in health. The seven health concept scales are:

- Physical Functioning (e.g. walking, climbing stairs, carrying groceries)
- Role physical (limitations in ability to work or perform normal usual activities)
- Bodily pain (intensity of bodily pain or discomfort)
- Vitality (energy level or fatigue)
- Social functioning (impact of health or emotional problems on social activities)
- Role-emotional (impact of emotional problems on work or usual activities)
- Mental health (anxiety, depression, loss of control, sense of psychological well-being)

SF-36 has been shown to be valid for use in subjects with IBS and to be reliable and responsive to change in IBS subjects .

f)Productivity (Resource Utilization) Measures

At the Randomization and Week 12 (or Final) Visit, subjects were asked to answer questions, referring to the "past four weeks", about the following:

the number of days they were unable to attend work/school/college/main activity because of their IBS

the number of days they had to cut-back on work/school /college/main activity because of their IBS

their level of productivity when they had to work with symptoms of IBS.

During the treatment and follow-up phases, patients in paid employment were also asked to record weekly the number of hours missed from their paid job via the touch-tone telephone electronic data entry system. The relationship between adequate relief from IBS pain and discomfort and hours missed from work was explored across the treatment groups.

## V – SAFETY MEASURES

### A – Adverse Events

An AE was any untoward medical occurrence in a subject administered a pharmaceutical product and which did not necessarily have a causal relationship with this treatment. An AE could therefore have been any unfavorable and unintended sign (that could have included a clinically significant abnormal laboratory finding), symptom, or disease

temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
An AE included:

an exacerbation of a pre-existing illness
an increase in frequency or intensity of a pre-existing episodic event or condition
a condition detected or diagnosed during Screening or after trial medication administration even though it may have been present prior to the start of the study
continuous persistent disease/symptoms present at baseline that worsened following the start of the study
where a subject reported four consecutive days of no stool, "constipation". was recorded as an AE. Action taken with study drug was recorded as "temporarily interrupted. Where a subject reported eight consecutive days of no stool, action taken with study drug was recorded as "permanently discontinued"., and the subject was withdrawn from the study.
An AE did not include:

medical or surgical procedures (e.g. surgery, endoscopy, tooth extraction, transfusion). The condition that led to the procedure was an AE
pre-existing disease or conditions present or detected at the start of the study that did not worsen
situations where an untoward medical occurrence had not occurred (e.g. hospitalizations for cosmetic or elective surgery or social/convenience admissions)
the disease being studied or signs/symptoms associated with the disease unless more severe than expected for the subject's condition
overdose of either trial medication or concurrent medication with the maximum allowable dose as state out any clinical signs or symptoms. An overdose was defined as any dose that exceeded the maximum allowable dose as stated in the protocol.

A serious adverse event (SAE) included any experience or event that:
was fatal
was life-threatening (i.e. at immediate risk of death from the event as it occurred)
was disabling or incapacitating
required inpatient hospitalization or prolonged a current hospitalization
was a congenital anomaly in the offspring of a subject who received trial medication
was cancer
was an event resulting from an overdose of the trial medication. An overdose was defined as any dose that exceeded the maximum allowable dose as stated in the protocol
was an event which, though not included above, may have jeopardized the subject or may have required intervention to prevent one of the outcomes listed above.
If, in the investigator's opinion, worsening of IBS symptoms other than abdominal pain and discomfort were inconsistent with the subject's usual clinical course, then these symptoms were recorded as AEs. Worsening of a subject's IBS symptoms that met the definition of serious was to be reported as a serious adverse event. Normal fluctuations in a subject's IBS symptoms were not recorded as AEs

**B – Clinical Laboratory Tests**

A standard battery of laboratory blood tests including clinical chemistry and haematology was performed at the Screening, Week 4, 8, 12 (or Final), and (if necessary) Follow-up Visits. Laboratory tests included the following:

| Haematology | Serum Chemistry | Other |
|---|---|---|
| haematocrit | sodium | |
| haemoglobin | potassium | serum beta chorionic gonadotrophin (β-hCG) pregnancy test |
| red blood cell count | calcium | |
| platelets | creatinine | |
| white blood cell count | blood urea nitrogen (BUN) | thyroid stimulating |
| neutrophils | alanine aminotransferase (ALT) | hormone* (TSH) |
| lymphocytes | aspartate aminotransferase (AST) | |
| monocytes | alkaline phosphatase | |
| eosinophils | total bilirubin | |
| basophils | total protein | |
| bands | albumin | |

* At Screening only, if not done within previous 12 months

All clinically significant abnormal laboratory results that were assumed to be drug-related or of uncertain causality were repeated within two weeks. Any abnormal values that persisted were followed at the discretion of the investigator, following consultation with the sponsor. If a subject was discontinued for any abnormal laboratory value, a follow-up laboratory test had to be performed within two weeks.

Additional laboratory tests, performed at Screening only, included: a lactose intolerance test, according to a defined algorithm; stool occult blood, which could be omitted following Protocol Amendment; and stool ova and parasites (if not done within the previous three months).

**C – Other Safety Measures**

A physical examination was performed at the Screening and Week 12 Visits. Results were documented in the subjects' hospital or medical notes only.

Optional Genotyping

Increasing evidence exists that an individual's genetic composition not only affects disease susceptibility and progression of disease, but also impacts drug response and disease outcome.

Blood samples were collected on a voluntary basis from randomized subjects to distinguish variants of candidate genes associated with clinical response, tolerability, or adverse events during treatment with alosetron, and to determine variants of candidate genes associated with IBS severity in identified samples. Furthermore, the variants of any gene which may be associated with alosetron, IBS or any other disease were studied in non-identified samples (i.e. deoxyribonucleic acid [DNA] samples which were identified only by new identifying numbers which replaced the clinical trial subject number of the donor).

## VI –DATA ANALYSIS METHODS

### A – Sample Size

The total sample size for this study was determined on the basis of anticipated differences between treatment groups in the proportion of female subjects with adequate relief of abdominal pain and discomfort on at least two weeks per month, plus an allowance for dropouts. The proportion of subjects with adequate relief on at least two weeks per month was expected to be about 43% in subjects receiving trimebutine 200mg tds, and at least 55% for alosetron 1mg bd.

The methods of Fleiss were used to determine the sample size necessary to detect differences in the proportion of subjects with adequate relief between the two treatment groups. The sample size was chosen with 80% power at the □=0.05 level of significance. The number of subjects per treatment group necessary to detect a 12% difference between trimebutine and alosetron was N=288 per group. To allow for a 20% dropout rate, a target sample size of N=350 subjects per treatment group was chosen for a total of N=700 subjects.

### B – Population Subgroups

**1) Total ITT Population**

The Total ITT Population was to consist of all randomized subjects. Subjects who participated in the Screening Phase but who were not subsequently randomized to treatment were excluded from this population. The Total ITT Population constituted the primary population for analyses of efficacy and Health Outcomes data.

**2) Diarrhea-predominant ITT Population**

The Diarrhea-predominant ITT Population was to consist of all randomized subjects who, according to their disease history, were, in the opinion of the investigator, classified as suffering from diarrhea-predominant IBS. Subjects who participated in the Screening Phase but who were not subsequently randomized to treatment were excluded from this population. The Diarrhea-predominant ITT Population constituted a secondary population for analyses of efficacy and Health Outcomes parameters.

**3) Alternating ITT Population**

The Alternating ITT Population was to consist of all randomized subjects who were classified, in the opinion of the investigator, as suffering from IBS alternating between constipation and diarrhea. Subjects who participated in the Screening Phase but who were not subsequently randomized to treatment were excluded from this population. The Alternating ITT Population constituted a secondary population for analyses of efficacy and Health Outcomes data.

**4) Safety Population**

The Safety Population was to consist of all randomized subjects, excluding those who did not take at least one dose of study medication: i.e. subjects with no treatment start date were excluded from this population. This was the primary population for all analyses of safety data.

Key safety analyses excluding the data of the twenty-three subjects excluded from the ITT Population, and with these data alone are included in Attachment 1 for reference.

**5) Per Protocol Population**

Contrary to the protocol, a Per Protocol Population was not defined, as analyses based on this population were not required for the regulatory agencies. This change from the protocol was stated in the DAP.

**6) Other Population Subgroups**

The effects of IBS subtype, age, race, hormone use and baseline pain severity on the primary efficacy measure (adequate relief) were assessed as supportive analyses. The response variables for these analyses were the number of months that a subject was a responder for adequate relief. Contrary to the protocol, 1) subgroup analyses were not performed by baseline stool consistency, since the IBS subtype populations provide a more meaningful analysis. 2) Subgroup analyses by whether or not the subject menstruated during the study are replaced by the analysis detailed in c).3) Subgroup analyses were not performed for the secondary efficacy endpoint.

The subgroups were defined as follows:

IBS subtype: Diarrhea-predominant, Alternating or Constipation-predominant, as defined by the investigator. Although not defined as a subgroup analysis in the protocol, key analyses were performed for subgroups by IBS subtype regardless of whether an interaction was found. This was because the results suggested the presence of a qualitative treatment-by-IBS subtype interaction. Also, one of the three phase III studies showed a significant treatment by IBS subtype interaction (such that greater efficacy of alosetron over placebo was apparent on the diarrhea-predominant sub-group) and another showed a greater effect of alosetron in diarrhea-predominant IBS compared with alternating constipation and diarrhea IBS. In addition, the indication for alosetron in the USA, and the proposed indication in Europe, Canada and all other countries, is for women with diarrhea-predominant IBS.

Age: <65 and >65 years

Race: White/non-White

Hormone use: Hormone Use/No Hormone Use

Baseline pain severity: 2.0 and □2.0. (1=Mild, 2=Moderate, 3=Intense, 4=Severe)

(This additional analysis was requested by some regulatory authorities)

**C – Prematurely Discontinued Subjects and Missing Data**

The handling of missing data caused by prematurely discontinued subjects was managed according to the last observation carried forward (LOCF) principle whereby missing values were replaced with the last previous non-missing value. If there was no available baseline or post-baseline data to carry forward for a subject, then the least favorable outcome was assumed for the response variable. For SCL-90R ®, missing values were not included in the calculation of the mean of responses to the 90 questions (global severity index [GSI]).

**D – Protocol Deviations**

The number and percentage of subjects with major protocol violations are tabulated by decreasing order of frequency. *Major protocol violations were defined as follows:*

subject did not receive at least one dose of study medication

subject did not have a diagnosis of IBS

subject had evidence of a biochemical or structural abnormality of the digestive tract

subject took prohibited medications exceeding the permitted duration (macrolides for any duration; antibiotics for more than 14 days; all other prohibited medications for more than 7 consecutive days [medications prohibited during the study are listed in Section IV B-10) subject violated screening criteria for pain or stool consistency
subject was on a non-stable dose of antidepressants, antipsychotics, thyroid medications, calcium channel blockers, nitrates, anxiolytics, bulking agents, pancreatic enzymes or fibre replacements subject was less than 80% compliant in taking the study medication at all three months.subject was less than 50% compliant with the telephone diary system at all three months during the treatment phase.
Compliance with the telephone diary system was evaluated at Month 1 (from, and including the date of randomization, up to and including the Week 4 visit date), Month 2 (from, but not including, the Week 4 visit date, up to and including the Week 8 visit date), and Month 3 (from, but not including, the Week 8 visit date, up to and including the Week 12 visit date). The proportion of days that a subject was compliant with the telephone diary system was defined as the sum of all the days that a subject completed a call to the system, divided by the number of days in the month. Subjects who were less than 50% compliant for all three months were considered to be major protocol violators.

**E – Treatment Compliance**
Study drug compliance was assessed for each subject at the Week 4, 8 and 12 visits. For subjects who returned study drug, the site determined whether the subject was at least 80% compliant in taking medication, and the assessment of compliance was recorded on the CRF. For subjects who did not return the study drug, compliance for that period was defined as missing, and as non-compliant in terms of protocol violations. Compliance was summarized by treatment group and visit.

**F – Efficacy Analysis**
IBS is a multi-faceted disease characterized by abdominal pain and discomfort. Adequate relief of IBS pain and discomfort was the primary measure of efficacy.

**1) Primary Efficacy Measure**
:
Adequate Relief of IBS Pain and Discomfort

Primary Analysis:
Monthly Adequate Relief of IBS Pain and Discomfort
Sensitivity Analyses
Supportive Analyses:
Subgroup Analysis of Monthly Adequate Relief Responders
Weekly Adequate Relief of IBS Pain and Discomfort
Weekly Adequate Relief of IBS Pain and Discomfort and Menstruation
Average Adequate Relief of IBS Pain and Discomfort

Two protocol-defined measures were not analyzed:
- Correlation between weekly adequate relief of IBS pain and discomfort and other weekly efficacy measures was originally defined in the protocol in order to validate

the primary efficacy measure, adequate relief of IBS pain and discomfort. The analysis was not performed, since the measure of adequate relief was shown to be well -validated in three previously reported replicate studies and was shown to be well correlated with all other efficacy endpoints.

- Analysis of adequate relief responders, defined as 6 out of 12 weeks with adequate relief, was planned in subjects who completed the study. This was not analyzed since the information is provided in greater detail by the primary efficacy analysis

**2) Secondary Efficacy Measures**

- Proportion of pain and discomfort-free days
- Monthly Responders for Pain and Discomfort-Free Days
- Change from Baseline in Proportion of Pain and Discomfort-Free Days at each Month

**3) Other Efficacy Measures**

- Subject Self-rating of Pain and Discomfort
- Change from Baseline in Daily Pain and Discomfort Severity
- Lower GI Functions (stool consistency, stool frequency, and percentage of days with symptoms of urgency, bloating and sense of incomplete evacuation)
- Change from Baseline in Lower GI Functions
- SCL-90R ®

**4) Safety Analysis**

- Extent of Exposure
- Adverse Events
- Serious Adverse Events
- Pregnancies
- Clinical Laboratory Evaluations
- Other Safety Measures:
  Incidence of Constipation

## VI – RESULTS

### A – Population Studies

O ne thousand three hundred and ninety-five (1395) subjects were screened for participation in the study Forty-four percent (611/1395) of these subjects were not randomized to treatment for the following reasons: screening criteria not met(75%, 460/611); consent withdrawn (5%, 30/611); adverse event (<0.01%, 3/611); failed to return (<0.01%, 3/611); and "other" reasons (19%, 114/611).

Fifty-six percent (784/1395) of the subjects screened were randomized to treatment; 51% (402/784) to the alosetron 1mg bd group and 49% (382/784) to the trimebutine 200mg tds group. All subjects randomized to treatment consumed at least one dose of study medication and are included in the Safety Population. Twenty-three subjects (one center) were excluded from the Intent-to-Treat Population due to inability to confirm entry criteria , leaving 390 in the alosetron 1mg bd group and 371 in the trimebutine 200mg tds group.

In both treatment groups, about three quarters of subjects (73% and 68% in the two groups, respectively) were designated by the investigator, based on their IBS history, as diarrhea-predominant and 23% as alternating constipation and diarrhea. Enrolment by cluster/country and investigator is detailed in . The individual subject randomization schedule and screen failure are presented in. The percentage of randomized subjects who completed the study was 78% (597/761) overall, with 76% (295/390) in the alosetron 1mg bd group and 81% (302/371) in the trimebutine 200mg tds group Twenty-two percent (164/761) of the subjects in the Total ITT Population withdrew from the study during the Treatment Phase; 24% (95/390) and 19% (69/371) in the alosetron and trimebutine groups, respectively. All reasons for premature withdrawal from the study are summarized in the table below. The main reason in both treatment groups was an AE (64% of subjects who were withdrawn in the alosetron group and 54% of subjects who were withdrawn in the trimebutine group). The AE accounting for increased withdrawal from the alosetron 1mg bd group was constipation.

Premature Study Withdrawal by Reason: Total ITT Population

| | Alosetron 1mg bd n (%)[1] | Trimebutine 200mg tds n (%)[1] | Total n (%)[1] |
|---|---|---|---|
| Number of subjects withdrawing prematurely n (%)[2] | 95 (24) | 69 (19) | 164 (22) |
| Adverse event | 61 (64) | 37 (54) | 98 (60) |
| Consent withdrawn | 7 (7) | 4 (6) | 11 (7) |
| Lost to follow-up | 10 (11) | 10 (14) | 20 (12) |
| Protocol violation | 4 (4) | 4 (6) | 8 (5) |
| Lack of efficacy | 2 (2) | 5 (7) | 7 (4) |
| Other | 11 (12) | 9 (13) | 20 (12) |

1: Percentage of withdrawn subjects; 2: Percentage of population

Approximately half of the subjects in the Total ITT Population who discontinued prematurely did so within the first 4 weeks of treatment (54%, 89/164); and the majority within 8 weeks of starting treatment (87%, 143/164).

**B – Protocol Violations**

Review of data and monitoring visits for one center involved in this study led to concerns that the protocol had not been adhered to at this site (Investigator 52378). These data (accounting for twenty-three subjects) were excluded from the ITT Population due to inability to confirm entry criteria. However, to be conservative, the safety data were included in safety analyses. This reviewer plans to request CRFs and additional information, as needed, for individual review of those patients.

Twenty percent (150/761) of the subjects in the Total ITT Population had major protocol violations: 20% (78/390) in the alosetron 1mg bd group and 19% (72/371) in the trimebutine 200mg tds group The most common protocol violations were:

use of prohibited medications for seven or more consecutive days (except for

antibiotics where use for more than 14 days or macrolide antibiotics taken for any duration during the study constituted a major violation), (64/150, 43% of subjects with protocol violations),

<80% compliance with the telephone diary system at all three months, (48/150, 32% of subjects with protocol violations),
violation of screening criteria for pain or stool consistency (11/150, 7% of subjects with protocol violations) □use of a non-stable dose of selected medication (28/150, 19% of subjects with protocol violations).

Some subjects violated for more than one reason.
The incidence of each type of protocol violation was comparable between treatment groups with the exception of the number of subjects on a non-stable dose of selected medication, which occurred more frequently among the trimebutine-treated subjects with protocol violations (28%) than among the alosetron-treated subjects with protocol violations (10%).
Twelve subjects (seven on alosetron 1mg bd and five on trimebutine 200mg tds) did not satisfy one or more inclusion or exclusion criteria
The treatment assignment was revealed for 2 subjects; Subject 3156 in the alosetron 1mg bd group and Subject 2484 in the trimebutine 200mg tds group. One subject requested treatment unblinding due to lack of efficacy. The other subject opened the capsules to reveal the treatment.

**C – Concurrent Therapy**
The majority of subjects in the Total ITT Population reported using some form of concurrent therapy during the study (76% in the alosetron 1mg bd group and 74% in the trimebutine 200mg tds group) . The types of agents used and the proportions were similar in both treatment groups. The most common categories of drugs used were hormonal agents for contraception or as replacement therapy (e.g. estrogens and progestogens combined 19% of all subjects, estrogens alone 13%), paracetamol 16%, benzodiazepines 13%, non-aspirin NSAIDs 11%, and laxatives 9%. Although routine laxative use was disallowed, it was permitted for colon preparations associated with colonoscopies.
D – Efficacy Results
Efficacy results are presented in this report for the Total ITT Population (the primary efficacy population, N=761), the Diarrhea-predominant (N=551) Population and the Alternating ITT Population (N=182). Twenty-seven subjects were classified as constipation-predominant, and these were included only in the Total ITT Population. Data for twenty-three subjects (one center) were excluded from ITT analyses due to inability to confirm entry criteria.
For the purposes of this report, statistical significance has been declared at the two-sided 5% level.

- A similar number of months as an adequate relief responder (adequate relief for at least two weeks per month) was reported by subjects treated with alosetron 1mg bd or trimebutine 200mg tds (42% and 37% of subjects were responders at all 3 months, respectively) in the Total ITT Population. This was the primary efficacy endpoint.

Analysis of subgroup effects suggested the presence of a qualitative treatment-by-IBS subtype interaction, with diarrhea-predominant subjects benefiting more from treatment with alosetron, and alternating constipation and diarrh ea subjects

benefiting more from treatment with trimebutine. The differences were numerical, not statistical.

The percentage of adequate relief responders at all 3 months reported by diarrhea-predominant subjects was 46% with alosetron 1mg bd and 39% with trimebutine 200mg tds.

In the analyses of adequate relief of IBS pain and discomfort by week, alosetron showed significant benefit over trimebutine at most weeks (Weeks 3, 4, 6, 8, 9, 10 and 12) in subjects diagnosed with diarrhea-predominant IBS.

For diarrhea-predominant subjects, trimebutine had a significant benefit over alosetron in increasing the proportion of pain and discomfort free days at Month 1, but not at Months 2 or 3.

In subjects with diarrhea-predominant IBS, both alosetron and trimebutine reduced the symptoms of urgency (from a median percentage of approximately 78% at baseline to approximately 30% at Month 3), with no significant differences between the two treatments.

In subjects with diarrhea-predominant IBS, alosetron led to a statistically significantly ($p<0.001$) greater firming of stool consistency compared with trimebutine and a numerically greater reduction in stool frequency (from 2.5 stools passed per day during Screening to 1.50 times at month 3 in the alosetron group and a change from 2.50 times during screening to 1.79 in the trimebutine group).

All treatment effects were apparent early in treatment (within 1 to 3 weeks) and were sustained throughout treatment.

**Humanistic Measures**

All analyses of health-related Quality of Life (QOL) and productivity (resource utilization) parameters were performed on three populations: the Total Intent-to-Treat (Total ITT) Population, the DIARRHEA-predominant ITT Population, and the Alternating ITT Population.

Translated versions of the QOL instruments were available for only 7 out of the 14 countries that participated in the study. In addition, pooling data across regions with cultural differences in the perceptions of the domains addressed in the QOL questionnaires may lessen the sensitivity of the instruments to detect statistically significant differences between treatments.

**E – Safety Results**

The safety analyses were performed on the Safety Population (n=784). defined as all subjects who consumed at least one dose of study drug.

**1) Extent of Exposure**

Eighty-one percent (325/402) of subjects in the alosetron group and 87% (332/382) of subjects in the trimebutine group received study drug for eight or more weeks

**2) Adverse Events**

Sixty-one percent (61%, 247/402) of subjects in the alosetron 1mg bd group reported a total of 662 AEs during the Treatment Phase. Within the trimebutine 200mg tds group, 60% (229/382) of subjects reported a total of 645 AEs. The difference in the proportion of subjects experiencing AEs between the groups was not significantly different(p=0.715)
The following table summarises the most commonly reported AEs (defined as those occurring in >5% of subjects in either treatment group)
The incidence of individual AE was similar between treatment groups except for constipation (reported in 20 % of the alosetron 1 mg bd treated subjects and 7 % of the trimebutine 200 mg tds treated subjects.

**Most Common Treatment-Emergent Adverse Events (≥5% of subjects)**

| | | Alosetron 1mg bd (N=402) | | Trimebutine 200mg tds (N=382) | |
|---|---|---|---|---|---|
| Body System | Adverse Event | No. of Events | No. (%) of Subjects | No. of Events | No. (%) of Subjects |
| Any Body System | Any Event | 662 | 247 (61%) | 645 | 229 (60%) |
| Gastrointestinal | Constipation | 111 | 82 (20%) | 31 | 25 (7%) |
| | Nausea | 28 | 27 (7%) | 45 | 35 (9%) |
| | Abdominal discomfort & pain | 36 | 29 (7%) | 37 | 27 (7%) |
| | Diarrhoea | 16 | 15 (4%) | 29 | 24 (6%) |
| Neurology | Headaches | 55 | 42 (10%) | 78 | 53 (14%) |
| Non-Site Specific | Malaise & Fatigue | 17 | 16 (4%) | 20 | 18 (5%) |

**3) Drug-related Adverse Events**

Adverse events included in drug-related AE analyses were those judged by the investigator as having a reasonable possibility of being caused by the study medication.
Thirty-six percent (36%, 144/402) of subjects in the alosetron 1mg bd group had 299 drug-related AEs reported and 27% (104/382) of subjects in the trimebutine 200mg tds group had 254 drug-related AEs reported during the Treatment Phase (p=0.011)
The proportion of subjects with drug-related gastrointestinal events was significantly different between groups. Twenty-nine percent (29%, 116/402) of subjects in the alosetron 1mg bd group had drug-related gastrointestinal AEs compared with 19% (72/382) of subjects in the trimebutine 200mg tds group (p=0.001). In particular, the incidence of drug-related constipation differed between groups (20%, 81/402 in the alosetron 1mg bd group and 7%, 25/382 in the trimebutine 200mg tds group)

Constipation was the most common cause of withdrawals in both treatment groups although the proportion was higher in the trimebutine group (7% of the alosetron 1mg bd group compared with 2% of the trimebutine 200mg tds group).
Among the 98 subjects withdrawn due to AEs during the study, ten subjects were withdrawn due to serious adverse events.

**4) Constipation**

Constipation was recorded as an AE for 20% (82/402) of subjects in the alosetron 1mg bd group and 7% (25/382) in the trimebutine 200mg tds group . In the alosetron 1mg bd group, most subjects who reported constipation as an adverse event did so during the first four weeks of the Treatment Phase (77%, 63/82) with fewer subjects reporting constipation as treatment progressed This pattern was true of both the diarrhea-predominant and alternating constipation/diarrhea
IBS subjects in the alosetron 1mg bd group
Of the 82 subjects in the alosetron group reporting constipation, 77% (63/82) reported only one occurrence of constipation and 12% (10/82) two occurrences
Similarly, in the trimebutine group, 80% (20/25) of subjects reporting constipation reported only a single incidence of the AE
The median duration of the AEs of constipation in the alosetron group was 5 days; the majority (73%) of events were mild or moderate in severity
The median duration of AEs of constipation in the alosetron group was similar in subjects diagnosed with diarrhea-predominant or alternating IBS, but the percentage with severe constipation was slightly higher in the alternating group
While experiencing constipation, the majority of subjects passed at least one stool per day and had a stool consistency score of 2 (hard) or more.
Thirty-seven percent (30/82) of subjects in the alosetron group and 24% (6/25) of subjects in the trimebutine group who reported constipation as an AE were withdrawn from the study due to constipation
Using observed data, 12% (50/402) of subjects in the alosetron group and 3% (11/382) of subjects in the trimebutine 200mg tds group had at least one cycle of four days without stool The majority of these subjects only reported a single episode of four days without stool. LOCF data overestimate the numbers of cycles of four days with no stool.
Using observed data, two subjects (<1%) in the alosetron group and one in the trimebutine group had eight days without stool.

**5) Deaths**

There were no deaths in the alosetron group.
One woman in the trimebutine group became jaundiced four days after onset of treatment and was diagnosed with metastatic cancer of the pancreas and died later on.

**6) Serious Adverse Events**

No cases of Alosetron Associated Ischemic Bowel Disease (AAIscBD) or serious complications of constipation were reported in this series.

During the Treatment Phase, 2% (8/402) of subjects in the alosetron 1mg bd group reported a total of 10 SAEs, and 1% (5/382) of subjects in the trimebutine 200mg tds group reported a total of 6 SAEs (See Table in page ).

Serious adverse events occurring in two or more subjects included abdominal pain and discomfort (2 subjects in the alosetron 1mg bd group) and constipation (2 subjects in the alosetron 1mg bd group)

Five of the 10 SAEs in the alosetron 1mg bd group were considered drug related by the investigator Subject 2330; ileus, Subject 2541; constipation, Subject 27655; lower abdominal pain, Subject 3773; constipation and abdominal pain. None of the SAEs in the trimebutine 200mg tds group were considered drug related by the investigator. All drug-related SAEs resolved without sequelae.

Nine subjects who reported, in total, 12 SAEs were withdrawn from the study. Seven of the nine subjects were in the alosetron 1mg bd group and reported nine SAEs. The remaining two subjects were in the trimebutine 200mg tds group, and reported a total of three SAEs (see Tables in page ).

Three subjects, all in the alosetron group, were withdrawn from the study due to SAEs which were considered by the investigator to be related to study drug (Subjects 2330, 27665 and 3773)

All subjects who reported SAEs were <65 years of age and white.

**7) Withdrawals Due to Adverse Events by Subgroup**

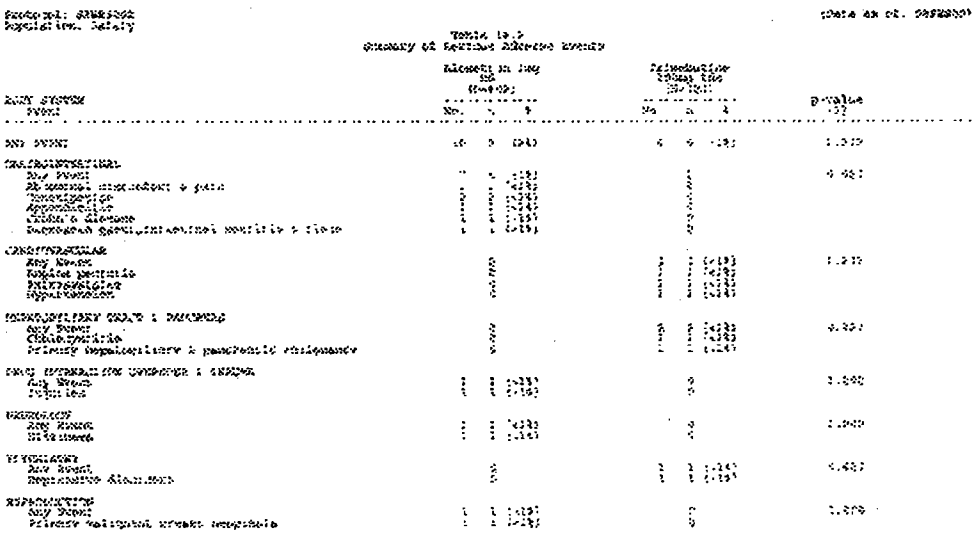
Within the alosetron 1mg bd group, 39 subjects (13%, 39/298) with diarrhea-predominant IBS reported 65 AEs which led to withdrawal, and 21 subjects (23%, 21/90) with alternating constipation/diarrhea IBS had 32 AEs leading to withdrawal . Five percent (14/298) of subjects with diarrhea-predominant IBS and 17% (15/90) of subjects with alternating constipation/diarrhea IBS were withdrawn from the study due to constipation .

Within the trimebutine 200mg tds group, 27 subjects (10%, 27/262) with diarrhea-predominant IBS reported 48 AEs which led to withdrawal, and 8 subjects (8%, 8/106) with alternating constipation/diarrhea IBS reported 19 AEs which led to withdrawal . Two percent (4/262) of trimebutine 200mg tds treated subjects in the diarrhea-predominant IBS subtype and 2% (2/106) of subjects with alternating constipation/diarrhea IBS were withdrawn from the study due toconstipation .

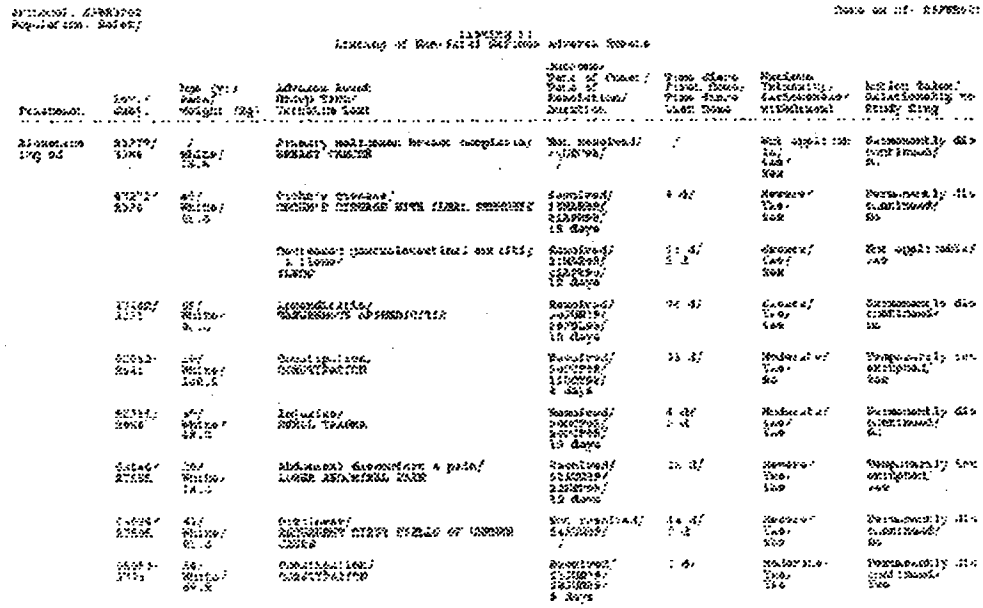
**8) Pregnancies**

Three patients became pregnant during the study at 11, 5 and 12 weeks of treatment. Two were on alosetron and one on trimebutine. Two patients underwent early termination of their pregnancies. The third subject, who was on the alosetron group, delivered a male infant with a mild hypospadias (this was considered a SAE).

# SUMMARY OF SERIOUS ADVERSE EVENTS



# NON-FATAL SERIOUS ADVERSE EVENTS



**8) Clinical Laboratory Evaluations**

Hepatic Function

Mean levels of transaminases, alkaline phosphatase, and total bilirubin levels were comparable between treatment groups and remained constant throughout the Treatment Phase (see Table in page 28 ).

Clinically important liver function test elevations were defined program-wide as: ALT ≥3-fold normal, alkaline phosphatase or bilirubin ≥2-fold normal occurring during treatment or follow up. The following table provides clinical information on individual subjects exhibiting ALT abnormalities exceeding 3-fold normal during study drug treatment or follow up. Information includes pattern of ALT elevation, pertinent adverse events, and concomitant medications (administered within 30 days of peak ALT). In total, 2/402 (0.5%) of alosetron-treated subjects and 3/382 (0.8%) of trimebutine-treated subjects exhibited 3-fold or greater ALT elevation (see following table). No subject exhibiting an ALT elevation exceeding 3-fold normal, exhibited an increase in bilirubin or alkaline phosphatase of >2-fold during study drug treatment or follow-up. The range of peak ALT was slightly higher in trimebutine-treated subjects (5.1-7.4 fold normal) than alosetron-treated subjects (4.2-4.5 fold normal).

**Summary of subjects with ALT exceeding 3-fold normal during treatment and followup in S3BB3002**

| Subject, Study Drug | ALT – Fold Normal | Information on ALT | Background Information (Demographics, Pertinent Adverse Events, Medications within 30 days of peak ALT) |
|---|---|---|---|
| 2644 Alosetron | 4.2 | Baseline normal ALT Peak ALT 4.2-fold normal on treatment Day 30; no followup ALT information | 36-year-old female **Adverse events**: (4-fold) Elevated ALT Value, (Slightly) Elevated AST Value **Medications**: Ranitidine, atenolol |
| 3614 Alosetron | 4.5 | Pretreatment ALT 2.4-fold normal; Peak ALT 4.5-fold normal on treatment Day 28; subsequent ALT 4.4 fold normal 15 days post-treatment | 62-year-old female **Adverse events**: elevation of transaminases **Medications**: isosorbide dinitrate, nifedipine, propafenone |
| 2596 Trimebutine | 5.7 | Baseline normal ALT Peak ALT 5.7-fold normal on treatment Day 78; decreased to ALT 3.1-fold normal 32 days post-treatment | 41-year-old-female **Adverse events**: elevation of ALT **Medications**: none reported |
| 3210 Trimebutine | 5.1 | Baseline normal ALT Peak ALT 5.1-fold normal on treatment Day 81; decreased to normal ALT 12 days post-treatment | 40-year-old-female **Adverse events**: none reported **Medications**: none reported |
| 3218 Trimebutine | 7.4 | Baseline normal ALT Peak ALT 7.4-fold normal on treatment Day 99; decreased to ALT 1.9-fold normal 28 days post-treatment | 59-year-old-female **Adverse events**: Iatrogenic hepatitis **Medications**: Verapamil, estriol, enalapril |

Source: Listings 11 and 17

Patterns suggestive of possible drug-induced hepatotoxicity were evident in all patients: two alosetron-treated subjects (Patients 2644 and 3614) and three trimebutine-treated subjects (Patients 2596, 3210, and 3218). In the alosetron-treated subjects, a chronological relationship of ALT elevation to study drug treatment was noted in both subjects, however, resolution of ALT elevation with "dechallenge" was not seen in Patient 3614 and no follow-up informationwas available for Subject 2644.

Hematology and Clinical Chemistry

There was no apparent difference in the occurrence of reference range shifts from baseline to low or high values at any follow-up visit, between the alosetron 1mg bd and trimebutine 200mg tds treatment groups, for any hematology or clinical chemistry analyte measured For the majority of subjects there was either no change, or a shift to normal range, in their hematology or clinical chemistry test results at follow-up.

## VII – DISCUSSION

**A – Protocol design**

S3BB3002 is a randomized, double blind, multicenter clinical trial carried out between May 1998 and November 1999 at 125 sites in Europe, Canada and Mexico.

The sponsor chose as control trimebutine maleate, a medication not available in the US market, that is commonly used in other countries for the symptomatic treatment of IBS. The sponsor doesn't specify why this "active" controls was chosen over placebo in designing this clinical trial. This reviewer doesn't see any clinical or ethical issues that might have prevented the use of placebo as control in this study. There is no evidence supporting the efficacy of trimebutine in the treatment of IBS, as it is repeatedly stated by the sponsor throughout the S3BB3002 report. Further, trimebutine is a 30 year old drug, studied by different methods than those currently used for the diagnosis of IBS (Rome criteria, Manning) and for the assessment of IBS symptoms (validated questionnaires). In the case of IBS patients, no serious harm (such as death or irreversible morbidity), would have been caused by depriving patients of available symptomatic treatments, all of which lack solid evidence of effectiveness.

Because of these reasons, assay sensitivity can not be establish, since it can not be assumed that control trimebutine is an effective treatment. If it is not known whether the trial had assay sensitivity, finding no difference between trimebutine and alosetron means that either both drugs were effective or that neither drug was effective. Thus, S3BB3002 is not a non-inferiority trial, and analysis of the data will have to show either superiority or be a just simple (meaningless?) comparison.

Probably at the time when this research protocol was designed, the European regulatory agencies still favored active control trials instead of placebo-controlled because of humanitarian reasons. In 2000 the Declaration of Helsinky was amended allowing the use of placebos or no treatment "in studies where no proven prophylactic, diagnostic, or therapeutic method exist". Subsequently, the International Commission on Harmonization issued ICH E-10 Guidance and the FDA published a guidance entitled Choice of Control Group and Related Issues, both of which clarified the issue of controls in clinical trials.

**B – Efficacy Results**

'In general, diarrhea predominant patients (IBS-D) benefited more from alosetron treatment, whereas alternators (IBS-A) benefited more from trimebutine.

Adequate relief responders (ARR) responded about equally to both treatments, in the total ITT population, and in the IBS-D sub-group. The difference became statistically significant in the IBS-D group during some weeks: 3, 4, 6, 8, 10, 12.

There was no significant difference between treatment groups for symptoms of urgency or the number of bowel movements per day (a numerical difference in favor of alosetron was observed for the latter).

There was a statistically significant difference in favor of alosetron in firming of the stool observations.

Psychological testing with the SCL-90 was unaffected by either therapy.

The IBSQOL instrument in which higher scores indicate higher quality of life, showed no difference with either treatment in the total ITT population. Alosetron produced statistically significant higher scores in the IBS-D patients, while trimebutine improved the scores of the trimebutine group. Measurements with the SF-36 showed no difference

in the total ITT population and marginal improvements in the IBS-D with alosetron and in the IBS-A with trimebutine.
This results are equivocal at best from the point of view of the tested drug, and fail to prove its superiority over the accepted drug overseas, trimebutine.

**C – Safety Results**
There were no cases of ischemic bowel disease, or complications of constipation. These were SAE observed after the alosetron was released for sale in February 2000, and were the cause of its withdrawal in november of the same year.
Constipation was the most common AE reported in the alosetron treatment group, observed in 20 % of the cases, in contrast to 7 % in the trimebutine treatment group. The incidence of constipation leading to withdrawal also differed between groups: 7 % in the alosetron group and 2 % in the trimebutine group. The proportion of withdrawals due to gastrointestinal AEs was statistically different at the level of p=0.001, between alosetron (11 %, 45/402) and trimebutine (2 %, 6/382).
The SAEs are listed in Table . We have requested from the sponsor the CRFs and original records of some selected cases for individual review, as follows:
Patient 2330: 45 y/o/f with 4 year history of "abdominal complaints" (not specified what complaints), developed lower abdominal pain and ultrasound evidence of ileal stenosis suggestive of Crohn's disease. The patient underwent surgery two days later.
REASON FOR REQUEST: Ultrasound is an unusual method to diagnose bowel obstruction. Crohn's disease is usually not diagnosed by ultrasound but by other means. There is no surgical or pathology report. The possibility that this was an episode of ischemic bowel with stricture should be ruled out.
Patient 27655: After four weeks of treatment with alosetron this 20 y/o/f develop lower abdominal pains. The patient received antibiotics without improvement and had to be hospitalized. A laparoscopy revealed endometriosis and the patient was treated with tramadol hydrochloride. The event resolved approximately seven weeks after onset.
REASON FOR REQUEST: Endometriosis is not an unusual finding at laparoscopy, and does not necessarily mean that it is the cause of symptoms.
Patient 27595: After five weeks of treatment with alosetron this 55 y/o/f patient developed otitis and one week later had a syncopal episode at home associated with chest pain, nausea, vomiting and urinary incontinence. The patient had had similar episodes (dizzie spells, sweats, dyspnea, incontinence, occasional syncope) in the past and epilepsy had been ruled out. Studies would continue on out patient bases. Ultimate outcome is unknown.
REASON FOR REQUEST: There are 5 HT3 receptors in the left ventricle, left coronary artery, pericardial sac of many animal species, that account for the von Bezold-Jarisch reflex (transient, intense, bradychardia after injection of a bolus of serotonin), abolished by administration of 5 HT 3 antagonists. This reviewer is concerned that the potential cardiovascular effects of alosetron administration have been underestimated by the sponsor (see: I - Introduction and Background Information).
Case 03773: This 54 y/o/f patient needed digital disimpaction as consequence of "worsening of constipation" due to alosetron administration.
REASON FOR REQUEST: If this patient had IBS with constipation, she shouldn't have been entered in the study.

Patient 3231: This 55 y/o/f developed acute gangrenous appendicitis after 11 weeks of alosetron treatment. She underwent "surgery" the same day and was discharged from the hospital 10 days later. It is unclear when alosetron treatment was discontinued.
REASON FOR REQUEST: There are no operative or pathology reports. Similar symptoms can be caused by other disease entities like, for example, ischemic bowel, particularly in this age group

## VIII – CONCLUSIONS

**Efficacy**

1) S3BB3002 is an "active" control clinical trial with a protocol satisfactory for foreign regulatory agencies at the time of its design, probably 1996-1997.
2) There is no evidence that the "active" control, trmebutine maleate, is effective in the symptomatic treatment of IBS.
3) The "Information and Background" provided by the sponsor makes no reference to the cardiovascular effects of serotonin or the role of 5 HT3 receptor sites in cardiovascular physiology. This lack of information is of concern, in view of subsequent events in which administration of alosetron was associated with ischemic bowel disease that led to surgeries, deaths and ultimately to the withdrawal of the product from the US market.
4) S3BB3002 fails to prove superiority of alosetron in doses of 1 mb bd over trimebutine 200 mg tds in the primary efficacy measure: adequate relief of IBS pain and discomfort in non-constipated patients
5) IBS-D patients seem to benefit more from alosetron treatment, whereas IBS – Aseem to benefit more from trimebutine
6) When the analyses of adquate relief of IBS pain and discomfort is made weekly, the difference in favor of alosetron reaches statistical significance in weeks 3, 4, 6, 8, 9, 10 and 12, in IBS-D patients.
7) There was also a statistically significant diference in favor of alosetron in the measurement of firming of the stools, in IBS-D patients.
8) 8) The humanistic measures (IBSQOL, SF36 [in the IBD-D group two scales, Bodily Pain and Social Functioning, reached statistical significance], resource utilization, SCL – 90) also failed to prove alosetron's superiority

**Safety.**

9) S3BB3002 was most useful in providing information about alosetron' safety profile. None of the 402 patients that received alosetron developed ischemic bowel disease or serious complications of constipation leading to perforation, surgery or death.
10) Eighty one percent of the patients on alosetron (325/402) and 87 % (332/382) of the patients on trimebutine received study drug for eight or more weeks
11) The difference in the proportion of patients experiencing AEs between treatment and control groups was not significantly different.
12) Constipation was the AE that was significantly more frequently reported in the alosetron group (20 %, 82/402) than in the trimebutine group (7 %, 25/382). While experiencing "constipation" most of the subjects had at least one bowel movement a day.

13) From the data obtained from S3BB3002, alosetron seem to be fairly well tolerated, with a safety profile similar to trimebutine maleate, with the exemption of a more marked tendency to produce constipation, as defined in this protocol.

14) From the data obtained from S3BB3002, alosetron seem to be fairly well tolerated, with a safety profile similar to trimebutine maleate, with the exemption of a more marked tendency to produce constipation, as defined in this protocol.

## IX – RECOMMENDATIONS FOR REGULATORY ACTION

1) The observations made in this medical review will be pooled with the observations made in the other reviews of this sNDA and a final integrated report will be issued.
2) The CRFs and original medical records of some selected patients will be requested from the sponsor for individual review ( see VIII – C -- Safety Results, and 23 patients of investigator 52378).

XXXXX

## 3) CLINICAL REVIEW OF S3B30006: A ONE YEAR RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ALOSETRON (GR68755) 1 MG BID IN FEMALE SUBJECTS WITH IRRITABLE BOWEL SYNDROME.

**Summary of Patients with Ischemic Colitis**
**Occurring in Association with Alosetron Usage in Clinical Studies**

| No | Study No S3B | Patient No | Age | Time to Onset (days) | Hospitalization | Surgical Procedure | Transfusion | Outcome |
|---|---|---|---|---|---|---|---|---|
| Total Patients in Study # S3B3006 patients = | | | ≈ | 0 | Lotronex-treated patients = | | Placebo-treated | |

**Summary of Patients with Serious Complications of Severe Constipation**
**Occurring in Association with Alosetron Usage in Clinical Studies**

| No | Study No S3B | Patient No | Age | Time to Onset (days) | Hospitalization | Surgical Procedure | Transfusion | Outcome |
|---|---|---|---|---|---|---|---|---|
| Total Patients in Study # S3B3006 patients = | | = | 0 | Lotronex-treated patients = | | Placebo-treated | | |

**Summary of Patients with Mesenteric Vasculopathy**
**Occurring in Association with Alosetron Usage in Clinical Studies**

| No | Study No S3B | Patient No | Age | Time to Onset (days) | Hospitalization | Surgical Procedure | Transfusion | Outcome |
|---|---|---|---|---|---|---|---|---|
| Total Patients in Study # S3B3006 patients = | | = | 0 | Lotronex-treated patients = | | Placebo-treated | | |

**Summary of Patients with Miscellaneous SAEs***
**Occurring in Association with Alosetron Usage in Clinical Studies**

| No | Study No S3B | Patient No | Age | Time to Onset (days) | Hospitalization | Surgical Procedure | Transfusion | Outcome |
|---|---|---|---|---|---|---|---|---|
| 1 | 3006 | 19420 | 50 | 33 | YES-EVAL | NO-PAROTITIS DIARRHEA | 0 | UNKN |
| 2 | 3006 | 19443 | 40 | 150 | YES-RENAL COLIC | LITHOTRIPSY | 0 | UNEV. |
| 3 | 3006 | 20085 | 44 | 35 | FALL | CERV DISKECTOMY (3 MO LATER) | UNK | UNK |
| 4 | 3006 | 23342 | 24 | 270 | MVA | 0 | UNK | UNK |
| 5 | 3006 | 20656 | 51 | 210 | YES-CHOLELITHIASIS | ELECTIVE CHOLECYSTECTOMY | UNK | UNK |
| 6 | 3006 | 23245 | 49 | 150 | YES-METRORRHAGIA | HYSTERECTOMY | UNK | UNEV. |
| 7 | 3006 | 23331 | 53 | 240 | YES-SEIZ.-LOSS OF CONSCIOUSNESS | NECROTIZING FASCIITIS R NECK CHEST WALL-EXPL/DEBRIDMENT | UNK | UNK |
| 8 | 3006 | 23584 | 34 | 4 | YES-DISABLING R ABD WALL NUMBNESS | 0 | UNK | UNEV. |
| 9 | 3006 | 23588 | 24 | 77 | <24 HR-ABD PAIN | 0 | UNK | UNEV |
| 10 | 3006 | 20097 | 55 | 1 | YES-TIA | 0 | UNK | UNK |
| 11 | 3006 | 23649 | 54 | 270 | YES-R HEMIPARESIS | 0 | UNK | PERMANENT SEQ. |
| 12 | 3006 | 23831 | 22 | 14 | YES-ABD PAIN VOM DIARRHEA | 0 | UNK | UNK |
| 13 | 3006 | 20261 | 63 | 330 | YES-CHEST PAIN | CARDIAC CATH | UNK | UNK |
| 14 | 3006 | 19843 | 44 | 84 | YES-CHEST PAIN TACHYC. | 0 | UNK | UNK |
| 15 | 3006 | 19469 | 50 | 210 | YES-ANGINA PECT NAUSEA | CARDIAC CATH | UNK | UNK |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 16 | 3006 | 19572 | 31 | 49 | YES-CHEST PAIN-↑↑HT | CARDIAC CATH RENAL ARTERIOGRAM | UNK | UNK |
| 17 | 3006 | 20235 | 38 | 270 | YES-CHEST PAIN CYANOSIS | 0 | UNK | UNK |
| 18 | 3006 | 19648 | 35 | 83 | YES-ASTHMA | 0 | UNK | UNK |
| Total Patients in Study # S3B3006 patients = | | | = | 18 | Lotronex-treated patients = | | Placebo-treated | |

* Excludes patients included in the three prior categories i.e., ischemic colitis, serious complications of severe constipation, and vasculopathies.

**Summary of Patients with Rectal Bleeding, Bloody Stools and Diarrhea with Abdominal/GI Pain*Occurring in Association with Alosetron Usage in Clinical Studies**

| No | Study No S3B | Patient No | Age | Time to Onset (days) | Concomitant Medications | Adverse Event | | Outcome |
|---|---|---|---|---|---|---|---|---|
| Total Patients in Study #S3B3006 patients = | | | = | 0 | Lotronex-treated patients = | | Placebo-treated | |

* Excludes patients included in the three prior categories i.e., ischemic colitis, serious complications of severe constipation, and vasculopathies.

This was a randomized, double-blind, placebo-controlled, multicenter study in non-constipated female subjects with IBS in which subjects who satisfied the entry criteria wererandomized to receive either alosetron 1mg twice daily or placebo twice daily for 48 weeks.

The primary objectives of this study were as follows:

Compare the two treatment groups with respect to adequate relief of IBS pain and discomfort.

Compare the tolerability of the two treatments with respect to the incidence of adverse events (AEs)and abnormalities in laboratory tests.

A total of 714 subjects were randomized; 49% (351/714) were randomized to alosetron 1mg BID and 51% (363/714) were randomized to placebo. Forty percent (40%, 283/714) of subjects withdrew prematurely from the study; 60% (219/351) of subjects in the alosetron group and 60% (212/363) of subjects in the placebo group completed the study.

The primary measure of efficacy in this study compared the two treatment groups for adequate relief of IBS pain and discomfort. Secondary efficacy parameters included lower GI symptoms (sense of urgency, stool consistency, stool frequency, and bloating), pain and discomfort-free days, and the impact of rescue medications on efficacy. Health outcomes endpoints evaluated the two treatment groups with respect to changes in health-related quality of life (QOL) and productivity. Genetics measures included evaluation of genotypic variations associated with clinical response, adverse events, IBS symptoms, and the absorption, metabolism, distribution, and excretion of alosetron. Safety was evaluated through adverse event reporting and evaluation of shifts in laboratory values.

**Summary and Conclusions**

- A. had a favourable safety profile during this study. No cases of AAIscBD or complications (SAEs) of constipation were reported
- The data from Protocol S3B30006 is confirmatory of previous observations that A. produces adequate relief of pain and discomfort in patients with IBS-D.
- The benefit was sustained over one year of treatment, without evidence of tachyphylaxis.
- There is at least preliminary evidence that unlike loperamide, A. relieves diarrhea and pain in females with IBS-D.

## I – INTRODUCTION AND BACKGROUND INFORMATION

This report consists of two parts: the first one, that immediately precedes this writing, reviews protocol S3BB3002, a multinational study comparing A. 1mg bd with trimebutine maleate (and anti-spasmodic and mild visceral analgesic not available in the USA) 200 mg tds for 12 weeks, in the treatment of female patients with IBS. The methodology used in that study is the same as that used in protocol S3B30006, a one year study on the same group of patients, comparing A. at the same doses, with placebo.

The reader is thus referred to that review for definition of objectives, endpoints, stratification, inclusion and exclusion criteria and safety measurements. Protocol S3B30006 has some new variables in its methodology that will be described in this text. Thus, the core of the second part of this review will focus on the efficacy and safety results of S3B30006.

## II – METHODOLOGY – VARIABLES UNIQUE TO PROTOCOL S3B30006

### A – Optional Genotyping During the Clinical Study

Per protocol Amendment 02 and 05, blood samples were collected following separate informed consent being obtained from randomized subjects to determine variants of candidate genes associated with clinical response, tolerability, or adverse events during treatment with alosetron, and to determine variants of candidate genes associated with IBS severity in identified samples. Furthermore, the variants of any gene (which may or may not be associated with alosetron, IBS) may be studied in non-identified samples (i.e., by replacing the subject number with a new unique identifier, whereby it is not possible to trace the information to the clinical trial subject).

Refusal to participate did not indicate withdrawal from the main clinical study or involve any penalty or loss of benefits to which the subject was otherwise entitled. No administration of study drug beyond that detailed in the original clinical protocol was associated with this genotyping procedure.

**1) Blood Sampling**

One venous blood sample was collected into a tube containing liquid EDTA from subjects who consented to the genotyping substudy. Tubes were identified by protocol number, investigator number, and subject number.

The blood sample for genotyping was in addition to any blood samples that were taken for the main clinical study. This blood sample was taken on a single occasion, after the subject had fulfilled all the entry criteria and was randomized for the main clinical study. It was recommended that the blood sample be taken at the first available opportunity, but may have been taken at any time during the clinical phase.

**2) Sample Security**

All identified blood or DNA samples were stored under secure conditions with restricted access. Identified samples were sent to [redacted] aboratories, stored, and sent to DNA extraction laboratories [redacted] working with Glaxo Wellcome specifically on this project. The samples were then sent to GW (Glaxo Wellcome, now GSK) for genotyping analysis. No other laboratory was involved in the handling of the genotyping samples.

**3) Genotype Analysis**

Nineteen polymorphic sites within six candidate genes have been identified as being of interest for this study, as identified below.

| Genetic markers for S3B30006 | | | |
|---|---|---|---|
| Candidate Gene | Impact on: | Polymorphic | Number of | Possible |
| Marker | | Site | Alleles | Genotypes |
| | | Del/Ins | 2 | (1,1), (1,2), (2,2) |
| | | VNTR | 3 | (9,10), (9,12), |

| | | | | |
|---|---|---|---|---|
| | | | | (10,10), (10,12), (12,12) |
| | | T623C | 2 | (1,1), (1,2), (2,2) |
| 5HT transporter | Mode of action | G769T | 2 | (1,1), (1,2), (2,2) |
| | | A2631C | 2 | (1,1), (1,2), (2,2) |
| | | C867T | 2 | (1,1), (1,2), (2,2) |
| | | G160A | 2 | (1,1), (1,2), (2,2) |
| | | G674A | 2 | (1,1), (1,2), (2,2) |
| | | T3287C | 2 | (1,1), (1,2), (2,2) |
| | | A1596G | 2 | (1,1), (1,2), (2,2) |
| 5HT3R | Mode of action | C795A | 2 | (1,1), (1,2), (2,2) |
| | | C178T | 2 | (1,1), (1,2), (2,2) |
| CYP1A2 | Drug metabolism | T763C | 2 | (1,1), (1,2), (2,2) |
| | | C430T | 2 | (1,1), (1,2), (2,2) |
| CYP2C9 | Drug metabolism | | | |
| | | A1075C | 2 | (1,1), (1,2), (2,2) |
| CYP3A4-5 | Drug metabolism | A816G | 2 | (1,1), (1,2), (2,2) |
| | | T471C | 2 | (1,1), (1,2), (2,2) |
| UGT1A4 | Drug metabolism | T142G | 2 | (1,1), (1,2), (2,2) |
| | | C70A | 2 | (1,1), (1,2), (2,2) |

**4) Identified DNA samples:**

- Samples were only tested for variants of genes thought to be related to the pharmacological action and metabolism of alosetron and to IBS.
- Samples were not used for research into any other disease area.
- The link between the DNA sample and the clinical trial subject number will be removed, or the DNA sample destroyed, within 6 months of the issue of this clinical study report, but in no case more than 10 years after the sample was collected.

**5) Non-identified DNA samples:**

Once rendered non-identified, samples may be analyzed for variants in any gene irrespective of whether an involvement with IBS or response to alosetron is known, and may be stored indefinitely.

**6) Genotyping Populations for Analysis**

The following populations were considered for genotyping analysis:

- **Genotyping Population:** All randomized subjects who received at least one dose of study drug, consented to genetic sampling, and actually provided an analyzable genetic sample for at least one of the genetic markers of interest constitute the Genotyping Population.
- **Diarrhea-Predominant Genotyping Population**: All subjects in the Genotyping Population who were classified by the investigator (based on the subjects' IBS disease history) as having diarrhea-predominant IBS constitute the Diarrhea-Predominant Genotyping Population.

**Analysis of Clinical Outcomes**

The proportions of subjects consenting to both the identified and non-identified genotyping, along with the proportions of subjects who withdrew consent, were

summarized for all randomized subjects.
The proportions of subjects in the Genotyping Population providing data for each polymorphic site were summarized.
Demographic and baseline clinical characteristics/IBS symptoms and the frequency distribution of genotypes were summarized by treatment group for the Genotyping Population.
The following were summarized by genotype at each of the nineteen polymorphic sites for the Diarrhea-Predominant Genotyping Population:

- the frequency distribution of genotypes;
- 48-Week Average Adequate Relief Rate of IBS pain and discomfort during the treatment phase, using the LOCF approach for missing data.

The following were summarized by genotype at each of the nineteen polymorphic sites for the Genotyping Population:

- demographic and baseline clinical characteristics/IBS symptoms;
- proportion of subjects reporting constipation.

**B – Occurrence of bloody diarrhea or rectal bleeding with abdominal pain**
If a subject encountered either bloody diarrhea, or rectal bleeding with abdominal pain, the investigator was to immediately notify the GW Medical Monitor by phone. Depending on the clinical presentation of the subject, follow-up evaluations and information were recorded in the source documents and CRF and could include (as per protocol amendment 06):

- Stool cultures for E. coli 0157:H7, salmonella, shigella, yersinia, campylobacter, ova and parasites and Clostridium difficile toxin were to be performed no later than 7 days after the onset of the event.
- Endoscopic evaluation (flexible sigmoidoscopy or colonoscopy); biopsies may have been obtained for E. coli immunostaining.
- Thrombosis panel (including measurements of protein C, protein S, antithrombin III, Factor VIII, and homocysteine) performed by the central laboratory.
- The following may have been recorded:
    - any history of myocardial infarction, ischemic heart disease, or congestiveheart failure.
    - any history of colonic stricture
    - any history of thrombosis
    - current evidence of amphetamine or cocaine use.

**Subject Accountability (ITT Population)**

| | Placebo (N=363) | Alosetron 1mg BID (N=351) | Total (N=714) |
|---|---|---|---|
| Completed | 219 (60%) | 212 (60%) | 431 (60%) |
| Prematurely discontinued from the study - all reasons | 144 (40%) | 139 (40%) | 283 (40%) |
| Reason for premature discontinuation: | | | |
| Adverse event | 36 (10%) | 67 (19%) | 103 (14%) |
| Consent withdrawn | 24 (7%) | 29 (8%) | 53 (7%) |
| Lost to Follow-Up | 15 (4%) | 10 (3%) | 25 (4%) |
| Protocol violation | 4 (1%) | 5 (1%) | 9 (1%) |
| Lack of efficacy | 58 (16%) | 21 (6%) | 79 (11%) |
| Other | 7 (2%) | 7 (2%) | 14 (2%) |
| Pregnancy | 5 (1%) | 0 | 5 (<1%) |
| Death | 1 (<1%) | 0 | 1 (<1%) |

Source: Table 6.1

alosetron treatment group, the most common reason for premature discontinuation was due to an AE, which occurred at a higher percentage than in the placebo group (19% vs. 10%). In the placebo treatment group, the most common reason for premature discontinuation was "Lack of efficacy" which occurred at a higher percentage than in the alosetron group (16% vs. 6%). For the remaining subjects who discontinued, similar proportions of subjects between groups discontinued because
"Consent [was] Withdrawn", they were "Lost to Follow-Up", a "Protocol Violation" had occurred, or "Other", reasons. No deaths or pregnancies were reported among subjects who received alosetron. One death and five pregnancies were reported among placebo-treated subjects.
Because the ITT population is comprised mainly (~80%) of subjects who had diarrhea-predominant IBS (i.e., the DITT population, subject accountability was similar in these two populations, and approximately equal number of subjects in each treatment group in the DITT population (62%-64%) completed the study. In contrast, ~20% of subjects in the ITT population had an alternating bowel pattern (i.e., the AITT population), and the percentage of subjects who completed the study in both treatment groups was lower (46%-52%) compared with that in the DITT group.
A total of 1323 subjects were screened for participation in this study, and 609 subjects were not randomized. Among those subjects who were not randomized, the main reasons were that entry criteria were not met (76% for all reasons combined),
"Consent withdrawn", (10%), "Protocol violation", (5%), "Lost to Follow-Up",(1%), "Eligibility not checked" (1%), Adverse event (<1%), or "Other" (6%) reasons.
Most subjects remained in the study for the entire duration of the study. Among subjects who prematurely withdrew during the 48-Week
Treatment Phase, more than half of all subjects in the ITT population (57%, 155/272) and in the DITT population (55%, 109/200) had done so by Month 2 . On a treatment visit month basis, the percentage of subjects who prematurely withdrew was very similar in both treatment groups within each of these populations.

The blind was broken for one subject (Subject 19350, alosetron treatment group) who intentionally unblinded the label on her medication box approximately one week after discontinuing her treatment and approximately 5-6 weeks after discontinuing her symptom assessments in the telephone diary system. This subject took her medication for approximately 19 weeks, reported no adequate relief of IBS pain and discomfort during the trial, withdrew her consent and prematurely discontinued.

**IV – Summary of Efficacy Results**

- Alosetron 1mg BID provided significantly greater adequate relief of IBS pain and discomfort (~ 8%, p=0.010) and satisfactory control of urgency (p=o.oo1 without laxative use) than placebo in subjects with diarrhea-predominant IBS. These improvements commenced by Week 1 of treatment and persisted throughout the 48-week Treatment Phase with no evidence of tachyphylaxis.
- From exploratory analyses in subjects with alternating constipation/diarrhea IBS, alosetron 1mg BID appeared to produce no benefit compared to placebo.

- There was no evidence of differential treatment effects among the subgroups examined (age, hormone use, child-bearing ability, menstruation status, race or baseline pain severity).
- In weeks during which alosetron-treated subjects reported constipation, the adequate relief rate was lower for both the diarrhea-predominant and alternating IBS populations. However, constipation typically occurred during the first month of treatment, and had a short duration.
- Laxative and antidiarrheal rescue use had no positive or synergistic effects on either adequate relief of IBS pain and discomfort or satisfactory control of urgency; however, not unexpectedly, rescue medication use did have an impact on the satisfactory control rates for both stool consistency and stool frequency in that satisfactory control rates for alosetron-treated subjects were significantly higher than placebo-treated subjects only in weeks without laxative or antidiarrheal use.
- The 48-week average adequate relief of IBS pain and discomfort was strongly and significantly positively correlated with the percentage of pain-free days and with individual IBS symptoms including satisfactory control of urgency, satisfactory control of stool consistency, satisfactory control of stool frequency, and bloating.
- There was a significant difference between treatment groups for the IBSQOL emotional scale (p=0.022). Treatment differences for the remaining eight scales were not significantly different.
- In subjects with diarrhea-predominant IBS, there were no statistically significant between treatment differences at Month 12 on the SF-36.
- The 48-Week Average Adequate Relief Rate was significantly correlated with changes from baseline for all SF-36 scales in subjects with diarrhea predominant IBS. In subjects with alternating IBS, there were significant correlations on all scales with the exception of the mental health scale.
- Alosetron had no effect on the average number of work hours missed among subjects with either diarrhea-predominant or alternating IBS.
- Alosetron had no effect on average productivity at Month 12 among subjects with either diarrhea-predominant or alternating IBS.
- There were no negative changes from baseline in the alosetron group in either the diarrhea-predominant or alternating population, and in no instance was there a statistically significant improvement in the placebo group relative to the alosetron group.

**V – Summary of Safety Results**

- The overall Safety Population is comprised of 710 subjects (362 received placebo, 348 received 1 mg alosetron BID) who were randomized and consumed at least one dose of study medication and is four subject less than the ITT Population (N=714).
- Of the 348 patients exposed to alosetron, 202 were treated for one year, and 241 for between six months and one year.
- Treatment-emergent AEs were reported in a significantly higher proportion of subjects who received alosetron (85%) compared with subjects who received placebo (72%), p=0.001. AEs involving the gastrointestinal system, specifically constipation, account for all of this difference in the incidence of AEs.

- The only adverse event occurring notably more frequently in alosetron-treated subjects was constipation, which was reported by 23% (79/348) of subjects who received alosetron compared with 5% of (17/362) subjects who received placebo. Laxatives were allowed for constipation and no complications from constipation occurred.
- Among alosetron-treated subjects developing constipation, most experienced a single episode during the first month of treatment, of mild or moderate severity, that lasted for about one week.
- There were no apparent notable differences in the overall incidence of AEs or the incidence of constipation on the basis of age, race, hormone use.
- Laxative use had a minimal effect on the proportion of alosetron-treated subjects who continued the study, temporarily interrupted alosetron administration, or permanently stopped alosetron administration.
- No treatment emergent deaths or pregnancies were reported among subjects who received alosetron.
- The overall incidence of SAEs was similar among subjects who received alosetron or placebo. Neither ischemic colitis nor constipation or its sequelae were reported as an SAE in either treatment group.
- The incidence of withdrawals due to AEs was 10% (36/362) in the placebo group and 19% (67/348) in the alosetron group. Accounting for this difference was a higher incidence of withdrawals due to constipation in the alosetron group (11%). About half of the 39 cases of constipation that withdrew from the study were severe. The other half were mild or moderate. In all cases the constipation resolved. and in no case was constipation judged by the investigator to be an SAE.
- Hematologic and chemistry laboratory toxicity grading assessment revealed no meaningful differences between the placebo and alosetron treatment groups. Detailed assessment of ALT elevations in alosetron-treated subjects suggest that alosetron is not associated with hepatotoxicity. Three alosetron-treated subjects exhibited ALT elevations >3 fold ULN: two exhibited underlying liver disease (biopsy-proven primary biliary cirrhosis and hepatitis C) and one exhibited near normalization of the ALT despite continued alosetron administration.
- The genetic studies demonstrated no association between the selected variants of candidate genes and either clinical response (48 week average adequate relief) or tolerability (constipation). This data must be interpreted with caution since it is only exploratory in nature.

## VI – DISCUSSION

### A – *Methodology*

The sponsor introduces two new variables of great clinical significance, which are inter-related: a genetic study of the population and a comprehensive work up of patients with rectal bleeding. These two elements were highlighted by this reviewer in his previous review of Alosetron Associated Ischemic Bowel Disease (AAIscBD), dated 13 December, 2000. It seems that the scientists and consultants of GSK sense, as we did here at the Agency, that AAIscBD develops in a subset of patients that are genetically different, and as a consequence of that, they metabolize A. along different pathways, and

produce vasoactive metabolites, or they belong to this ~ 8% of the population that has a hypercoagulable state (thus the sophisticated thrombosis panel) and A. triggers a messenger in the splachnic bed that leads to AAIscBD.
The genetic studies were inconclusive, but there were no cases of AAIscBD or severe complications of constipation!

**B – Efficacy Results**
This study, like previous ones is confirmatory that A. works better in IBS-D patients than in IBS-A patients.
Of great interest is the fact that the effect was sustained throughout the 48 weeks of the study. There was no tachyphylaxis.
The sponsor also claims that the adequate relief rates were significantly higher among subjects who received A. compared with subjects who received placebo, regardless of antidiarrheal medication used, reinforcing the notion that A. effectively treats the pain and discomfort associated with IBS-D, whereas loperamide does not (ITT population, p=0.001) The data seems to support this important claim, although it must be noted that the adequate relief rates were lower in both treatment groups (ITT and IBS-D ITT) for subjects who used antidiarrheal medication.

**C-Safety Results**
The safety data were assessed from 348 subjects.. This is not an insignificant number of patients treated long-term. Constipation did not get worse with extended exposure. There were no cases of AAIscBD and no subject exhibited an SAE of constipation
Although this information has to be interpreted with great caution, and one should wait for the rest of the data on this sNDA, the present data shows a favorable safety profile of this drug over a one year treatment period.

## VI – CONCLUSIONS

- The data from Protocol S3B30006 is confirmatory of previous observations that A. produces adequate relief of pain and discomfort in patients with IBS-D.
- The benefit was sustained over one year of treatment, without evidence of tachyphylaxis.
- There is at least preliminary evidence that unlike loperamide, A. relieves diarrhea and pain in females with IBS-D.
- A. had a favourable safety profile during this study. No cases of AAIscBD or complications (SAEs) of constipation were reported.

## VII – RECOMMENDATIONS FOR REGULATORY ACTION

1) The observations made in this medical review will be pooled with the observations made in the other reviews of this sNDA and a final integrated report will be issued.
2) The CRFs and original medical records of some patients may be reviewed individually for completness.

## VIII – REFERENCES

1). Dancy CP, Backhouse S. Towards a better understanding of subjects with irritable bowel syndrome. Journal of Advanced Nursing 1993;18:1443-1450.
2). Corney RH, Stanton R. Physical symptom severity, psychological and social dysfunction in a series of outpatients with IBS. Journal of Psychosomatic Research 1990;34:483-491.
3) Ringel Y, Sperber A D and Drossman D A Irritable Bowel Syndrome. Annual Reviews Medicine 2001.52:319-338
4) Page I M The discovery of serotonin Perspectives in Biology and Medicine 1976;20(1):1-8
5) Saxena P R and Villalon C M Cardiovascular Effects of Serotonin Agonists and Antagonists J Cardiovasc Pharmacol 1990,15,7:S17-34

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PUBLIC HEALTH SERVICE

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

# MEDICAL OFFICER'S REVIEW

NDA: 21-107 supplement

Document identification: S3BB3001

Sponsor: GlaxoSmithKline

Drug name: Lotronex (alosetron hydrochloride) tablets 1 mg

Indication: Irritable bowel syndrome with diarrhea predominance

Date submitted: August 23, 2001 / December 20, 2001

Review completed: November 21, 2001 / February 8, 2002

Reviewer: Edvardas Kaminskas, M.D.

Materials reviewed:

| | |
|---|---|
| October 15, 1999 | Medical Officer's Review (Safety) |
| October 15, 1999 | Medical Officer's Review (Efficacy) |
| November 17, 1999 | Medical Team Leader's secondary review |
| November 30, 1999 | Medical Officer's Comments on Gastrointestinal Advisory Committee meeting on November 16, 1999 |
| November 30, 1999 | Medical Officer's 90-day safety update |
| January 14, 2000 | Division Director's Memorandum |
| April 6, 2000 | Medical Officer's supplemental Safety Update-2 |
| February 14, 2001 | Minutes of Type C Industry Meeting |
| July 31, 2001 | S-002 Proposed Labeling Review |
| August 29, 2001 | Review of alosetron-associated deaths reported post-marketing |
| August 23, 2001 | SNDA, Study # S3BB3001 |
| Martindale's | DrugDex drug evaluation of mebeverine |
| Tasman-Jones C | Mebeverine in patients with irritable colon syndrome: double blind study. NZ Med J 1973; 77:232-5 |
| Van Outryve M, Mayeur S, Meeus A, Rosillon D et al. | A double-blind crossover comparison study of the safety and efficacy of mebeverine with mebeverine sustained release in the treatment of irritable bowel syndrome. J Clin Ther 1995; 20:277-282 |
| Evans PP, Bak Y-T & Kellow JE | Mebeverine alters small bowel motility in irritable bowel syndrome. Aliment Pharmacol Ther 1996; 10:787-793 |
| Washington N, Ridley P, Thomas, Spiller RC et al. | Mebeverine decreases mass movements and stool frequency in lactulose-induced diarrhea. Aliment Pharmacol Ther 1998; 12:583-8 |

| | |
|---|---|
| Jones RH, Holtmann G, Rodrigo L et al. | Alosetron relieves pain and improves bowel function compared with mebeverine in female nonconstipated irritable bowel syndrome patients. Aliment Pharmacol Ther 1999; 13:1419-1427 |
| January 28, 2002 | Review of case report forms for patients with adverse events submitted by the sponsor. |

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**Executive Summary**

## I. Summary of Clinical Findings

### A. Brief Overview of the Clinical Program

Background. The results of trial S3BB3001 are submitted by the sponsor as part of a 40-study supplement to NDA 21-107. The drug is Lotronex (alosetron) with the indication being irritable bowel syndrome with diarrhea predominance in female patients. Lotronex was approved for this indication on February 9, 2000, and marketing was begun in March, 2000. The Agency and the sponsor were aware of the common occurrence of severe constipation and of the rare occurrence of ischemic colitis as undesirable side-effects of the medication. Both of these adverse events tended to resolve spontaneously. After marketing, a number of serious adverse events, including deaths due to perforation of the colon, necrosis of the small bowel, severe constipation leading to hospitalization and surgery, led to a reassessment of Lotronex and its withdrawal from the market on November 28, 2000. The sponsor describes the data in the submitted supplement as demonstrating that the drug is safe in an appropriately selected and monitored patient population.

Study design and execution. Trial S3BB3001 was conducted in a large number of centers in Europe, Australia, New Zealand, South Africa, and Israel. It was a double-blind, randomized, parallel group study in which the subjects were treated either with Lotronex 1mg BID or with mebeverine 135 mg TID for 12 weeks. After the treatment period, patients were observed over a 4-week period for recurrence of former symptoms. Mebeverine is a smooth muscle relaxant, a derivative of papaverine, used widely in Europe for irritable bowel syndrome; it is not FDA-approved.

Study population. The study subjects had to meet the Rome diagnostic criteria for irritable bowel syndrome, which had to be either of diarrhea-predominant or of alternating diarrhea-constipation type, and to be female with a restricted child-bearing potential. In addition, the study subjects were required to have had a colonoscopy or sigmoidoscopy and barium enema, to demonstrate reliable self-assessments, and to meet the criteria for abdominal pain and discomfort, and for stool consistency. The exclusion criteria were comprehensive.

Six-hundred-fifty-three patients were selected from 1,153 screened. Most (86%) of those rejected had failed to meet the screening criteria. Three-hundred-nineteen patients were assigned to treatment with Lotrenex; 304, to treatment with mebeverine. Over 70% in each treatment group had diarrhea-predominant IBS; about 25% in each group had the alternating type.

Study completion and premature withdrawals. About 20% of patients withdrew prematurely from each group. Adverse events were the most common reason for withdrawal. Constipation was the most common adverse event leading to

premature withdrawal in the alosetron group; no single type of adverse event led to premature withdrawal in the mebeverine group.

B. Efficacy

| | |
|---|---|
| Primary endpoint: "the proportion of patients with adequate relief of IBS abdominal pain / discomfort at least two weeks per month" | After the first month of treatment, the proportion of subjects reporting relief was greater in the Lotronex group than in the mebeverine group (56% vs. 43%, p=0.001 in the 2nd month; 58% vs. 48%, p=0.009 in the 3rd month). |
| Primary endpoint (supportive analysis): "the proportion of subjects reporting adequate relief of IBS pain / discomfort at each week" | Of the subjects who completed the entire 12-week course of treatment, 63% of the Lotronex group and 47% of the mebeverine group had adequate relief during at least 6 of 12 weeks (difference significant at p<0.001). |
| Secondary measure: percentages of IBS pain / discomfort-free days | The proportion of subjects in the Lotronex group with pain-free days increased from 21% to 40-45% in months 2 and 3. The proportion in the mebeverine group increased from 23% to 32-35% (differences at months 2 and 3 significant at p=0.035 and p=0.013). |
| Secondary measure: Patient's self-rating of discomfort | Patients with diarrhea-predominant IBS responded better to Lotronex than to mebeverine, but only in Month 3 (p=0.039). No difference in the responses to the two drugs in the total ITT population. |
| Secondary measure: Sense of urgency | Proportion of days with a sense of urgency decreased from 71% to 40%, 33%, and 29% after 1, 2, and 3 months in the Lotronex group, and from 73% to 50%, 47%, and 42% after 1, 2, 3 months in mebeverine group (differences significant at p<0.001). |
| Secondary measure: Lower GI functions | Firming of stools was greater in the Lotronex group than in the mebeverine group (p<0.001). Stool frequency was decreased in both groups. There was no improvement in the sense of incomplete evacuation in either group. There was no significant change in days with bloating in either group. |
| Secondary measure: SCL-90R | Neither drug affected global indices of psychological distress. |
| Secondary measure: Health outcomes | Treatment with Lotronex was associated with greater improvement in quality of life, as measured by social functioning, energy, mental health, and food scales, than treatment with mebeverine (differences significant at p=0.05). |

C. Safety issues in the Lotronex group

| | |
|---|---|
| Deaths | None |
| Ischemic colitis, bowel necrosis, | None |

| | |
|---|---|
| perforation, peritonitis | |
| Constipation requiring surgery | None |
| Hepatitis | None |
| Lotronex-related severe adverse events (10 other severe events in 8 subjects were not Lotronex-related) | 1. Pt. # 726. **Erosive gastritis**<br>2. Pt. #1702. **Colitis (sigmoiditis), diverticuli, hyponatremia, seizures**. *Reviewer: possible ischemic colitis.* |
| Possible Lotronex-related severe adverse events | 1. Pt. # 2175 had moderate rectal bleeding and diarrhea 3 days after completing the 12-week trial with Lotronex. Not resolved. No follow-up. *Reviewer: possible ischemic colitis.*<br>2. Pt. #2240 had rectal bleeding for 2 days 21 days after completing the 12-week trial with Lotronex. *Reviewer: possible ischemic colitis.*<br>3. Pt. #2315 had abdominal pain, constipation, rectal bleeding, anal soreness 6 days after starting Lotronex. No follow-up. *Reviewer: possible ischemic colitis.* |
| Lotronex-related adverse events | 276 events in 128 patients (40% of ITT population). Most common was **constipation** (79 events in 66 patients – in 21% of ITT patients); constipation occurred in 3% of mebeverine ITT population. Other adverse events occurred at similar frequencies in both treatment groups. |
| All adverse events | 620 events in 220 patients (69% of ITT population) in the Lotronex group; 529 events in 196 patients (64% of ITT population) in the mebeverine group. In the Lotronex group the most common events were constipation (87 in 71 patients), abdominal pain & discomfort (35 in 29 patients), headaches (39 in 31 patients, nausea (27 in 23 patients). In the mebeverine group the most common were headaches (52 in 44 patients), nausea (29 in 26 patients). |

The most common adverse event in the Lotronex group leading to premature withdrawal from the study was constipation (23 of the 42 patients who withdrew prematurely). In contrast, only 3 of the 30 patients, who withdrew prematurely from the mebeverine group, withdrew because of constipation.

This reviewer was not able to identify patients at higher than average risk for constipation. The age range of these patients was about the same as in the total population; *the elderly were not at higher risk.* Patients' weights varied more than three-fold, yet the *light patients were not at higher risk*, in spite of receiving the same dose as the heavy patients. Diarrhea-predominant IBS patients reported constipation as an adverse event about as frequently as alternating IBS patients (21% and 25%, respectively). It should be noted that in S3BB3002, patients with alternating type of IBS reported severe constipation more frequently than patients with diarrhea-predominant IBS.

D. Dosing - All patients in the Lotronex group received 1mg BID. All patients in the mebeverine group received 135mg TID.

E. Special Populations - 98% of study subjects where whites.

## II. Conclusions

1. The efficacy of Lotronex 1mg BID in relieving abdominal pain and discomfort in IBS patients was about the same as in the pivotal trials S3BA3001 and S3BA3002 placebo-controlled trials. The efficacy of mebeverine in this trial is uncertain in the absence of a placebo control. Patients with alternating pattern of IBS responded as well as patients with diarrhea-predominant IBS; this finding differs from the results in the pivotal trials, in which only patients with diarrhea-predominant IBS responded.

2. The main adverse event was constipation, experienced by 21% of subjects treated with Lotronex (previous 12-week trials documented an incidence of 20.0% - 29.8%). Constipation was the main cause of premature withdrawals of patients from the trial, as in previous trials.

3. There were no deaths, hospitalizations, or surgical procedures that could be related to the use of Lotronex. There were no documented cases of ischemic colitis. There were four patients with rectal bleeding who may have had ischemic colitis. Lotronex may have possibly aggravated some adverse events, which could be more probably related to other drugs.

4. Lotronex appears to be a more effective agent for the control of symptoms of IBS than mebeverine, but also has a worse safety profile.

**Clinical Review**

**I. Introduction and Background**

Alosetron (Lotronox) is a serotonin receptor-type 3 antagonist related to ondansetron, granisetron, and dolasetron that are approved for the treatment or prevention of nausea and vomiting caused by cancer chemotherapy or by surgical anesthesia and operative procedures. Alosetron uniquely has been studied by the sponsor for the treatment of the symptoms of irritable bowel syndrome (IBS).

The sponsor submitted NDA 20-107 for Lotronex (alosetron) for the indication of treatment of irritable bowel syndrome on June 29, 1999. The NDA was granted priority status because alosetron appeared to represent a significant advance in the treatment of IBS. The application was supported by two principal clinical efficacy trials in 1273 women with non-constipated forms of IBS comparing alosetron 1 mg b.i.d. with placebo for 12 weeks. The Table below from p. 57 of Medical Officer's Review (Safety) of the initial NDA shows the numbers of patients in the two principal clinical efficacy trials, in the two dose-ranging studies, and in the treatment arms of each study.

**12-Week, Placebo-Controlled Alosetron Studies (Primary Safety Database)**

| Study started-ended | Sites | P M/F | A 0.1 M/F | A 0.5 M/F | A 1.0 M/F | A 2.0 M/F | A 4.0 M/F | A 8.0 M/F | *Total M/F* | Duration |
|---|---|---|---|---|---|---|---|---|---|---|
| S3B-P12 Jul'93-Sep'94 | 43 Eur | 33/84 | 38/77 | 31/85 | | 25/89 | | | 127/ 335 | 12 weeks |
| S3BA2001 Oct'95-Dec'96 | 71 U.S. | 21/59 | | | 18/54 | 23/51 | 21/54 | 28/40 | 111/ 258 | 12 weeks |
| S3BA3001 Sep'97-Dec'98 | 112 U.S. | 0/317 | | | 0/309 | | | | 0/626 | 12 weeks |
| S3BA3002 Sep'97-Oct'98 | 120 U.S. | 0/323 | | | 0/324 | | | | 0/647 | 12 weeks |

*Note: Doses b.i.d.: P, placebo, A 0.1 to 8.0, alosetron 0.1 to 8.0 mg M/F, males, females.*
*S3BA3003*, partial report as of 26 Feb'99 on 728 of 859 patients entered by 225 Sep'98.*

The designs of the two pivotal trials S3BA3001 and S3BA3002 were identical. These trials were 18-week, multicenter, randomized, double-blind, parallel, placebo-controlled studies of alosetron in female patients with irritable bowel syndrome. The first 2 weeks of each trial consisted of the Screening Phase, which was followed by a 12-week Treatment Phase, which was followed by a 4-week Post-Treatment follow-up period.

To be included in the Screening Phase patients were required to fulfill the *Rome Criteria for the diagnosis of IBS*, defined as follows:

> At least 6 months of recurrent symptoms:
>
> a) Abdominal pain/discomfort which is i) relieved by defecation, ii) and/or associated with a change in stool frequency, iii) and/or associated with a change in stool consistency
>
> AND
>
> b) two or more of the following, at least 2 days per week: i) altered stool frequency (> 3 bowel movements per day or < 3 bowel movements per week), ii) altered stool form (lumpy/hard or loose/watery), iii) altered stool passage (straining, urgency, or feeling of incomplete evacuation), iv) passage of mucus, v) bloating or feeling of abdominal distension

During the Screening Phase patients had to have
(1) documented presence of abdominal pain/discomfort with an overall severity score between 1.0 (mild) and 3.3 (3 = intense),
(2) documented stool consistency score of 2.5 or higher (2 = hard, 3 = formed),
(3) recorded at least 12 days of daily self-assessments.

Patients met the inclusion criteria if
(1) female
(2) at least 18 years old
(3) ambulatory outpatients
(4) had a lower endoscopic examination within the last 5 years
(5) did not meet any of the large number of exclusion criteria (described in the Safety and Efficacy reviews)

A. Efficacy assessment

The primary efficacy measure or endpoint was ***adequate relief of IBS pain/ discomfort.*** The assessment was carried out by telephone with the following question: "In the last 7 days, have you had adequate relief of your Irritable Bowel Syndrome pain or discomfort?" The acceptable patient response was "yes/no" using a touch-tone data entry system. The primary efficacy parameter was the proportion of subjects with adequate relief of abdominal pain on at least 2 weeks per month. A ***"treatment responder"*** is a patient who reports adequate relief for at least ***6 of the 12 weeks*** during the treatment phase. (The sponsor changed the primary efficacy endpoint **post-hoc** in the dose-ranging studies from "the proportion and number of pain-free days" to "the adequate relief of abdominal pain/discomfort" because of "subject perception in determining pain relief" [NDA Efficacy Review, p. 44]).

Secondary efficacy measures or endpoints were:

- proportion of pain/discomfort-free days. A "monthly responder" was defined by at least 50% pain/discomfort-free days with at least 14 daily pain assessments per month. Patients with fewer than 14 daily pain assessments, or with <50% proportion of pain-free days were considered "non-responders."
- lower GI functions: stool consistency, stool frequency, sense of urgency, bloating, and sense of incomplete evacuation.
- psychological distress evaluation at randomization and at the final visit using the Symptom Checklist-90-Revised.
- quality of life measures, including the Irritable Bowel Syndrome Quality of Life questionnaire, a quality of life questionnaire, and the SF-36 health-related quality of life questionnaire.

The following two tables show the primary efficacy endpoint data for the two pivotal trials (from pp. 18 and 33 of the NDA efficacy review, from the sponsor's Table T-7.1, vol. 167).

**Primary Efficacy Results. Trial A3001**

**Number of Months with Adequate Relief of Abdominal Pain/Discomfort** [Patients Discontinued Prematurely With Missing Data Were Included With The Last Observation Carried Forward (LOCF)].

| Number of Months Patient has Adequate Relief (Responder) | Placebo (N=317) | Alosetron (N=309) | Statistical Significance |
|---|---|---|---|
| 0 | 135 (43%) | 100 (32%) | |
| 1 | 53 (17%) | 36 (12%) | |
| 2 | 47 (15%) | 46 (15%) | |
| *3* | *82 (26%)* | *127 (41%)* | *<0.001 (A>P)* |

**Primary Efficacy Results. Trial A3002**

**Number of Months with Adequate relief of Abdominal Pain/Discomfort** [Patients Discontinued Prematurely With Missing Data Were Included With LOCF]

| **Number of Months Patient has Adequate Relief (Responder)** | **Placebo** (N=323) | **Alosetron** (N=324) | Statistical Significance |
|---|---|---|---|
| 0 | 129 (40%) | 108 (33%) | |
| 1 | 42 (13%) | 37 (11%) | |
| 2 | 58 (18%) | 46 (14%) | |
| *3* | *94 (29%)* | *133 (41%)* | *0.012* |

The above tables show that **after three months** a statistically significant higher proportion of IBS women treated with alosetron had adequate relief of abdominal discomfort (41% in both studies) than IBS women treated with placebo (26% and 29%). Alosetron was no better than placebo during shorter periods of treatment of one or two months.

The above data include all randomized-treated patients (Intention-To-Treat). The sponsor's submitted table of efficacy (shown below) excluded 169 women with self-classified "alternating constipation-diarrhea" IBS and 11 women with "constipation-predominant" IBS in S3BA3001, and 180 with "alternating" and 9 with "constipation-predominant" IBS in S3BA3002. In this **subset of non-constipation-predominant IBS**, alosetron was efficacious during the entire 3-month treatment period, as shown below (from NDA safety review, p. 56). Patients with "alternating constipation/diarrhea" pattern of IBS had some response to alosetron, but the difference from placebo-treated controls was not significant (35% vs. 26%).

**Treatment Randomization of Women Participating in Pivotal Clinical Trials**

| | placebo | alosetron | total |
|---|---|---|---|
| Study S3BA3001 | 317 | 309 | 626 |
| Study S3BA3002 | 323 | 324 | 647 |
| both | 640 | 633 | 1273 |

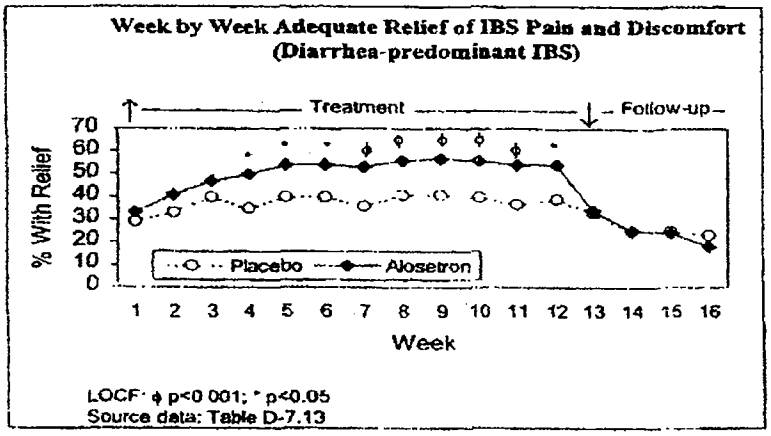
The results summarized from these two trials (Volume 208, page 25) were as follows:

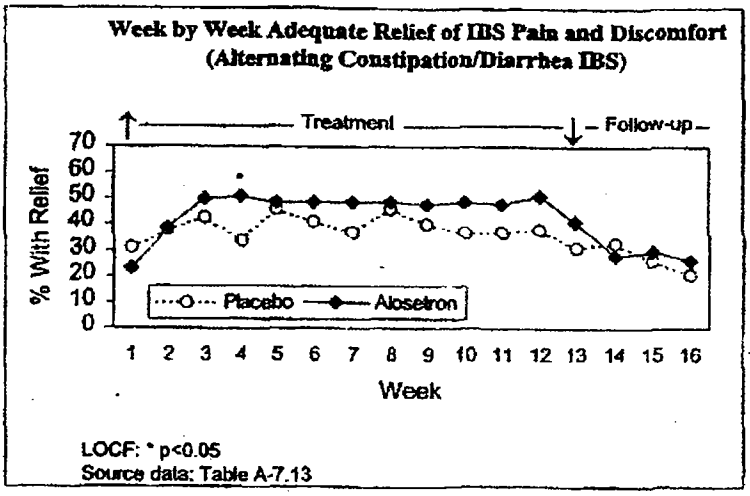
**Monthly Responders for Adequate Relief of IBS Discomfort in Women with Diarrhea-Predominant IBS Patterns in Pivotal Clinical Trials**

| Study S3BA3001 | MONTH 1 | MONTH 2 | MONTH 3 |
|---|---|---|---|
| alosetron | 112/224 (50%) | 129/224 (58%) | 135/224 (60%) |
| placebo | 87/222 (39%) | 96/222 (43%) | 92/222 (41%) |
| *p-value* | 0.022 | 0.003 | <0.001 |
| Study S3BA3002 | MONTH 1 | MONTH 2 | MONTH 3 |
| alosetron | 139/237 (59%) | 140/237 (59%) | 145/237 (61%) |
| placebo | 89/221 (40%) | 104/221 (47%) | 100/221 (45%) |
| *p-value* | <0.001 | 0.013 | <0.001 |

Week-by-week analysis of adequacy of IBS pain relief in alosetron-treated patients, shown in the Figures below, demonstrate
(1) significant differences from placebo-treated patients from week 4 to week 12 in diarrhea-predominant IBS
(2) non-significant differences from placebo-treated patients in patients with alternating constipation/diarrhea IBS
(3) disappearance of therapeutic effect upon discontinuation of the drug after 12 weeks.

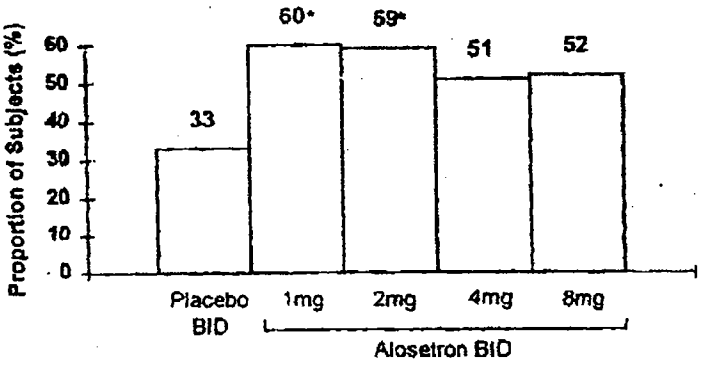
The figures show the results from S3BA3001; the results from S3BA3002 are similar, except that patients with alternating constipation/diarrhea IBS showed **no response** to alosetron.




The dose-ranging SB3A2001 study demonstrated a therapeutic response to 1mg or 2 mg alosetron in female IBS patients (figure below). The response occurred during the first month of treatment and persisted during the 3-month treatment period (table below).

**Proportion of IBS Pain/Discomfort Responders by Group Among Females (Adequate Relief for 6 of 12 Weeks Among Completers)**



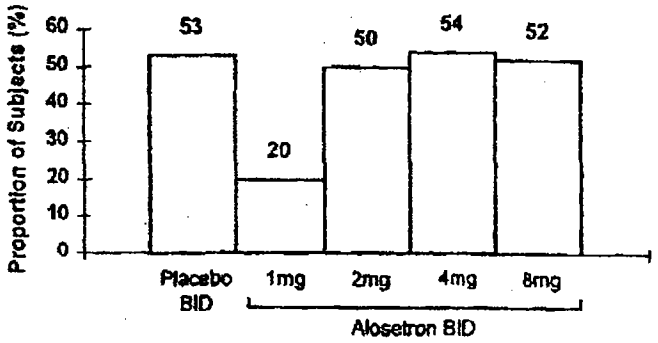

* Statistically different from placebo BID ($p<0.05$)

**Female Subjects: Monthly Responders for Adequate Relief of IBS Pain/Discomfort**

| | Month 1 | Month 2 | Month 3 |
|---|---|---|---|
| alosetron 1mg BID | 28/53, 53% | 33/53, 62% | 32/53, 60% |
| placebo BID | 19/59, 32% | 25/59, 42% | 21/59, 36% |
| *p*-value | 0.038 | 0.050 | 0.013 |

Alosetron did not relieve pain/discomfort among **male** IBS patients (figure below) any better than placebo. (*This Reviewer's note: Male patients responded much better than female patients to placebo: 53% vs. 33%. The response to alosetron was about the same in both sexes, except to the 1mg BID dose in the males).*

**Proportion of IBS Pain/Discomfort Responders by Group Among Males (Adequate Relief for 6 of 12 Weeks Among Completers)**




The Medical Reviewer summarized the efficacy of alosetron in IBS as follows:

- alosetron showed significant efficacy over placebo in the adequate relief of abdominal pain/discomfort in IBS patients over a 3-month treatment period. Shorter treatment periods failed to reveal any differences between treatments.
- A more encompassing primary efficacy outcome is needed to capture lower bowel functions as a measure of adequate relief of IBS symptoms.
- There were no differences between alosetron and placebo in the proportion of pain-free days experienced by patients.
- The overall intensity of abdominal pain decreased from "moderate" at baseline (1.9) to "mild" (1.0) by the end of the 3-month treatment period.
- Alosetron treatment was significantly (?) superior to placebo in improving relevant IBS bowel abnormalities, such as stool consistency (from about 3.1 to 2.4), stool frequency (from 2.5 per day to 1.75) and stool urgency (reducing the number of days on which patients felt urgency by 10-12%).
- Women with menses showed a greater response to alosetron than women without menses in one study, but not in the second.

*This Reviewer's Comment: According to these studies, alosetron appears to have some efficacy in women with diarrhea (or non-constipation) predominant IBS. Treatment with alosetron, compared to treatment with placebo, resulted in 11% - 19% more IBS patients experiencing an adequate relief of pain/discomfort. Alosetron appears not to be effective in males with IBS (who responded to placebo as vigorously as to alosetron), or in women with constipation predominant (or alternating) IBS (whose response did not reach statistical significance).*

B. Safety assessment

The primary safety database comprised 1,263 patients (1,079 women and 184 men) who received alosetron, and 834 patients (780 women and 54 men) who received placebo for up to 12 weeks in the two principal efficacy studies and in

the two dose-ranging studies. In addition, some data were available from a year-long, placebo-controlled continuation study (S3BA3003, for patients who had completed the two principal efficacy studies) of 637 women and 222 men with IBS randomized to either placebo or 1 mg alosteron b.i.d.

In all studies, safety was evaluated by monitoring adverse events and reasons for patient withdrawals, and by periodic clinical blood testing for cell counts and chemistries. Special studies of ECG effects and pure-tone audiograms were done to exclude possible arrythmogenic or deafness-inducing effects of alosetron.

The composite table of treatment-emergent adverse events is shown below. **Constipation** was seen significantly more frequently in alosetron-treated patients than in placebo-treated patients (Reviewer's Table 1), and the increased frequency was dose-related in the 0.1 - 1.0 mg b.i.d. range (it did not increase further as the dose was increased to 8.0 mg b.i.d.). Subgroup analysis by gender, race, age, and hormonal status did not reveal differences in susceptibility to constipation.

Constipation was an important reason for patients dropping withdrawing from the 12-week studies (about 10%). Premature withdrawals from the study were far more common in the one-year continuation study of patients who had completed the 12-week studies S3BA3001 or -3002. About 41% of patients withdrew from the study, most of them within the first 6 months.

The Table below is an interim analysis listing adverse events that caused premature withdrawal in the continuation study; the data is for 298 patients who withdrew prematurely, but the 12-month study was still on-going, when these data were collected.

**Adverse Events Causing Premature Withdrawal, S3BA3003**

| patients | Placebo BID n = 175 | A 1 mg BID n = 542 | Difference p-value |
|---|---|---|---|
| Withdrawn prematurely | 61 (35%) | 237 (43%) | N.S. |
| **Any adverse event** | **18 (10.3%)** | **129 (23.8%)** | **0.0001** |
| **Gastrointestinal event** | **13 ( 7.4%)** | **110 (20.3%)** | **< 0.0001** |
| **constipation** | **1 (0.6%)** | **88 (16.2%)** | **<< 0.0001** |
| all other gi events* | 19 (10.9%) | 59 (10.7%0 | N.S. |
| Neurological event | 5 (2.9%) | 13 (2.4%) | N.S. |
| headache | 2 (1.1%) | 8 (1.5%) | N.S. |
| Cardiovascular event | 0 | 3 (0.6%) | N.S. |
| arrhythmias | 0 | 2 (0.4%) | N.S. |
| Malaise or fatigue | 1 (0.6%) | 2 (0.4 %) | N.S |
| All other system AEs* | 4 (2.3%) | 26 (4.5%) | N.S. |

*Note BID, twice daily. A. alosetron; *, some patients had more than one AE.*

Additional information to the above table: there were 2 deaths (cardiovascular) and 2 pregnancies in the alosetron group; 10.3% of patients in the placebo group

withdrew because of lack of efficacy vs. 3.6% in the alosetron group. The final tabulation for the 12 month results was similar to the above tabulation.

The prominence of **severe constipation** in the Safety Database and in the continuation study above is striking, as shown in the Table below. Constipation was about six times more frequent in alosetron-treated patients than in placebo-treated patients. The incidence was the highest in the continuation study, suggesting that the incidence of constipation increases with length of exposure.

Reviewer's Table 1. Constipation in four double-blind, placebo-controlled studies of alosetron

| Study no. | Placebo No. of patients | Placebo, % patients with Constipation | Alosetron 1 mg b.i.d. No. of patients | Alosetron,% patients with constipation |
|---|---|---|---|---|
| S3BA2001 | 80 | 6.5% | 70 | 20.0% |
| S3BA3001 | 316 | 6.6% | 309 | 25.9% |
| S3BA3002 | 321 | 3.1% | 322 | 29.8% |
| S3BA3003 | 210 | 4.8% | 649 | 32.2% |
| Total | 927 | 5.0% | 1,350 | 29.6% |

Abdominal pain was more frequent in alosetron-treated patients, as shown in This Reviewer's Table 2. Again, the incidence of abdominal pain/discomfort increased with the length of exposure to alosetron.

This Reviewer's Table 2. Abdominal pain/discomfort in four double-blind, placebo-controlled studies of alosetron

| Study no. | Placebo No. of patients | Placebo, % patients with abd. Pain | Alosetron 1 mg b.i.d. No. of patients | Alosetron, % patients with abd. pain |
|---|---|---|---|---|
| S3BA2001 | 80 | 7.5% | 70 | 11.4% |
| S3BA3001 | 316 | 6.0% | 309 | 8.7% |
| S3BA3002 | 321 | 7.2% | 322 | 10.9% |
| S3BA3003 | 210 | 11.0% | 640 | 17.8% |
| Total | 927 | 7.7% | 1,350 | 13.6% |

Alosteron-treated men were as susceptible to constipation and abdominal pain as women.

Other common adverse events were not significantly more prevalent in the alosetron-treated than in the placebo-treated patients.

A much rarer but much more serious adverse effect was **ischemic colitis**, single cases of which occurred in three of the trials (S3BA2001, S3BA3001 and S3BA3002)(an incidence of 3/921 patients or 0.33%). Each of the patients presented with abdominal pain and rectal bleeding; the onset was after 2 days, 37 days and 54 days of treatment with alosetron 1 mg BID. All three patients were hospitalized and survived. Treatment with alosetron was not resumed. A fourth case was reported on November 12, 1999 by the sponsor.

**Seven** other possible instance of **ischemic colitis** occurred in the continuation study S3BA3003. These patients all developed severe abdominal pain and rectal bleeding at various times after starting alosetron (4 - 142 days). The patients did not undergo diagnostic work ups; four were withdrawn from the study. If these 7 cases indeed had ischemic colitis, then the incidence (7/553 patients or 1.3%) is much higher than the above from proven cases. No cases of ischemic colitis occurred among placebo-treated patients.

There was one case of hepatotoxicity with elevations of ALT, AST, alkaline phosphatase and bilirubin, which subsided after alosetron was discontinued. Patient then had an ERCP under general anesthesia, following which she went into pulmonary edema, but survived.

C. Post-Marketing Safety-related Events

The marketing application for Lotronex (alosetron hydrochloride) tablets was approved on February 9, 2000 for the treatment of irritable bowel syndrome in women whose predominant bowel symptom is diarrhea. Marketing started in March, 2000 and over the following nine months over 300,000 patients filled over 450,000 prescriptions for alosetron.

During this post-marketing period, FDA received reports of serious adverse events of **ischemic colitis** and **complications of severe constipation**, including **deaths**, associated with the use of Lotronex. After failing to reach an agreement with FDA on an acceptable risk management plan, the sponsor ceased distribution of Lotronex and withdrew all supplies from the market, effective November 28, 2000.

By the time of Lotroniex withdrawal thirteen (13) deaths were reported to the FDA in association with the use of alosetron during marketing in addition to cases of ischemic colitis and serious complications of constipation.

- Deaths. The FDA reviewers concluded that 3 deaths were *probably related* to alosetron use and 2 deaths were *possibly related* to alosetron use. In 2 other deaths alosetron use was a possible contributor. Alosetron played no role in the remaining 6 deaths. Shown below is condensed information from Table 1 in the review by Drs. Kress, Barreira, and Gallo-Torres on August 29, 2001.

Reviewer's Table 3. Deaths related to alosetron use in the post-marketing period

| Case # | Clinical findings | Pathological findings | Cause of death | Relationship to alosetron |
|---|---|---|---|---|
| # 21 | 70 y.o. F, abd. Pain, perforated colon, **ischemic colitis**, fresh thrombosis of mesenteric arteries + veins | Transmural **perforation** of colon | Transmural RS **perforation**, peritonitis | PROBABLE |
| # 64 | 67 y.o. F, abd. Pain, massive dilatation of colon, **ischemic colitis, necrotic sigmoid colon** | **Ischemic colitis**, distention of colon, **necrosis RS colon** | **Ischemic colitis**, necrotic RS colon | PROBABLE |
| # 69 | 82 y.o. F, **constipation, bowel** ischemia, **ruptured colon**, sepsis, diverticulitis | diverticulitis with perforation | **RS colon perforation**, diverticulitis | PROBABLE |
| # 105 | 70 y.o. F, abdominal pain, **perforation of colon**, cardiac arrest | no hospital records | **Perforation of colon** | POSSIBLE, addit. info. needed |
| # 157 | 46 y.o. F, abdominal pain, **bloody diarrhea, necrosis small bowel, perforation, SMA occlusion** | acute enteritis, **acute cecal inflammation** | **necrosis of small bowel with perforation** | POSSIBLE |
| # 43 | 81 y.o. UGI bleeding, diffuse ischemia, necrotic esophagus, stomach & small intestine | (no autopsy) | **ulceration of UGI tract** | Possible contributor, pt. on Fosamax |
| # 66 | 59 y.o. **ischemia** and **necrosis small bowel** and **colon**, 6 mo hx of abd. pain, wt. Loss | **superior mesenteric artery thrombosis** | **necrosis small bowel and colon** | Possible contributor, mesenteric insufficiency |

The above cases demonstrate 3 types of adverse experiences that resulted in death: 1) ischemic colitis resulting in necrosis and perforation, 2) complications of severe constipation that required surgery, including fecal impaction with intestinal obstruction, ischemic ulceration and gangrenous colitis, and 3) arterial and/or venous thrombosis of mesenteric vessels of the small bowel resulting in ischemia and necrosis.

- Ischemic colitis for the most part was self-limited and characterized by severe crampy abdominal pain, diarrhea and rectal bleeding. Over 60% of patients with this syndrome required hospitalization and 10% required surgery.
- Severe constipation, sometimes accompanied by rectal bleeding, resulting in fecal impaction, intestinal obstruction, and ischemic ulceration induced by hard feces. One-half of these patients required hospitalization and one-quarter required surgery.
- *This Reviewer's Note: It is noteworthy that only 2 deaths occurred in patients younger than 67: one was 46, the other was 59; 2 patients were in the early 80's, 2 were 70 years old, one was 67. The average age for the group was 67.9 years.*

The sponsor submitted on August 23, 2001 the completed sections of the proposed supplement to the NDA (sNDA) consisting of 28 of the 40 new studies. The remaining 12 studies will be submitted on October 5, 2001.

This review evaluates the data in study S3BB3001, in which women with IBS were randomized to receive either alosetron or mebeverine for 12 weeks. The primary focus of the review is on safety, but efficacy will be evaluated as well.

The results of this study have been published (Jones RH, Holtmann G, Rodrigo L et al. Alosetron relieves pain and improves bowel function compared to mebeverine in female nonconstipated irritable bowel syndrome patients. Aliment Pharmacol Ther 1999; 13: 1419-1427.)

## II. Summary of Protocol S3BB3001

**Title:** A multicentre, randomized, double-blind comparison of alosetron 1 mg BID against mebeverine 135 mg TID for 12 weeks in the treatment of female patients with irritable bowel syndrome (IBS)

### A. Objectives:

**Primary Objectives:**

1. To compare the two treatment groups (alosetron 1 mg BID and mebeverine 135 mg TID) with respect to proportion of subjects who report adequate relief of their IBS pain and discomfort.

2. To compare the safety and tolerability of the two treatments.

**Secondary Objectives:**

To compare the two treatment groups with respect to:

1. changes in the proportion pain and discomfort-free days experienced by subjects.
2. changes in mean severity scores for abdominal pain and discomfort.
3. proportion of subjects reporting at least 50% of abdominal pain and discomfort-free days at each month.
4. self-ratings of the following GI symptoms: a) sense of urgency, b) stool consistency, c) stool frequency, d) sense of incomplete evacuation, e) bloating.
5. changes in SCL-90R scores
6. changes in quality of life scores and productivity (resource utilization).

### B. Study Design:

This was an international, multicenter, randomized, double-blind, parallel group study. The study was designed to enroll 600 adult female subjects at sites in United Kingdom, Ireland, Sweden, Denmark, Iceland, Norway, Germany, Switzerland, Belgium, The Netherlands, Spain, Israel, Australia, New Zealand, and South Africa. Recruitment period was between October, 1997 and February, 1999, when the planned sample size was attained.

Subjects with symptoms fulfilling the Rome criteria for IBS for 6 months were screened during a 2 week period to confirm active disease. Subjects meeting the threshold criteria for the severity of abdominal pain/discomfort and for stool consistency were randomized to 12 week treatment periods with either alosetron 1 mg BID or mebeverine 135 mg TID. After completing the treatment period, subjects were followed for 4 weeks.

Subjects recorded abdominal pain/discomfort and other GI symptoms on a touch-tone telephone electronic data entry system for the total study duration of 18 weeks.

Study Design issues:

- There was no placebo control group. Active treatment control drug was mebeverine, which is commonly prescribed for the treatment of IBS in the countries where the trial was held. Mebeverine is not FDA-approved.
- IBS may be subclassified as diarrhea-predominant, constipation-predominant, or alternating diarrhea-constipation types. Since constipation is a common side-effect of alosetron, the study was designed for diarrhea-predominant and alternating IBS types.

  As a precaution, subjects who had no stool for 4 days were instructed to discontinue the drug for up to 4 days. Constipation was recorded as an adverse event. If defecation returned, the subject restarted the study drug. If stool was absent for 8 days, the subject withdrew from the study and the study drug was discontinued.

C. **Subjects:**

**Inclusion Criteria:**

- Female, at least 18 years old
- Signed an informed consent
- An ambulatory outpatient
- Not lactating, not pregnant, restricted child-bearing potential
- Colonoscopy or flexible sigmoidoscopy plus barium enema after onset

of IBS and within 5 years of randomization

- Meets Rome Diagnostic Criteria for IBS (stated above in Background)
- Abdominal pain/discomfort score between 1.0 and 3.3 (1 = mild, 2 = moderate, 3 = intense, 4 = severe)
- Stool consistency of >2.5 (1 = very hard. 2 = hard, 3 = formed, 4 = loose, 5 = watery).
- Has recorded at least 12 days of daily self-assessments.

**Exclusion Criteria:**

- Unstable cardiovascular, renal, hepatic, pulmonary, endocrine, metabolic, hematological or GI condition
- Biochemical or structural abnormality of the digestive tract, including inflammatory bowel disease, GI surgery (except appendectomy, cholecystectomy, benign polypectomy, and hiatal hernia)
- Current evidence of diverticulitis, erosive esophagitis, symptomatic GERD, duodenal ulcer, gastric ulcer, gastroparesis, GI malignancy or obstruction, carcinoid syndrome, pancreatitis, symptomatic cholelithiasis, amyloidosis, ileus, or laxative abuse.
- A major psychiatric disorder (DSM-IIIR or DSM-IV) within the past 2 years which required hospitalization or involved an attempted suicide, including major depression or psychoses. Other such subjects who were not on a stable dose of medication for at least 6 months. A history of alcohol or substance abuse within the past 2 years.
- Hepatic dysfunction (ALT or AST > 2.5 times the upper limit of normal.
- Abnormal TSH.
- Renal impairment (serum creatinine > 200μmol/L)
- Any evidence of, or treatment of, malignancy within the previous 5 years (other than localized basal cell, squamous skin cancer or localized cancer *in situ* that had been resected).
- Use of an investigational drug or participation in an investigational study within 30 days of the screening phase.
- Concurrent use of any prohibited medication, such as (a non-exhaustive list): antibiotics, anticholinergics, cholestyramine, cholinomimetic agents, codeine, docusate, enemas, GI preparations (anacids, antidiarrheal agents, aninausea agents, antispasmodic agents, 5-ASA preparations, bismuth compounds, laxatives, prokinetic agents, stool softeners, sulfasalazine), agents indicated for IBS, iron, morphine, narcotics, tramadol, theophylline, warfarin, NSAIDs (exc. ASA 325 mg per day), analgesics, anti-Parkinson's agents, antipsychotics, isoniazid, rifampicin, anticonvulsants, peppermint oil, leuprolide, stimulants.
- Inability/unwillingness to follow directions, unable to understand how to use the telephone touch tone electronic data entry system.

**Criteria for Premature Treatment and/or Study Discontinuation**

A subject could be withdrawn from the study at any time at either the investigator's or the subject's discretion, or due to absence of stool for 8 consecutive days.

**Concurrent Therapy**

The following medications were permitted, provided the subject had received stable doses for 30 days before the screening visit: antianginals, antidepressants, antihypercholesterolemics (exc. cholestyramine), antihyperglycemics, antihypertensives, anxiolytics, bulking agents, pancreatic enzymes, thyroid replacement therapy.

**The Study Population: Accounting of Subjects**

- Screening and selection:

| | |
|---|---|
| Total screened | 1,153 |
| Total randomized to treatment | 653 (54%) |
| Total rejected<br>--screening criteria not met<br>--consent withdrawn<br>--failed to return<br>--other reasons | 530 (46%)<br>455<br>36<br>2<br>37 |

- Treatment assignment:

| Treatment | Total no. | Diarrhea-predominant | Alternating pattern |
|---|---|---|---|
| Alosetron 1mg BID** | 319 (51% of total) | 233 (73% of the group) | 86 (24% of the group)* |
| Mebeverine 135mg TID | 304 (49% of total) | 216 (71% of the group) | 88 (25% of the total)* |

*4% of patients in each group were constipation-predominant.
** One subject in the alosetron group did not consume any medication, thus the Safety Population for this group was 318.

- Study completion and premature withdrawal:

| Treatment | Total patient no. | No. of patients completed study | No. of patients who withdrew |
|---|---|---|---|
| Alosetron | 319 | 251 (79%) | 68 (21%) |
| Mebeverine | 304 | 246 (81%) | 58 (19%) |
| Total | 623 | 497 (80%) | 126 (20%) |

The reasons for premature withdrawals of subjects are shown in the sponsor's table below (Table 2.2 ).

**Premature Study Withdrawals by Reason: Total ITT Population**

| | Alosetron 1mg bd n (%)[1] | Mebeverine 135mg tds n (%)[1] | Total n (%)[1] |
|---|---|---|---|
| Number of subjects withdrawing prematurely n (%)[2] | 68 (21) | 58 (19) | 126 (20) |
| Adverse event | 42 (62) | 30 (52) | 72 (57) |
| *Consent withdrawn* | *8 (12)* | *5 (9)* | *13 (10)* |
| Lost to follow-up | 3 (4) | 4 (7) | 7 (6) |
| Protocol violation | 4 (6) | 6 (10) | 10 (8) |
| Lack of efficacy | 5 (7) | 10 (17) | 15 (12) |
| Other | 6 [3-5] (9) | 3 [9-11] (5) | 9 (7) |

Source Table 2.2, Listing 5
[1]: Percentage of withdrawn subjects; [2]: Percentage of population; [3]: Subject 355 improved on lactose-free diet; [4]: Subject 1198 had faecal parasites; [5]: Subject 1721 moved away; [6]: Subject 1376 failed to return at the 12 weeks visit; [7]: Subject 1892 took prohibited medication for adverse event; [8]: Subject 2188 had abdominal pain; [9]: Subject 1985 had increased IBS pain; [10]: Subject 1175 had indefinite diagnosis of IBS; [11]: Subject 2184 had another treatment pack dispensed in error at Week 4.

The majority of subjects in the total ITT Population who discontinued prematurely did so within the first 4 weeks treatment, as shown below in sponsor's Table 2.3.

Table 2.3
Summary of Times of Premature Withdrawal

| | Alosetron 1 mg bd (N=319) | Mebeverine 132 mg tds (N=304) | Total (N=623) |
|---|---|---|---|
| Number of Subjects Prematurely Discontinuing | 68 (21%) | 58 (19%) | 126 (20%) |
| Times of Premature Withdrawal: | | | |
| By Week 4 | 46 (68%) | 32 (55%) | 78 (62%) |
| By Week 8 | 63 (93%) | 48 (83%) | 111 (88%) |
| By Week 12 | 68 (100%) | 58 (100%) | 126 (100%) |

Adverse events were the most common reason for withdrawal from the study in both arms of the study. The adverse events differed in the two arms. The predominant adverse event in the alosetron arm was **constipation** (in 23 patients [34% of the patients who withdrew prematurely]), followed by abdominal pain/discomfort (in 8 patients or 12% of patients who withdrew). There was no predominant adverse event in mebeverine arm. The table below (sponsor's table 14.3) describes the adverse events leading to premature withdrawal.

Among the 72 subjects who were withdrawn due to adverse events, nine (13%) were withdrawn because of **serious adverse events**. Four of these subjects were in the alosetron group; two of them suffered adverse events that were related to alosetron (**erosive gastritis**, and **sigmoiditis**, respectively). Five subjects were in the mebeverine group; two of them suffered adverse events that were related to mebeverine (worsening of abdominal pain, and violent abdominal

pain and constipation, respectively). These case histories will be described below in the Safety section.

**Adverse Events Leading to Withdrawal of Two or More Subjects**

| Body System | Adverse event leading to withdrawal (group term) | Alosetron 1mg bd (N=318) | | Mebeverine 135mg tds (N=304) | |
|---|---|---|---|---|---|
| | | No. of Events | No. (%) of Subjects | No. of Events | No. (%) of Subjects |
| Any Body System | Any Event | 78 | 42 (13%) | 56 | 30 (10%) |
| Gastrointestinal | Constipation | 23 | 23 (7%) | 3 | 3 (<1%) |
| | Abdominal discomfort & pain | 8 | 8 (3%) | 3 | 3 (<1%) |
| | Nausea | 2 | 2 (<1%) | 4 | 4 (1%) |
| | Diarrhoea | 2 | 2 (<1%) | 3 | 3 (<1%) |
| | Gastrointestinal discomfort & pain | 3 | 3 (<1%) | 2 | 2 (<1%) |
| | Vomiting | 2 | 2 (<1%) | 1 | 1 (<1%) |
| | Oesophagitis | 2 | 2 (<1%) | 0 | 0 |
| Non-Site Specific | Malaise & Fatigue | 3 | 3 (<1%) | 2 | 2 (<1%) |
| | Faintness | 2 | 2 (<1%) | 0 | 0 |
| | Pain | 2 | 2 (<1%) | 0 | 0 |
| Neurology | Headaches | 5 | 5 (2%) | 4 | 4 (1%) |
| Skin | Skin rashes | 1 | 1 (<1%) | 2 | 2 (<1%) |
| Psychiatry | Agitation | 0 | 0 | 2 | 2 (<1%) |

Source: Table 14.3

## Study population: Characteristics

- The demographic and baseline characteristics of study participants are shown below (Sponsor's Table 5.0). The patients who failed the screening process had very similar characteristics (not shown).

Table 5.0
Summary of Demographic and Baseline Characteristics

| | | Alosetron 1mg bd (N=319) | Mebeverine 135mg tds (N=304) | Total (N=623) |
|---|---|---|---|---|
| Age (y) | n | 319 | 304 | 623 |
| | Mean | 44.2 | 44.5 | 44.4 |
| | SD | 13.[illegible] | 13.9 | 13.8 |
| | Median | 44.0 | 45.5 | 45.0 |
| | Min. | 17 | 17 | 17 |
| | Max. | 75 | 74 | 75 |
| Race | n | 319 | 304 | 623 |
| | Asian | 1 (<1%) | 1 (<1%) | 2 (<1%) |
| | White | 315 (99%) | 298 (98%) | 613 (98%) |
| | Other | 3 (<1%) | 5 (2%) | 8 (1%) |
| Height (cm) | n | 319 | 303 | 622 |
| | Mean | 163.[illegible] | 163.5 | 163.6 |
| | SD | [illegible].1 | 6.6 | 6.9 |
| | Median | 164.[illegible] | 163.0 | 164.0 |
| | Min. | 133 | 145 | 133 |
| | Max. | 183 | 180 | 183 |
| Weight (kg) | n | 319 | 303 | 622 |
| | Mean | 67.[illegible] | 68.16 | 67.84 |
| | SD | 15.[illegible] | 15.98 | 14.23 |
| | Median | 66.[illegible] | 65.00 | 65.00 |
| | Min. | 40.[illegible] | 36.0 | 36.0 |
| | Max. | 128.[illegible] | 133.0 | 133.0 |

Table 5.0
Summary of Demographic and Baseline Characteristics

| | | Alosetron 1mg bd (N=319) | Mebeverine 135mg tds (N=304) | Total (N=623) |
|---|---|---|---|---|
| Childbearing Potential | n | 319 | 304 | 623 |
| | Potentially able | 144 (45%) | 141 (46%) | 285 (46%) |
| | Post-menopause | 109 (34%) | 116 (38%) | 225 (36%) |
| | Sterile | 66 (21%) | 47 (15%) | 113 (18%) |
| Use of Female Sex Hormones | n | 319 | 302 | 621 |
| | Use hormonal contraceptive | 88 (28%) | 80 (26%) | 168 (27%) |
| | No use of female sex hormones | 181 (57%) | 176 (58%) | 357 (57%) |
| | Use hormonal replacement | 50 (16%) | 46 (15%) | 96 (15%) |
| Menstruated during study | n | 318 | 302 | 620 |
| | No | 10 (3%) | 7 (2%) | 17 (3%) |
| | Yes | 168 (53%) | 149 (49%) | 317 (51%) |
| | Not applicable | 140 (44%) | 146 (48%) | 286 (46%) |

This Reviewer notes the very wide age range (17 - 75 y.o.) with a mean and median of 44 years of age. This is of interest because most of the severe adverse events in the post-marketing experience occurred in the elderly.

This Reviewer also notes the very wide range of heights and weights. Converted to English measures, the subjects' heights ranged from 4'4" to 6'0", with a mean and median of 5'4". The subjects' weights ranged from 79 lbs. to 293 lbs. with a mean of 149 lbs. and a median of 143 lbs. This is of interest because fixed doses of the drugs were administered to all subjects. Pharmacokinetics and pharmacodynamics may have been vastly different among the study subjects at extremes of heights and weights, and it is possible that both the efficacy of the drugs and the occurrence of adverse events may have been influenced by this wide range of subject population.

Sponsor's Table 6.0 presents the summary of study subjects' IBS histories. The Reviewer notes that 72% of patients had diarrhea-predominant IBS and 24% had alternating IBS type, and that the median time of IBS symptoms was about 5.4 years with a range of 0.5 year to 52 years.

(Data as of: 12AUG99)

Table 6.0
Summary of Irritable Bowel Syndrome History

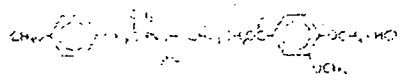
| | Alosetron 1mg bd (N=319) | Mebeverine 135 mg tds (N=304) | Total (N=623) |
|---|---|---|---|
| Six Months of Abdominal Pain/Discomfort [1]: | 319 (100%) | 304 (100%) | 623 (100%) |
| Relieved with defecation | 238 (75%) | 233 (77%) | 471 (76%) |
| Associated with Change in Stool Frequency | 254 (80%) | 253 (83%) | 507 (81%) |
| Associated with Change in Stool Consistency | 262 (82%) | 240 (79%) | 502 (81%) |
| Symptoms Occurring at Least Two Days Per Week [1]: | 319 (100%) | 304 (100%) | 623 (100%) |
| Altered Stool Frequency | 271 (85%) | 250 (82%) | 521 (84%) |
| Altered Stool Form | 288 (90%) | 267 (88%) | 555 (89%) |
| Altered Stool Passage | 262 (82%) | 249 (82%) | 511 (82%) |
| Passage of Mucus | 163 (51%) | 143 (47%) | 306 (49%) |
| Bloating/Abdominal Distension | 291 (91%) | 271 (89%) | 562 (90%) |
| Time in Years Since Onset of IBS Symptoms | 319 | 303 | 622 |
| Mean | 8.61 | 9.73 | 9.15 |
| SD | 8.50 | 10.07 | 9.31 |
| Median | 5.40 | 5.10 | 5.40 |
| Min. | 0.5 | 0.6 | 0.5 |
| Max. | 52.0 | 45.7 | 52.0 |
| Sub-Type of IBS | | | |
| Alternating Constipation and Diarrhoea | 76 (24%) | 73 (24%) | 149 (24%) |
| Diarrhoea Predominant | 232 (73%) | 217 (71%) | 449 (72%) |
| Constipation Predominant | 11 (3%) | 14 (5%) | 25 (4%) |

## D. Study drugs:

1. Alosetron (Lotronex, GlaxoSmithKline) was described in the NDA Medical Officer Reviews.

2. Mebeverine hydrochloride BP tablets (Colofac, Solvay Healthcare) were used as an active comparator to alosetron. Mebeverine is 3,4-dimethoxy-benzoic acid 4-[ethyl-[2-(4-mehoxyphenyl)-1-methylethyl]amino]butyl ester. It is a musculotropic spasmolytic derived from papaverine, which was used for some decades as a smooth muscle relaxant and vasodilator. The formula (from the USP Dictionary of USAN and International Drug Names) is shown below.

**Mebeverine Hydrochloride** [*1966*] (me bev' er een). $C_{25}H_{35}NO_5.HCl$. 466.02. [Mebeverine is INN and BAN.] (1) Benzoic acid, 3,4-dimethoxy-, 4-[ethyl[2-(4-methoxyphenyl)-1-methylethyl]amino]butyl ester, hydrochloride; (2) 4-[Ethyl(*p*-methoxy-α-methylphenethyl)amino]butyl veratrate hydrochloride. *CAS-2753-45-9; CAS-3625-06-7* [mebeverine]. *Relaxant (smooth muscle).* ✧*CSAG-144*



Mebeverine is a musculotropic spasmolytic is used for irritable bowel syndrome, barium enema preparation (reducing pain and discomfort of the examination), and post-vagotomy diarrhea (DrugDex Drug Evaluations). The usual dose for adults and children over 10 years of age is 135 mg TID.

Pharmacokinetics: Following oral administration mebeverine is almost entirely absorbed in the duodenum and is distributed to all tissues. The drug is 76% bound to albumin. Mebeverine is metabolized by esterases. About 95% - 98% of all metabolites are renally excreted within 8 h after administration.

Precautions: In patients with marked renal insufficiency, hepatic impairment, cardiac problems. Contraindicated in patients with cystic fibrosis. Can be used safely in patients with celiac disease, glaucoma, and prostatic hypertrophy.

Side effects: Dizziness, headache, nausea, generalized peritonitis (one case in a patient with distal intestinal syndrome in cystic fibrosis), skin reactions.

Mechanism of action: Mebeverine exhibits selective activity on smooth muscles of the GI tract, qualitatitively comparable to papaverine, but 3 - 5 times stronger. Mebeverine may alter contractile activity and small bowel activity in patients with irritable bowel syndrome (Evans, Bak & Kellow. Aliment Pharmacol Ther 1996; 10:787-793). Mebeverine may also exhibit prokinetic and antispasmodic activity in the small intestine.

Irritable Bowel Syndrome: A double-blind, cross-over, placebo-controlled clinical trial with mebeverine was carried out by Tasman-Jones (NZ Med J 1973; 77: 232-5) in which ten patients responded better to mebeverine than to placebo. Mebeverine was found to normalize small bowel motility in IBS, while having no effect in controls (Evans, Bak & Kellow. Aliment Pharmacol Ther 1996; 10:787-793). Washington et al. (Aliment Pharmacol Ther 1998; 12:583-8) found that mebeverine reduces the diarrheal effct of lactulose by decreasing the mass movements induced in the ascending colon. A double-blind, cross-over study (Van Outryve et al. (J Clin Pharm Ther 1995; 20:277-282)) compared mebeverine regular release to mebeverine sustained release in 60 irritable bowel syndrome patients treated for 6 weeks. A decrease in symptoms was observed at 3 weeks in at least 70% of both groups, and at 6 weeks symptoms had disappeared in about 30% patients, except for abdominal pain. The intensity of abdominal pain was lower in about 50% of patients. Bloating, flatulence and constipation disappeared in about 62% of patients. IBS patients with diarrhea or alternating defecation pattern responded better than patients with constipation. Adverse events occurred in about 13% - 20% of patients but were not drug-related according to the investigators.

**E. Study plan:**

The overall study time and events table is shown in sponsor's Table 1.0 below. The study drugs were, as previously noted, alosetron 1mg BID or mebeverine

135mg TID. A summary of exposure to study medication is shown below (sponsor's Table 3.0).

**TABLE 1.0 FLOWCHART/TIME AND EVENTS TABLE**

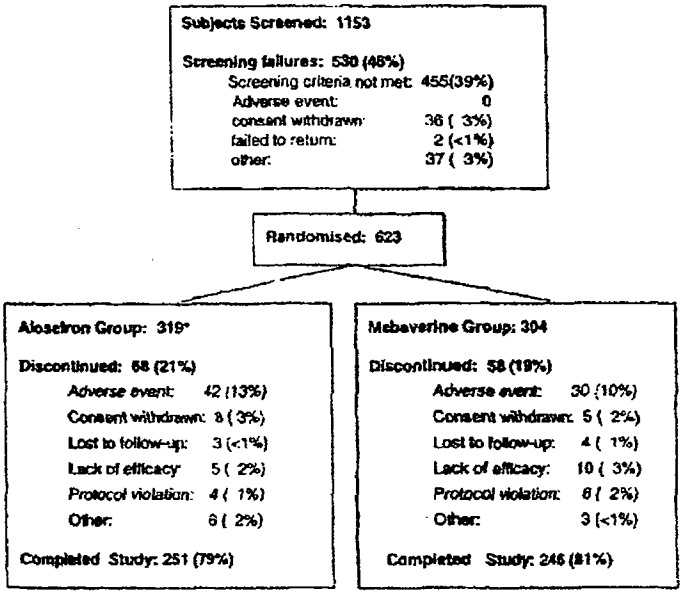
| | Screening Phase | | Treatment Phase | | | | Follow-Up | |
|---|---|---|---|---|---|---|---|---|
| Study Day | -14±2 | 7[a,b] Days | R | 28±4 | 56±4 | 84±4 | Telephone +28±4 | Visit |
| Study Week | -2 | | R | 4 | 8 | 12 | 16 | As needed |
| Informed Consent | X | | | | | | | |
| Procedures: | | | | | | | | |
| Demographic Data/Height/Weight | X | | | | | | | |
| Medical History | X | | | | | | | |
| Physical Examination | X | | | | | X | | |
| Lactose Hydrogen Breath Test[c] | X | | | | | | | |
| Stool Occult Blood | X | | | | | | | |
| Stool Ova and Parasites (if not done within previous 3 months) | X | | | | | | | |
| Sigmoidoscopy[a] | | X | | | | | | |
| Colonoscopy[b] | | X | | | | | | |
| Clinical Labs[d] | X | | X[f] | X | X | X | | (X)[e] |
| Adverse Events | X | X | X | X | X | X | X[f] | (X)[e] |
| Concurrent Medications | X | | X | X | X | X | X[f] | (X)[e] |
| Menstrual History[g] | X | | X | X | X | X | X[f] | (X)[e] |
| Daily Self Rating IBS Pain and discomfort, Symptoms | X--> | X--> | X--> | X--> | X--> | X--> | X | |
| Self-Rating SCL-90R[e,b] | | | X | | | X | | |
| Self-Rating QOL IBS Disease Specific[h] | | | X | | | X | | |
| Self-Rating QOL SF-36[h] | | | X | | | X | | |
| Self-Rating Resource Utilization[h] | | | X | | | X | | |
| Assign Subject Number | X | | | | | | | |
| Assign Treatment Number | | | X | | | | | |
| Dispense Medication | | | X | X | X | | | |
| Drug Accountability | | | | X | X | X | | (X)[e] |
| Schedule Next Appointment | X | | X | X | X | (X) | | |

R Randomisation to study drug/start study drug

Table 3.0
Summary of Exposure to Study Medication

| Days of Exposure [1] | Alosetron 1mg bd (N=319) | | Mebeverine 135mg tds (N=304) | |
|---|---|---|---|---|
| 0 | 1 | (<1%) | 0 | |
| 1 - 28 | 38 | (12%) | 29 | (10%) |
| 29 - 56 | 19 | (6%) | 20 | (7%) |
| 57 - 84 | 109 | (34%) | 92 | (30%) |
| > 84 | 152 | (48%) | 163 | (54%) |
| Unknown | 0 | | 0 | |

Subject progression through the study is graphically illustrated below (sponsor's figure, p. 46)



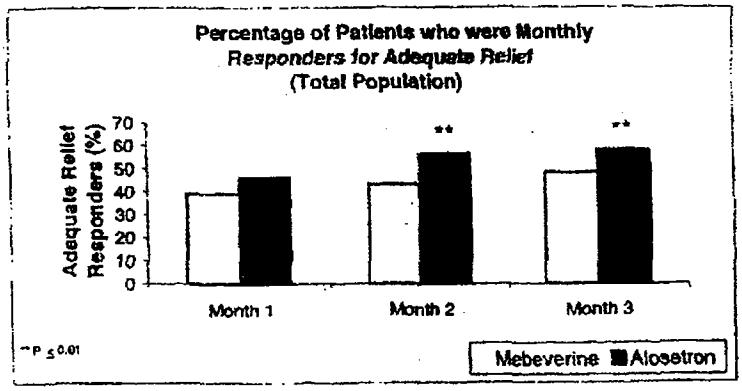

*One subject randomised did not consume treatment and was not included in the safety population

- **Protocol deviations:** Forty-three percent of subjects had major protocol violations, about equally distributed between alosetron and mebeverine groups. The most common protocol violation was the use of prohibited medications for 7 or more consecutive days. The most common medications were analgesics, including NSAIDs, and antibiotics. Other key protocol violations affecting more than 10% of protocol violators were: <80% compliance in taking study medications, < 50% compliance with the telephone data entry system.
- **Concurrent therapy:** About 85% of patients in each treatment arm reported using some form of concurrent therapy during the study. The most common categories of drugs were contraceptive drugs, replacement hormones, paracetamol, NSAIDs, benzodiazepenes, corticosteroids, penicillins, laxatives and fiber (7%), and thyroid preparations. The concurrent therapies were similar in the two treatment groups.
- **Treatment compliance:** Compliance was similar between the two groups, with 92% - 97% of subjects assessed at each visit showing >80% compliance.

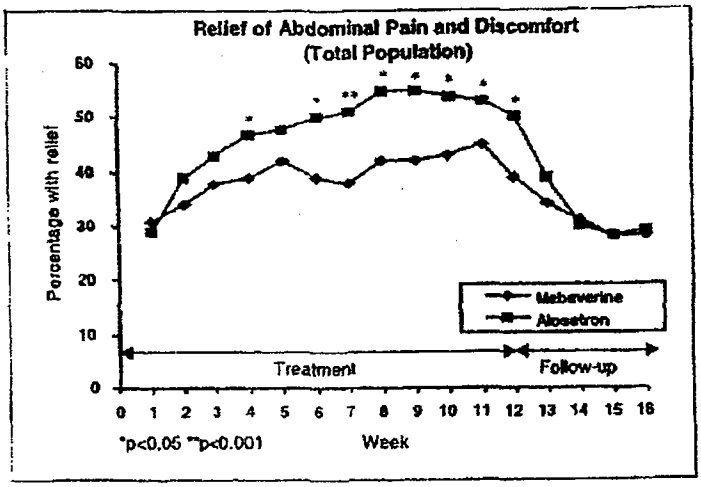
**F. Efficacy:**

1. Primary Measure: Adequate Relief of IBS Pain and Discomfort

The sponsor presented the results for the total ITT population in each symptom/sign category, and for the diarrhea-predominant population. The alternating type IBS population was too small for statistical analyses. Alosetron was superior to mebeverine in relieving the signs and symptoms of IBS in the total ITT population and in the diarrhea-predominant population. These findings differ from those of the primary NDA pivotal studies, in which only the diarrhea-predominant IBS patients responded to alosetron. The figure below shows that the proportion of subjects in the total ITT population reporting adequate relief of IBS pain and discomfort for at least 2 weeks per month was greater in the alosetron group than in the mebeverine group (56% vs. 43%, p=0.001 for month 2; 58% vs. 48%, p=0.009 for month 3).




Weekly data for adequate relief of IBS pain and discomfort are shown in the figure below. Statistical significance is demonstrated between weeks 4 and 12, after which time relief of pain and discomfort reverts to pre-treatment percentage.
The maximum difference between groups at any week was a 13% advantage of alosetron over mebeverine.




Of the subjects (ITT population) who completed the 12 week course of treatment, 63% of the alosetron group and 47% of the mebeverine group had adequate relief of IBS pain/discomfort during at least 6 of the 12 weeks (sponsor's Table 8.11).

2. Secondary measure: Pain- and discomfort-free days (ITT population)

The proportion of subjects reporting at least 50% of days with no pain or discomfort was greater in the 2nd and 3rd months of treatment with alosetron than with mebeverine, as shown below (from sponsor's Table 9.5).

Reviewer's Table 4. Proportion of patients reporting on pain- and discomfort-free days

| Treatment month | Patients on alosetron | Patients on mebeverine | Treatment difference | p-value |
|---|---|---|---|---|
| 1 | 67 (21%) | 70 (23%) | - 2% | 0.552 |
| 2 | 129 (40%) | 98 (32%) | 8.2% | 0.035 |
| 3 | 143 (45%) | 107 (35%) | 9.6% | 0.013 |

3. Secondary measure: Sense of urgency (ITT population)

The proportion of days that patients experienced a sense of urgency decreased in both alosetron and in mebeverine groups, but significantly more in the former. The following Reviewer's Table is from the sponsor's Table 11.1.

Reviewer's Table 5. Sense of Urgency - Proportion of days symptoms experienced by month

| Time period | Alosetron % days | Mebeverine % days | p-value |
|---|---|---|---|
| Baseline, Mean<br>Median | 66.9<br>71.4 | 67.8<br>73.3 | |
| Month 1, Mean<br>Median | 46.1<br>40.0 | 54.5<br>50.0 | <0.001 |
| Month 2, Mean<br>Median | 39.5<br>33.3 | 50.4<br>46.6 | <0.001 |
| Month 3, Mean<br>Median | 38.4<br>29.4 | 47.7<br>41.7 | <0.001 |
| Weeks 13 - 16 (post-Treatment), Mean/Median | 44.8/40.0<br>49.9/50.0<br>49.4/50.0<br>50.1/50.0 | 47.2/40.4<br>47.8/42.9<br>50.3/50.0<br>51.2/50.0 | 0.44<br>0.28<br>0.83<br>0.85 |

4. Secondary measure: Stool consistency (ITT population)

The median stool consistency at baseline was 3.40 in the alosetron group and 3.44 in the mebeverine group (scoring: 2=hard, 3=formed, 4=loose). Significant firming of stool occurred in the alosetron group: from 3.40 to 2.57 at month 3; less so in the mebeverine group: from 3.44 to 3.14, $p<0.001$ (Table 11.11).

5. Secondary measure: Stool frequency (ITT population)

The median of the subjects' mean daily stool frequency at baseline was 2.36 in the alosetron group and 2.35 in the mebeverine group. After 3 months of treatment, these values decreased to 1.63 in the alosetron group and to 1.95 in the mebeverine group (Table 11.17 and p.61).

6. Secondary measure: Sense of incomplete evacuation (ITT population)

At baseline about 77% of subjects in both groups had a sense of incomplete evacuation. After 3 months of treatment the extent of improvement in each group was **not** statistically significant.

7. Secondary measure: Percentage of days with bloating (ITT population)

The median of the subjects' mean percentage days with bloating at baseline was 92% in the alosetron group and 89% in the mebeverine group. The slight improvement seen during weeks 5 - 12 was **not** statistically different from baseline.

8. Secondary measure: SCL-90R

**No** evidence of any effect by either treatment on global indices of psychological distress.

9. Health outcomes measures

Treatment with alosetron was associated with greater improvement in quality of life, as measured by IBSQOL, as compared to treatment with mebeverine. Social functioning, energy, mental health, and food scales showed improvements that were statistically significant at the 0.05 level. The improvements in the sleep scale and in social functioning scale were at borderline significance (p=0.083).

## G. Safety assessment:

1. Deaths - none

2. Serious Adverse Events

During the Treatment Phase, 10 of the subjects in the alosetron group experienced a total of 15 serous adverse events (SAEs). Two of these (**erosive gastritis** and **sigmoiditis**) were considered to be drug-related by the investigators. All of the SAEs are shown in the following Reviewer's Table from information in Listing 13.

Reviewer's Table 5. Non-Fatal Serious Adverse Events in the Alosetron Group

| Investigator# Subj.# | Age/ Wt(kg) | Adverse event | Time since 1st dose/ last dose | Maximum intensity | Withdrawal/ relationship to drug? |
|---|---|---|---|---|---|
| 10277-725 | 46/50.3 | Diarrhea,vomiting, Rx w/ fundoplication | 10 days | Moderate | No/no |
| 10277-726 | 53/73.0 | **Erosive gastritis** | 8 days | Severe | **Yes/yes** |
| 34701-981 | 55/83.0 | Arthritis, joint surgery | 77 days | Mild | No/no |
| 38068-1644 | 53/55.4 | nausea, vomiting | 78 days | Severe | No/no |
| 38853-1509 | 47/ 82.0 | exacerbation of reflux esophagitis | 39 days | Moderate | Yes/no |
| 46947-1186 | 67/70.0 | acute gastroenteritis | 101 d./16 d. | Moderate | N/A /no |
| 49851-1702 | 42/74.0 | **Colitis (sigmoiditis), diverticuli, hypo-natremia, seizures** | 47 days | Moderate | No/**yes** |
| 50293-1316 | 40/66.5 | Neck pain | 83 days | Severe | No/no |
| 51781-442 | 62/67.0 | Seizures | 85 d./1d. | Severe | N/A/no |
| 54489-2272 | 27/65.0 | Vertebral a. dissection | 82 days | Severe | Yes/no |

*Reviewer's Comments:*

*Case 10277-726 was that of a 73 y.o. who had been receiving long-term ibuprofen and paracetamol for back pain and treatment of 7 months of dyspepsia. After starting on alosetron patient also started on a one-week course of fluconazole. A week later her abdominal pain worsened and patient was found to have erosive gastritis. The investigator thought that abdominal pain may have possibly been worsened by alosetron. This Reviewer agrees, but thinks that the main culprits were ibuprofen and fluconazole.*

*Case 38068-1644 was that of a 53 y.o. had a history of nausea and vomiting after surgery for disc hernia. After 11 weeks of alosetron therapy the patient experienced a severe worsening of nausea and vomiting, was hospitalized, and treated. The symptoms resolved within 5-6 hours, and patient was discharged. The investigator thought symptoms were not related to alosetron. This Reviewer agrees.*

*Case 38853-1509 was that of a 47 y.o. who was receiving concurrent medications for anxiety, hypertension, palpitations and reflux esophagitis. After 39 days of alosetron therapy, patient had an acute onset of dyspnea and chest pain. She was found to be hypoxic. Pulmonary embolism was ruled out on the basis of a normal lung scan and normal ultrasonography of the right leg. The investigator diagnosed an exacerbation of reflux esophagitis that was not related to alosetron. This Reviewer thinks that pulmonary embolism was not adequately ruled out, but agrees that the episode is not related to alosetron.*

*Case 46947-1186 was that of a 67 y.o., who 16 days after completing the 12 weeks of alosetron therapy was hospitalized with abdominal pain, vomiting, and diarrhea. She was diagnosed with acute gastroenteritis, and recovered with treatment. No relationship to alosetron.*

*Case 49851-1702 was that of 42 y.o. who 7 weeks after the start of alosetron was hospitalized with "sigmoiditis" (symptoms were not described), was treated with metronidazole and co-trimoxazole and was discharged after 3 days. The following day patient was readmitted with anorexia and malaise. She was found to be hyponatremic (120mmol/L) and had seizures. Patient recovered after treatment with fluids and benzodiazepenes. Colonoscopy revealed diverticulae, but there are no comments as to the cause of "sigmoiditis". Patient recovered from sigmoiditis within one week of onset. The investigator thought there was no relationship of the above events to alosetron. This Reviewer is uncertain because of insufficient information. The hyponatremia and seizures suggest that "sigmoiditis" caused diarrhea and dehydration. Was there bleeding? Was the investigator looking for ischemic colitis? Were diverticuli the culprit or an incidental finding? Diverticulitis is not the stated diagnosis.*

*Case 54489-2272 was that of a 27 y.o. who 12 after starting alosetron had an episode of nausea and vomiting. Two days later, after presenting with headache and diplopia, she was diagnosed to have vertebral artery dissection. Her condition resolved one week later.*

Three of 12 SAEs in 8 patients in the mebeverine group were considered to be drug-related by the investigators (two cases of abdominal pain/discomfort, and one of constipation). The other events were: acute gastroenteritis, cancer of the sigmoid colon, acute appendicitis, constipation, anal burning, oral burning, post-menopausal bleeding, peripheral arterial disease, and pneumonia.

3. Patient withdrawals due to adverse events in the alosetron group

By far the most common adverse event in the alosetron group leading to premature withdrawal from the study was **constipation.** Twenty-three patients of the 42 patients (55%) who withdrew did so because of constipation. (Only 3 patients of 30 patients (10%) in the mebeverine group withdrew prematurely because of constipation). The following Table provides some characteristics of the 22 out of 23 alosetron-treated patients who withdrew prematurely because of constipation.

Reviewer's Table 7. Characteristics of alosetron-treated patients who withdrew prematurely because of constipation

| | |
|---|---|
| Age, mean, (range) | 51.2 (22 - 70) years |
| Weight | 61.4 (49.6 - 81) kg |
| Time of exposure to alosetron | 11 patients for 1 - 5 days<br>7 patients for 6 - 14 days<br>1 patient each for 17, 21, 31 and 43 days |
| Time to resolution of constipation | In 7 patients in 4 - 7 days<br>In 3 patients in 8 - 13 days<br>In 3 patients in 14 days<br>In one each in 23, 35, 37, and 50 days<br>In 5 patients not resolved at the time of report |
| IBS type | 15/231 (6.5%) diarrhea-predominant<br>7/74 (9.5%) alternating constipation and diarrhea |

The age distribution in these patients was not very different than in the entire subject population (mean age 44.2 years, range 17 - 75). The subjects who withdrew prematurely had a mean weight of 67.5 kg, range 40 – 118 kg. Thus, neither elderly nor lighter individuals predominated in this group. One-half of the subjects withdrew within 5 days, some within 1-2 days, suggesting poor tolerance of the drug by some subjects.

There were no predominant adverse events leading to premature withdrawals in the mebeverine group. They affected less than 1% of the study population (1-3 patients).

4. Drug-related adverse events

Forty percent of the alosetron-treated patients experienced drug-related adverse events. The most common ones are shown in Reviewer's Table below (data from the sponsor's Supporting Table 14.1). Drug-related adverse events were less frequent in the mebeverine group (27%). **Constipation** was the most common in the alosetron group, experienced by 21% of all patients. Constipation occurred slightly more frequently in patients with alternating type of IBS (25%) than in patients with diarrhea-predominant IBS (21%). Constipation was a rare event in the mebeverine group, experienced by 2% of all patients. Headaches and nausea affected about 7%; malaise and fatigue, 3%; skin rashes, 2%.

Reviewer's Table 8. Alosetron-related adverse events

| Adverse event | No. of adverse events | No. of patients with adverse event | Percent of all patients (n=318) |
|---|---|---|---|
| Total | 276 | 128 | 40% |
| Gastrointestinal | 169 | 105 | 33% |
| Constipation | 79 | 66 | 21% |
| Abdominal discomfort/pain & GI discomfort/pain | 32 | 27 | 9% |
| Nausea | 17 | 15 | 5% |
| Dyspepsia | 9 | 9 | 3% |
| Vomiting | 6 | 6 | 2% |
| Abdominal distension | 9 | 9 | 3% |
| Neurological | 27 | 22 | 7% |
| Headaches | 17 | 15 | 5% |
| Non-specific | 18 | 17 | 5% |
| Malaise & fatigue | 12 | 11 | 3% |
| Skin | 21 | 17 | 5% |
| Ear, Nose & Throat | 7 | 5 | 2% |
| Musculoskeletal | 8 | 5 | 2% |

There were 3 patients with rectal bleeding and diarrhea, who may have had ischemic colitis (in addition to the patient with "sigmoiditis" described above). Case Report Forms on these patients were submitted by the sponsor on December 20, 2001. Patient #2175, a 32 year old woman with diarrhea-predominant IBS, started having rectal bleeding and diarrhea 3 days after completing the 12-week trial with alosetron. There was no follow-up. Patient #2240, a 33 year old woman with diarrhea-predominant IBS had rectal bleeding for 2 days 21 days after completing the 12-week trial with alosetron. Patient #2315, a 54 year old woman had abdominal pain, constipation, rectal bleeding and anal soreness for 5 days 6 days after starting alosetron. She withdrew from the trial.

5. All adverse events

There were 620 adverse events in 220 subjects in the alosetron group; 69% of subjects experienced an adverse event. There were 529 adverse events in 196 subjects in the mebeverine group; 64% of subjects experienced an adverse event. The most common ones are shown in sponsor's table below (data from Supporting Table 14.0).

**Most Common Treatment- Emergent Adverse Events (≥5% of subjects)**

| | | Alosetron 1mg bd (N=318) | | Mebeverine 135mg tds (N=304) | |
|---|---|---|---|---|---|
| Body System | Adverse Event | No. of Events | No. (%) of Subjects | No. of Events | No. (%) of Subjects |
| Any Body System | Any Event | 620 | 220 (69%) | 529 | 196 (64%) |
| Gastrointestinal | Constipation | 87 | 71 (22%) | 9 | 8 (3%) |
| | Nausea | 27 | 23 (7%) | 29 | 26 (9%) |
| | Abdominal discomfort & pain | 35 | 29 (9%) | 18 | 17 (6%) |
| | Diarrhoea | 16 | 16 (5%) | 14 | 13 (4%) |
| | Vomiting | 23 | 17 (5%) | 10 | 9 (3%) |
| Neurology | Headaches | 39 | 31 (10%) | 52 | 44 (14%) |
| Ear, Nose & Throat (ENT) | Viral ENT infections | 8 | 7 (2%) | 20 | 19 (6%) |
| Non-Site Specific | Malaise & Fatigue | 20 | 19 (6%) | 17 | 15 (5%) |
| Lower Respiratory | Viral respiratory infection | 26 | 24 (8%) | 19 | 17 (6%) |
| Musculoskeletal | Musculoskeletal pain | 10 | 10 (3%) | 21 | 18 (6%) |

Source: Table 14.0

In contrast to the alosetron group, the mebeverine group had only few instances of constipation and, as a result, had less than half the number of adverse events related to the gastrointestinal tract (26 events/100 ITT subjects vs. 59 events/100 ITT subjects in the alosetron group). There were more patients with headaches, viral ENT infections, and musculoskeletal pain. The latter events may be unrelated to the medication. There was one case of GI hemorrhage and one case of abnormal liver function tests (two such cases in the alosetron group).

## H. Statistical methods:

1. Sample size calculation

The sample size for this study was determined on the basis of anticipated differences between treatment groups in the primary measure (the proportion of female subjects with adequate relief of abdominal pain and discomfort on at least 2 weeks per month) plus an allowance for dropouts. The proportions of responding patients were expected to be at least 55% in the alosetron group and

about 40% in the mebeverine group (*Reviewer's note*: these estimates are based on the responses in the pivotal studies to alosetron and to placebo, respectively. It is difficult to estimate a mebeverine response rate from published data.)

The sample size was chosen with 90% power at the $\alpha$=0.05 level of significance. The number of subjects per treatment group necessary to detect a 15% difference between alosetron and mebeverine was N=244 per group. To allow for a 20% drop out rate (as in the pivotal studies), a target sample size of N=600 subjects was chosen (N=300 per treatment group.)

2. Interim analyses - none performed.

3. Analysis populations

Four populations were analyzed: total ITT (intent-to-treat, included all randomized subjects), diarrhea-predominant ITT, alternating pattern ITT, and the safety population (all randomized subjects who took at least one dose of study medication).

Subgroup analyses were carried out for age (above and below 65), race (white/ non-white), hormone use (yes/no), and childbearing potential (sterile/postmenopausal/potential childbearer).

Prematurely discontinued subjects and missing data were handled by the last observation carried forward (LOCF) principle.

## I. Ethical issues

1. Independent Ethics Committees or Institutional Review Boards - listed in the Appendix for each participating institution.

2. Informed consent - a signed informed consent form was obtained from each subject prior to initiation of procedures and enrolment in the study.

3. Conduct of the study - in accordance with Good Practice Guidelines and the Declaration of Helsinki, as amended in 1996.

4. Investigators and Study Administration

There was one Coordinating Investigator for the study. There was no Steering Committee. There was no independent Data Safety Monitoring Board. Advice was sought from the Glaxo Wellcome International IBS Advisory Board. The study was conducted by Glaxo Wellcome r

The randomization code was generated by the European Clinical Statistics Department, Glaxo Wellcome. Sealed individual treatment code envelopes were kept by all investigators.

5. Management of Centers

For the validity of statistical tests of treatment-by-investigator interaction, and to avoid the effective loss of centers with small numbers of subjects who had the same response, centers were pooled into clusters by geographical proximity. The minimum number of subjects forming a cluster was 20. The following geographical clusters were identified for pooling centers prior to unblinding:

| | | |
|---|---|---|
| UK, Ireland | Sweden | Denmark, Iceland, Norway |
| Australia, New Zealand | Germany, Switzerland, Israel | Belgium |
| South Africa | Spain | Netherlands |

6. Audits

Seven audits were carried out (Protocol, CRF, and 5 investigator sites) by Glaxo Wellcome World-wide Clinical Compliance Department or independent contractors between 2 July 1997 and 19 July 1999.

7. Financial disclosures

Patients were compensated according to the national compensation scheme of the country in which the study was performed, and Glaxo Wellcome Compensation Guidelines.

Financial disclosures by the investigators were not included in this submission and may be submitted in the entire 40-study submission.

**Reviewer's Summary and Comments**

1. The protocol for study S3BB3001 was the same as the protocols for the two pivotal trials S3BA3001 and S3BA3002, except that S3BB3001 had an active control arm, mebeverine, rather than placebo.

2. About 20% of study subjects withdrew prematurely from both arms of the study. Most withdrew because of adverse events. Constipation was the main reason for premature withdrawals in the alosetron group. There was no predominant adverse event leading to premature withdrawals in the mebeverine group. Lack of efficacy as a cause of withdrawal was more common in the mebeverine group than in the alosetron group.

3. There were 2 serious adverse events (SAEs) in the alosetron group that were possibly drug-related, one of erosive gastritis and one of colitis ("sigmoiditis") of uncertain pathogenesis. There were **no deaths, no diagnosed cases of**

**ischemic colitis, no cases of constipation requiring surgery, no cases of peritonitis**, and **no cases of perforation of the colon**. There were 3 cases of rectal bleeding and diarrhea that were not worked-up and could have been cases of ischemic colitis. In the mebeverine group there were 3 possibly drug-related SAEs: two cases of abdominal pain/discomfort and one case of constipation.

4. Constipation stood out as the most frequent adverse event in the alosetron group (87 events in 22% of subjects) in contrast to being a rare event in the mebeverine group (9 events in 3% of subjects). The high incidence of constipation in alosetron-treated patients is a consistent finding (25.9% of patients in S3BA3001, 29.8% in S3BA3002, and 31.0% in S3BA3003).

5. The frequencies of other adverse events were not significantly different between the alosetron and the mebeverine groups.

6. Alosetron was more effective than mebeverine in providing relief of abdominal pain and discomfort. Statistically significant difference was demonstrated between weeks 4 and 12, with a maximum therapeutic advantage of 13% (total ITT population). Among the subjects who completed the 12 week course of treatment the therapeutic advantage (adequate relief during at least 6 of the 12 weeks) was 16%. In the two pivotal trials the therapeutic advantage of alosetron vs. placebo was 15% and 16% in the diarrhea-predominant IBS and not significant in the alternating type of IBS. The therapeutic advantage of alosetron disappeared upon discontinuation of alosetron both in the trial under review and in the two pivotal trials.

7. Pain and discomfort-free days were more frequent in alosetron-treated than in mebeverine-treated patients. There were significantly fewer days with a sense of urgency in the alosetron-treated group than in the mebeverine-treated group. Stool frequency and stool looseness decreased more in alosetron-treated group than in mebeverine-treated group. Sense of incomplete evacuation and of bloating did not improve significantly with either medication.

8. Quality of life scores improved to a greater extent in the alosetron group than in the mebeverine group. SCL-90R scores did not change significantly with either medication.

**Reviewer's Conclusions**

1. The safety profile of alosetron in study S3BB3001 is very similar to that in the pivotal trials presented in the original NDA. Severe adverse events that occurred after the marketing of alosetron were not seen in this study. This discrepancy could be due to the differences between the selected population of the study, and the unselected, and possibly inappropriately treated, general population.

2. Alosetron was more effective than mebeverine in improving IBS symptoms. This increased effectiveness is offset by the poorer safety profile. The extent of improvement in the mebeverine group was about the same as in the placebo groups in the placebo-controlled pivotal trials. However, it is not possible to evaluate the effectiveness of mebeverine without an appropriately large, placebo-controlled, randomized trial.

## Addenda: Adverse Events Listings for Composite Summary of the Supplement

**Summary of Patients with Rectal Bleeding, Bloody Stools and Diarrhea with Abdominal/GI Pain Occurring in Association with Alosetron Usage in Clinical Studies**

| Patient number | Age | Time to onset | Concomitant medications | Adverse event and Outcome |
|---|---|---|---|---|
| 2175 | 32 | 84 on alosetron + 3 days off | Inderal, Valium, Panadol | Moderate rectal bleeding, moderate diarrhea. No follow-up. |
| 2315 | 54 | 6 days | | Constipation, abdominal pain, rectal bleeding, anal soreness. Resoved in 4 days. |
| 2240 | 33 | 84 on alosetron + 21 days off | Naproxen | Rectal bleeding for 2 days. Resolved. |

**Summary of Patients with Miscellaneous SAEs Occurring in Association with Alosetron Usage in Clinical Studies**

| Patient number | Age | Time to onset | Hospitalization | Surgical procedure, Transfusion?, Outcome |
|---|---|---|---|---|
| 1702 | 42 | 49 | Yes | Sigmoiditis, dehydration, hyponatremia, seizures. Colonoscopy: diverticuli. Recovered |

cc:

HFD-180
HFD-180/V. Raczkowski
HFD-180/H. Gallo-Torres
HFD-180/E. Kaminskas
HFD-180/T. Permutt
HFD-180/J. Choudary
HFD-180/L. Zhou
HFD-180/S. Doddapaneni
HFD-180/P/ Levine

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

/s/

Edvardas Kaminskas
2/8/02 01:54:02 PM
MEDICAL OFFICER

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MEDICAL OFFICER

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PID# D020044

DATE: March 26, 2002

FROM: Toni Piazza-Hepp, Pharm.D., Associate Director

THROUGH: Julie Beitz, M.D., Director
Division of Drug Risk Evaluation (DDRE)
Office of Drug Safety (ODS) HFD-400

TO: Victor Raczkowski, M.D., Acting Director
Division of Gastrointestinal and Hematologic Drug Products, HFD-180

SUBJECT: ALOSETRON (LOTRONEX®): REVIEW OF RISK MANAGEMENT PLAN

## EXECUTIVE SUMMARY

Alosetron (Lotronex®) was approved Feb 9, 2000. Based on information from the NDA database and post-marketing reports, there is a risk of ischemic colitis (IC) as well as a risk of complications of constipation (CC) in Lotronex users. Assessment of the risks and benefits eventually led to voluntary market suspension of Lotronex on November 28, 2000. Subsequent numerous communications to both the FDA and GSK from *stakeholders* (patients) has led to a supplemental NDA and reconsideration of the marketing status of the drug.

Following a model proposed in the May 1999 Report to the Commissioner by The Task Force on Risk Management, options for a Lotronex risk management plan (RMP) are discussed. These risk management options will be presented and discussed among *stakeholders* at the April 23, 2002 Advisory Committee meeting. The sponsor has proposed a plan whereby Lotronex would be marketed under the provisions of the Subpart H regulation. A risk management strategy will be *selected* and *implemented* based on input from the April 23 Advisory Committee along with negotiations between GSK and the FDA.

This document presents the features of current restricted distribution plans, advantages and disadvantages of selected plan features, a description and critique of the GlaxoSmithKline (GSK) proposed plan and four plan options ranging from more restrictive to less restrictive. The GSK plan to *evaluate results* is also briefly addressed.

Risk factors for the development of ischemic colitis have not been identified, so we expect reporting of this event to continue. The risk management plan should increase awareness that Lotronex should be stopped if constipation occurs, however, we did have reports of complications of constipation where the patients did not previously experience constipation symptoms. Health care professionals should be strongly encouraged to report such events.

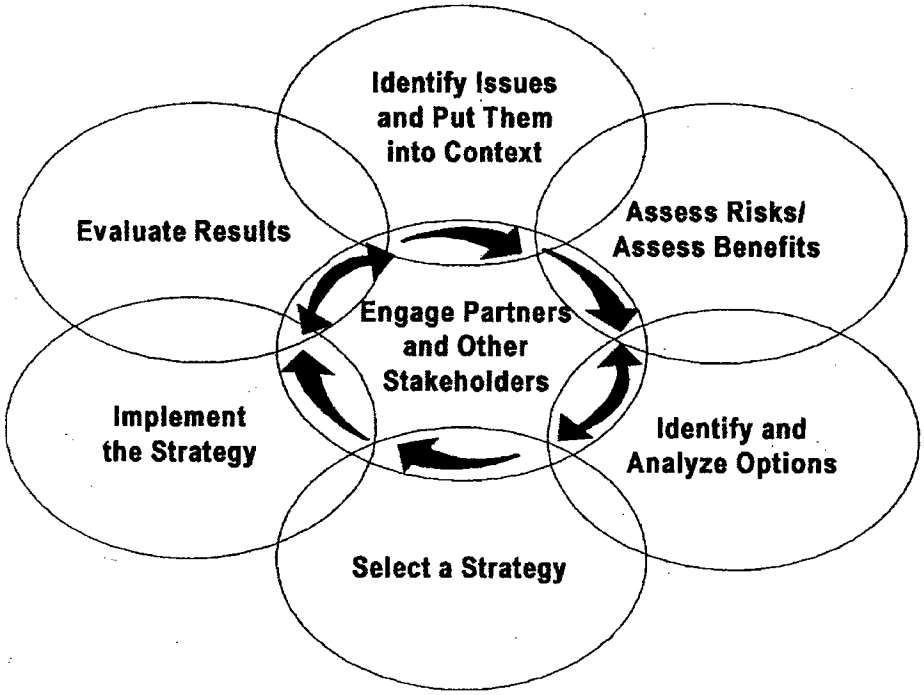
Compliance to the elements of the plan will probably be the most important measure of plan success. GSK should propose benchmarks for success of the risk management plan.

ODS recommends starting out with a more conservative (restrictive) approach in order to meet desired goals of the program, with the potential for modification in the future at a predetermined time point (e.g. one year). This would encourage the sponsor to vigorously implement and assess the risk management plan.

INTRODUCTION

The Food and Drug Administration is involved with managing the risks from medical products as part of our mission to ensure safety and effectiveness. In May 1999 The Task Force on Risk Management issued a Report to the Commissioner[1] addressing FDA's role in "making sure that products are developed, tested, manufactured, labeled, prescribed, dispensed, and used in a way that maximizes benefit and minimizes risk". The report evaluated existing risk management processes in the FDA and made a number of recommendations. One of the key recommendations was the need to apply a "systems framework to medical product risk management". A risk management model was subsequently proposed and is illustrated below. FDA activities were considered consistent with those presented in the model, however, the activities were assessed as fragmented, rather than part of an integrated systems effort. The report also addressed the need to engage healthcare partners and other stakeholders ("risk confrontation") as "a key process that needs to be part of any new risk management framework".

## Proposed Risk Management Model




1 *Managing the risks from medical product use; creating a risk management framework, Report to the Commissioner from the Task Force on Risk Management, FDA, May 1999. The full report may be found at: http://www.fda.gov/oc/tfrm/riskmanagement.pdf*

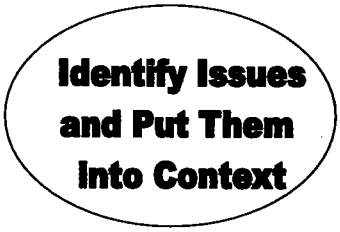
## FEATURES OF CURRENT RISK MANAGEMENT (RESTRICTED DISTRIBUTION) PROGRAMS

Risk management programs should thus be designed with the goal of optimizing benefits and minimizing risks while involving stakeholders in each step of the model. Features of individual restricted distribution plans related to safety issues currently in effect are included in this document as Attachment A (for the drugs approved under Subpart H) and Attachment B (for drugs not approved under Subpart H). Although no two plans are exactly alike, there are selected features common to various plans. For example, an **educational component** is a part of all plans, although these vary considerably, from professional and patient labeling (including MedGuides), to CME programs, website resources, videos and more. Education of stakeholders is essential to describe the program and to communicate risk vs. benefit information. Educational pieces could also be used to encourage enrollment in surveys, educate health care professionals to report adverse events and more. Some advantages and disadvantages of other selected plan features are highlighted in the table below.

| SELECTED FEATURES OF RESTRICTED DISTRIBUTION PROGRAMS | | |
|---|---|---|
| | **ADVANTAGES** | **DISADVANTAGES** |
| **REGISTRATION: PHYSICIAN** | •PROVIDES FOR REQUIRED EDUCATION ENHANCING PLAN-COMPLIANT PRESCRIBING<br>•TARGETS GROUP FOR SURVEYS, CHART AUDITS, EDUCATION, CAPTURING ADVERSE EVENT DATA | •BURDEN |
| **REGISTRATION: PATIENT** | •PROVIDES DENOMINATOR<br>•PROVIDES INFORMED PATIENT<br>•TARGETS GROUP FOR SURVEYS, EDUCATION | •PATIENT PRIVACY<br>•BURDEN |
| **REGISTRATION: PHARMACIST** | •PROVIDES FOR REQUIRED EDUCATION ENHANCING PLAN-COMPLIANT DISPENSING<br>•TARGETS GROUP FOR SURVEYS, PRESCRIPTION AUDITS, EDUCATION | •BURDEN |
| **PRESCRIBING RESTRICTIONS AND DISPENSING RESTRICTIONS (GENERAL)** | •LIMITS ACCESS TO ONLY PATIENTS WHO QUALIFY UNDER CONDITIONS OF THE PLAN | •DECREASED DRUG ACCESS; MAY ENCOURAGE ALTERNATE SOURCING<br>•BURDEN |
| **AUTHORIZED PRESCRIBER CHECK MECHANISM** | •ALLOWS RPH TO CONFIRM MD AS QUALIFIED/REGISTERED PRESCRIBER UNDER RMP | •PRACTICALITY OF PHARMACIST AS GATEKEEPER<br>•BURDEN |
| **LIMITED SUPPLY / NO REFILLS** | •LIMITS DRUG SUPPLY, ENSURING PT RETURNS FOR MD FOLLOWUP FREQUENTLY AND REGULARLY | |
| **SPECIAL PACKAGING** | •CAN INCLUDE LIMITED DRUG SUPPLY<br>•CAN PROVIDE SPECIAL SAFETY FEATURES<br>•MEANS FOR REINFORCING MESSAGES AND INSERTS SUCH AS MEDGUIDE, SURVEYS, ETC. | |

| | | |
|---|---|---|
| **PATIENT MONITORING BY PHYSICIANS (REGULAR INTERVALS)** | •ASSURES PATIENT FOLLOWUP<br>•OPPORTUNITY FOR REINFORCING EDUCATION<br>•OPPORTUNITY FOR OBTAINING ADVERSE EVENT INFORMATION | •ADDITIONAL DOCTORS VISITS OR OTHER MONITORING MEANS<br>•BURDEN |
| **SURVEYS VOLUNTARY** | •MEASURE PLAN COMPLIANCE | •INCOMPLETE DATA<br>•REPRESENTATIVENESS QUESTION<br>•BURDEN |
| **SURVEYS MANDATORY** | •MEASURE PLAN COMPLIANCE<br>•COMPLETE DATA | •BURDEN |

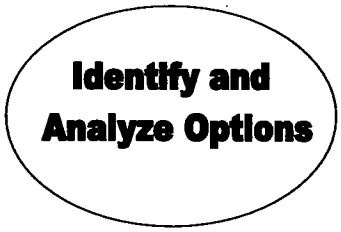
**LOTRONEX RISK MANAGEMENT PLAN**







Alosetron (Lotronex®) was approved Feb 9, 2000. Based on information from the NDA database and post-marketing reports, there is a risk of ischemic colitis (IC) as well as a risk of complications of constipation (CC) in Lotronex users. These risks have been discussed in previous reviews and will not be further addressed in this document. Assessment of the risks and benefits eventually led to voluntary market suspension of Lotronex on November 28, 2000. Subsequent numerous communications to both the FDA and GSK from *stakeholders* (patients) has led to submission of a supplemental new drug application (sNDA) and reconsideration of the marketing status of the drug.




The focus of the current consult is to evaluate the risk management plan (RMP) for alosetron (Lotronex) that was submitted to the FDA by GSK December 2001 and to present options to be considered for the RMP. The GSK proposal has some positive features and serves as a good starting point for the additional options being proposed by ODS. These risk management options will be presented and discussed among *stakeholders* at the April 23, 2002 Advisory Committee meeting. The sponsor has proposed a plan whereby Lotronex would be restricted under the provisions of the Subpart H regulation, which is reproduced below.

**21CFR 314 Subpart H: Accelerated approval for serious or life-threatening illnesses**

**314.520 Restricted - Approval with restrictions to assure safe use.**

(a) If FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to assure safe use of the drug product, such as:

(1) Distribution restricted to certain facilities or physicians with special training or experience;
(2) Distribution conditioned on the performance of specified medical procedures.
(3) The limitations imposed will be commensurate with the specific safety concerns presented by the drug product.

---

Under 314.530 FDA may withdraw approval, following a hearing, if it is demonstrated that postmarketing restrictions are inadequate to assure safe use or if the applicant fails to adhere to the agreed upon postmarketing restrictions under Subpart H.

Subpart H applies to drug products "treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments". The regulatory definition of serious under 312.32 and 314.80, which relate to premarketing and postmarketing safety reporting, respectively, includes any of the following outcomes: death, initial or prolonged hospitalization, life-threatening, significant disability/incapacity, congenital anomaly, or "important medical event". Disability is further defined under 314.80 as "a substantial disruption of a person's ability to conduct normal life functions".

The Lotronex plan as submitted by GSK is presented below. Included in the table are the features of the GSK proposed plan along with ODS suggested points to consider at each step (step numbers have been added by ODS for identification purposes). These points to consider are intended to stimulate discussion relating to a range of plan options, which will be presented later.

| **LOTRONEX RISK MANAGEMENT PLAN PROPOSED DECEMBER 2001** | |
|---|---|
| GSK PLAN: PROCESS | ODS SUGGESTED POINTS TO CONSIDER |
| STEP 1<br>✎MD receives patient-physician agreement kit (special stickers come with kit) upon request via 1-800 number or via sales reps<br>✎MD education via written materials: Dear Healthcare professional letter, other materials in pt-MD kit, via GSK website, from sales force | • Limit to gastroenterologists or physicians with significant gastroenterology training and experience or CME "certified" physicians<br>• Register all physicians<br>• GSK distribution of stickers and kits only to registered physicians |
| STEP 2<br>✎MD selects appropriate patient<br>(Women with DP-IBS who have failed traditional therapy) | • Subpart H by definition: "serious or life-threatening disease"- limit to serious / debilitating IBS (to be defined)<br>• No treatment of "presumptive" or "interim" IBS diagnoses<br>• Define "traditional therapy" |

| | |
|---|---|
| STEP 3<br>✎MD signs attestation statement on "patient-physician agreement document"<br>(of knowledge and experience in diagnosis and treatment of IBS and ability to diagnose and manage IC and CC) | • Limit to gastroenterologists or or physicians with significant gastroenterology training and experience or CME "certified" physicians<br>• Add MD agreement to report ischemic colitis and complications of constipation |
| STEP 4<br>✎Patient signs "patient-physician agreement document"<br>✎Pt education via prescriber with review of benefits and risks of Lotronex | • Regular pt. followup / monitoring by MDs missing (pt-MD agreement specifies pt. must initiate contact with MD if problems)<br>• Define "constipation"<br>• Register all patients |
| STEP 5<br>✎Pt-MD agreement document: copy to pt. and placed in medical record | • Register all physicians with GSK |
| STEP 6<br>✎MD affixes special sticker to "initial" prescription (no samples)<br>✎New labeling recommends first 4 weeks at 1mg daily then maintain that dose or increase to 1mg bid only if not responsive to 1mg daily | • Allow no refills (new Rx with each fill)<br>• Current plan allows for any MD to obtain sticker; could bypass all previous steps<br>• Sticker only on "initial" Rx; thus legitimate Rxs (refill) exist without stickers, diminishing sticker utlity |
| STEP 7<br>✎Any pharmacy may dispense Lotronex IF: special sticker is affixed to *initial* prescription<br>✎Pharmacist education via Dear Healthcare Professional letter plus special attachment | • All Rxs (new+refill) with sticker ("no sticker-no drug")<br>• No telephone or faxed Rxs<br>• Inpatient allowance of no sticker while in hospital if ordered by gastroenterologist<br>• Consider other means besides sticker method to check for authorized prescription |
| STEP 8<br>✎Lotronex dispensed in special carton with 30 tab supply plus MedGuide | • Reinforcing educational message (not to dispense unless sticker on Rx) on packaging<br>• Assure that existing supplies of Lotronex (old packaging) do not remain in pharmacies |
| STEP 9<br>✎Patient receives Lotronex supply | • Regular pt. Followup / monitoring by MDs is missing (pt-MD agreement specifies pt. must initiate contact with MD if problems)<br>• MD agreement to report ADRS: IC / CC |
| STEP 10<br>✎If Eckerd pharmacy, patient gets contacted within a week by Eckerd employee and invited to participate in survey by Slone Epidemiology Unit (SEU). Eckerd has 1700 pharmacies across the country, according to GSK submission.<br>✎Pt gets five dollars to participate in survey | • GSK must demonstrate survey representativeness<br>• Alternatively register all pts who would then participate in survey **or** MD solicit pt to participate in survey **or** include survey form in packaging |
| SPONSOR ADR REPORTING: IC and CC will be reported expeditiously (15-day reports) | |
| ADVERTISING: Preapproval of promotional activities, no direct to consumer (DTC) ads | |

GSK has proposed the use of stickers to provide a check mechanism for authorized

prescriptions. In the current version of the plan, any physician can obtain stickers and essentially bypass all the previous steps (such as the patient-physician agreement). There are no RMPs currently in place that use stickers; the new Accutane® program will do so, but has not begun as of this writing. Other mechanisms to authorize prescriptions should be considered; for example, registered physicians could be given an authorization number which could be written on the prescription (or have a place on the sticker for this with a 1-800 number for pharmacists to call for verification), there could be a listing of authorized physicians that pharmacists could access, or the patient could be required to bring a copy of the patient-physician agreement with the prescription.

The following general comments regarding the proposed RMP were shared with GSK at a meeting with the FDA on 2/25/02.

**Lotronex Risk Management Plan: General Comments 2/25/02**

- Subpart H: [21 CFR 314.520] Restricted - Approval with restrictions to assure safe use
  - -Applies to "serious or life-threatening disease"
    - •discuss limiting to "disabling" IBS (definition/guidelines needed)
    - •discuss need to rule out other GI pathology prior to starting Lotronex
  - -FDA may withdraw approval if it is demonstrated that postmarketing restrictions are inadequate to assure safe use or if applicant fails to adhere to postmarketing restrictions
    - •discuss adequacy or inadequacy of method(s) to measure adherence to restrictions: e.g. Eckerd Pharmacy / SEU plan expected to yield low sample size; probably inadequate to measure compliance to program/problems with representativeness
    - •consider registration of patients or other means to more widely distribute survey
- Monitoring of patients by physicians on a regular basis: completely missing from RMP
- Qualified MDs
  - -Consider need to limit to gastroenterologists
  - -Consider registration of MDs with GSK prior to receiving kit with stickers
- Discuss need for "no sticker-no drug" message: consider limited supply, no refills, no faxed or telephoned Rxs

## OPTIONS FOR A LOTRONEX RISK MANAGEMENT PLAN

Before options are entertained for any plan, goals of a program should be specified. It would be advantageous to identify the population who would receive the most benefit from the drug, identify risk factors for the development of serious adverse events (although there may be an absence of known risk factors), identify means whereby these risk factors could be avoided or heighten monitoring of patients with risk factors. Such risk factors can include but are not limited to drug interactions, symptoms, disease states and/or patient demographics. As stated previously, risk factors for the development of IC have not yet been identified in patients receiving Lotronex. Likewise, CC did occur in cases where the patients did not complain of constipation. Hence, the implementation of a RMP for Lotronex should not be expected to completely avoid these risks; rather the plan should aim more at selecting patients who will most benefit from the drug and monitoring these patients closely.

In the GSK submission, the stated goal of the Lotronex RMP "is to minimize the occurrence of adverse events resulting from avoidable risks and to mitigate the health consequences of adverse events that may occur." Further, it is stated that the plan design will "help ensure that LOTRONEX is prescribed only to appropriate, informed patients and to specifically address the risk issues of ischemic colitis and complications of constipation."

In a "Letter Regarding Lotronex" written by Janet Woodcock, M.D., CDER Director, December 18, 2000 (posted on the CDER website), goals of a Lotronex program are stated to include:

- safer use of Lotronex in appropriately informed patients
- continued access to Lotronex by severely affected IBS patients under closely monitored conditions
- continued clinical studies of the benefits and risks, and safe use of Lotronex

The following goals of a Lotronex RMP will be used for the purposes of discussing RMP options.

To assure access to Lotronex:
1) to informed, severely affected IBS patients
2) by informed, qualified physicians (prescribers)
3) with appropriate medical supervision
4) by informed pharmacists under a restricted distribution system
5) with auditing of plan effectiveness

There are a variety of ways that the Lotronex RMP could be designed; the table below presents some selected features and a range of plan options from more restrictive (column A) to less restrictive (column D). The plan could start out with a more conservative (restrictive) approach with the potential to be modified in the future. This would encourage the sponsor to vigorously implement and assess the RMP.

| | A | B | C | D<br>GSK PROPOSED PLAN |
|---|---|---|---|---|
| **MD REGISTRATION** | + | + | + | |
| **PT REGISTRATION** | + | + | | |
| **PHARMACIST REGISTRATION** | + | | | |
| **LIMIT TO GASTROENTER-OLOGISTS** | + | + | | |
| **LIMIT TO DEBILITATING DISEASE** | + | + | + | |
| **PT FOLLOWUP BY MDS** | + | + | + | |
| **AUTHORIZED PRESCRIBER CHECK MECHANISM** | + | + | + | ± |
| **LIMITED SUPPLY / NO REFILLS** | + | + | + | |
| **SPECIAL PACKAGING** | + | + | + | + |
| **AUDITING MECHANISM** | + | + | + | + |
| | | | | |
| **MEETS GOAL 1** | + | + | + | |
| **MEETS GOAL 2** | + | + | ± | ± |
| **MEETS GOAL 3** | + | + | + | |
| **MEETS GOAL 4** | + | ± | ± | ± |
| **MEETS GOAL 5** | + | + | ± | ± |

+ = feature included in the plan *or* meets the goal
± = may/may not be considered a feature of the plan *or* may/may not meet the goal
blank = not a feature of the plan *or* does not meet the goal




A risk management strategy will be *selected* and *implemented* based on input from the April 23 Advisory Committee along with negotiations between GSK and the FDA. GSK plans to meet quarterly with the FDA to review progress of the program.

The Lotronex GSK risk management plan does include a plan to *evaluate results*, which is an essential component of any plan. GSK plans a survey of patients using the experienced Slone Epidemiology Unit (SEU). The objectives are to describe patient characteristics, assess treatment appropriateness, assess risk and benefit awareness, examine use patterns and examine the occurrence of serious gastrointestinal adverse events. Patients are invited to participate if their Lotronex prescription is filled at an Eckerd pharmacy. Eckerd pharmacies represent an estimated 3% (1,700/55,000[2]) of U.S. chain and independent pharmacies. ODS has concerns whether the survey as planned will be representative of all Lotronex users. It is possible that the SEU survey via Eckerd pharmacies could be representative; however, the sponsor needs to show this. A UnitedHealthcare (UHC) database study of prescribing practices is also planned. Patients will be characterized by such factors as demographics, medical conditions (including duration of IBS diagnosis), and conditions and drugs contraindicative for Lotronex for the 6 months prior to a Lotronex prescription. Once a Lotronex prescription is dispensed, the patients will be followed for a one year period to evaluate Lotronex use patterns and dispensings of selected concomitant medications.

The usefulness of assessing post RMP adverse event reports must be considered. Again, risk factors for the development of IC have not been identified, so we expect reporting of this event to continue. The RMP should increase awareness that Lotronex should be stopped if constipation occurs, however, we did have reports of CC where the patients did not previously experience constipation symptoms. As GSK and the FDA receive these reports, we should determine (if possible) if the patients that did experience these adverse events complied with the required elements of the RMP. Health care professionals should be strongly encouraged to report such adverse events.

Compliance to the elements of the plan will probably be the most important measure of plan success. GSK should propose benchmarks for success of the RMP. These could include but are not limited to, level of patient participation in (and results of) the SEU survey, level of compliance with the use of stickers, level of compliance with MedGuide distribution, etc.

Further study is also planned; these studies are addressed elsewhere. These include epidemiologic studies evaluating the incidence of IC and severe constipation in Lotronex users, background incidence and risk factors for IC and severe constipation in IBS patients and four studies on optimal product use (dose titration, efficacy at lower dose, effect on work activity, etc.).

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2 *GSK sNDA states 1700 Eckerd pharmacies. National Community Pharmacists Association (www.ncpanet.org) states 55,011 total pharmacy stores in the U.S. (independent, chain, supermarket, mass merchandisers).*

## CONCLUSION

This document presents information on existing restricted distribution plans, describes and critiques the GSK Lotronex proposed plan and presents options to consider for the most appropriate Lotronex plan. ODS recommends starting out with a more conservative (restrictive) approach in order to meet desired goals of the program, with the potential for modification in the future at a predetermined time point (e.g. one year). This would encourage the sponsor to vigorously implement and assess the RMP.

Toni Piazza-Hepp, Pharm.D. 3/26/02

cc:

| | |
|---|---|
| NDA # | 21-107 |
| HFD-103 | Houn |
| HFD-180 | Raczkowski / Berrera / Gallo-Torres / Levine / Korvick |
| HFD-400 | Himmel / Seligman / Beitz / Piazza-Hepp / Corken / Green / Li / Brinker / Guinn / Trontell / Consult file |

**ATTACHMENT A : SELECTED FEATURES OF RESTRICTED DISTRIBUTION PROGRAMS UNDER SUBPART H**

| | **Fentanyl (Actiq®)** | **Thalidomide (Thalomid®)** | **Bosentan (Tracleer®)** | **Mifepristone (Mifeprex®)** |
|---|---|---|---|---|
| Approval date and indication for use | 1998<br>Breakthough cancer pain in opioid tolerant pts | 1998<br>Erythema nodosum leprosum | 2001<br>Pulmonary artery hypertension | 2000<br>Termination of pregnancy |
| Reason for Program and Date Begun | Child Safety, Appropriate Pt Selection, Abuse/Diversion 1999 | Pregnancy Prevention 1998 revised 2001 | Hepatotoxicity Pregnancy Prevention 2002 | Appropriate Pt Selection and Followup, Security of Drug Product 2000 |
| Medication Guide | | | X | X |
| Patient Package Insert | X | | | |
| Registration Required | | | | |
| • Physician (includes attestations on file w. firm) | | X | X | X |
| • Patient | | X | X | |
| • Pharmacy | | X | 4 Specialty Distributors | N/A: MD dispensing |
| Patient Informed Consent (IC) or Patient Agreement (PA) | | IC | | PA |
| Educational Component | X | X | X | X |
| Physican Agrees to Reporting of ADRs | | X | | X |
| Dispensing of Drug- Centralized | | | Specialty Distributor | |
| Dispensing of Drug- Selected Pharmacy Settings (e.g. hosp. only, received education program, etc.) | DEA Hospital & Distribution Registrants | Registered Pharmacies | | MD dispensing |
| Dispensing of Drug Contingent On: | | | | |
| • Required Registration(s) | | X | X | X |
| • Physician Specialty | | | | |
| • Physician "Qualifications" | | | | X |
| • Indication for Drug Use | | | X | X |
| • Presence/Absence of Patient Risk Factors | | X | | X |
| • Authorized Prescriber Check Mechanism | | Authorization # | Prescription = special form | N/A: MD dispensing |
| Limited Supply Dispensed/ No Refills | X (CII) | X | X | X |
| Special Packaging | X | | | X |
| Patient Monitoring by Physicians at Specified Intervals | | X | X | X |
| Auditing Mechanism in Place to Measure Outcomes Relevant to Program Compliance and/or Drug Risk | X | X | X | Proposed |

**ATTACHMENT B: SELECTED FEATURES OF RESTRICTED DISTRIBUTION PLANS NOT UNDER SUBPART H**

| | **Clozapine (Clozaril®, generic)** | **Isotretinoin (Accutane®)** | **Dofetilide (Tikosyn®)** | **Fentanyl (Oralet®)** | **Trovafloxacin (Trovan®)** |
|---|---|---|---|---|---|
| Approval date and indication for use | 1990 Schizophrenia | 1982 Cystic Acne | 1999 Atrial Fibrillation | 1993 Premed for Surgery or Painful Procedures | 1997 Life or Limb Threatening Infections |
| Reason for Program and Date Begun | Agranulocytosis 1990 revised: 1992 and 1998 | Pregnancy Prevention 1989 revised 2002 | Torsade de Pointes 2000 | Abuse/ Diversion 1993 | Hepatotoxicity 1998 |
| Medication Guide | | X | | | |
| Patient Package Insert | | | X | | |
| Registration Required | | | | | |
| • Physician (includes attestation on file with firm) | X | X | X | | |
| • Patient | X | | | | |
| • Pharmacy | X | | Centralized Process for Outpatient | | |
| • Institution | | | X | | |
| Patient Informed Consent (IC) or Patient Agreement (PA) | | IC | | | |
| Educational Component | X | X | X | X | X |
| Physican Agrees to Reporting of ADRs | | | | | |
| Dispensing of Drug- Centralized | | | OUTPT: Centralized Mail Order | | |
| Dispensing of Drug- Selected Pharmacy Settings (e.g. hosp. only, received education program, etc.) | Registered Pharmacies | | INPT: Institution Received Education Program | Targeted Hospitals Only | Hospital/ Institutional Only |
| Pharmacy Dispensing of Drug Contingent On: | | | | | |
| • Required Registration(s) | X | | | | |
| • Physician Specialty | | | | | |
| • Physician "Qualifications" | | | | | |
| • Indication for Drug Use | | | | | |
| • Presence/Absence of Patient Risk Factors | X | | | | |
| • Authorized Prescriber Check Mechanism | | Sticker | "Confirmed Pariticipant" List | | |
| Limited Number of Drug Units Dispensed / No Refills | X | X | | X (CII) | |
| Special Packaging | | X | | X | |
| Monitoring of Patients at Specified Intervals | X | X | | | |
| Auditing Mechanism in Place to Measure Outcomes Relevant to Program Compliance and/or Drug Risk | X | X | | | |

**Memorandum**

**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**

Date: March 20, 2002

From: David Hoberman, Ph.D., HFD-715

Subject: Lotronex Analyses

To: File (NDA# 21-107)

This memo contains material that I have developed over the past year or so relating to issues regarding safety and efficacy of Lotronex. Issues include Ischemic Colitis, Severe Constipation, thresholds for "high" efficacy regarding "urgency" to go to the bathroom, and Quality of Life.

Ischemic Colitis

**Table 1** contains person-time and events for the 20 studies with at least 100 patients. These studies accounted for all cases of ischemic colitis adjudicated by FDA. There were a total of 18 cases in the Lotronex groups and 1 case in the placebo groups. This set of studies accounts for approximately 99% of the person-time over all controlled studies. **Figure 1** is a plot of the hazard in the Lotronex group when the 20 chosen studies are pooled. **Table 2** displays the incidence densities in those trials with at least one case. The overall estimate of the incidence density in **Table 2** is based on pooling all 20 trials and produces essentially the result given by the sponsor in the current label: 1/1921 person-months **(p-m)** (the sponsor reported the figure 1/700 which resulted apparently by assuming that each trial was approximately 3 months, i.e., 3 x 1/1921= 1/640 is approximately the reported *risk* of ischemic colitis in the label. However, the sponsor did not explicitly address the issue of what follow-up period was used to define the risk). This is not necessarily the best analysis. For instance, it should be noted that the 2 year-long studies yielded no cases, raising the possibility that case ascertainment could be poor in those studies rendering a "best" estimate of the risk of ischemic colitis in likely users of Lotronex difficult or impossible to ascertain. It is clear that there is substantial variability in the estimates. This may be due to small numbers of events, making the fractions unstable, and/ or it may be due to unknown factors which are differentially distributed among the various patient samples.

Zili Li, M.D., Office of Drug Safety, has done an analysis considering the 11 larger studies of the 14 studies which enrolled patients from the target population: *Diarrhea-predominant women in the US.* Of the total of 18 cases, 16 came from this group of 11 studies. When these studies are simply pooled, a confidence interval for the exponential rate is (1/2091 p-m, 1/771 p-m) using Cox's approximation to the chi-square distribution,

with a point estimate of 1/1312 p-m. The estimated 3-month risk is therefore 1/447 with a confidence interval of (1/697, 1/257).

Severe Constipation

By protocol, severe constipation meant that if a patient did not pass a stool for 4 days, the patient discontinued the drug. If three of these episodes occurred then the patient was withdrawn from the trial. **Figure 2** gives the percentage of patients taking Lotronex who had the event in each of the 20 studies. **Figure 3** is the hazard plot constructed by pooling the 20 studies. The rising spikes far out in time are events, but the heights are artifacts. They result from the way the SAS computer program PROC LIFETEST computes the hazard at a discrete point. Since it is essentially the conditional probability of an event in the interval, and the denominator has decreased substantially by that time, the hazard looks "large" because of the unavoidable discreteness of the estimate. **Figure 4** illustrates the statistically significant relation between age and weight (by quartiles) to the risk of severe constipation. Note that the risk increases with increasing age and decreases with increasing weight.

Urgency

Urgency was measured by calculating the percentage of days over a period of time in which a patient experienced "urgency". **Table 3** displays results by pooling the 2 original trials (3001,3002) and separately for the pool of trials (30011, 30012) which enrolled patients with more severe urgency than previous trials. The approach taken in **Table 3** was suggested by John Senior, M.D. The problem is that the entries are cross sectional estimates which do not follow individual patients. The next figures address that issue. **Figures 5 and 6** illustrate the percentage of patients in the pool of studies 30011 and 30012) who have a 'response' which lasts for a defined period. The threshold of response is the following: Only patients who had at least 70% urgency at baseline are included in order to address the issue of the most severely affected patients. The horizontal axis is the threshold level of percentage of time with urgency to be called a responder, while the vertical axis is the percentage of patients who reach that threshold below 70% for all 3 months of the trial. **Figure 5** uses a stringent condition that the response must be for all 4 weeks of a month in order to be counted as a "monthly responder". **Figure 6** relaxes the "monthly responder" standard by saying that one must respond *any 2 weeks out of the month*, not all 4 weeks.

Quality of Life

The sponsor used 3 QOL instruments: A QOL questionnaire specifically for IBS patients (IBSQOL), the SF-36, and a work-related instrument. I chose selected items from the IBSQOL and information about days of lost work due to IBS. The QOL section is self-explanatory.

The results of this reviewer's analyses of the Social and Work Scales of the IBSQOL in trials 3001 and 3002 indicate that the Alosetron-treated patients do better than patients on placebo in all the noted aspects of the scales. "Better" is defined as the change in the percentage of patients who are severely affected at baseline and who then experience marked improvement within 3 months on therapy. In terms of the absolute benefit as defined by the percentage of alosetron-treated patients who are severely affected *and* who experience marked relief, between 10%-20% can expect to get this margin of benefit on Social scales and approximately 5% on the Work scales (See the 4$^{th}$ bars on each bar chart).

The QOL scales appear to indicate a clear benefit compared to placebo. However, in these trials, the results are less impressive when actually counting the number of school or work days lost as a result of the patient's IBS. Although the full distributions of lost days are statistically different between alosetron and placebo, producing before-and-after weekly strata reveals that there is little difference between the groups in terms of the actual number of days lost.

David Hoberman, Ph.D.

Concur: Dr. Permutt

Dr. Nevius

cc:
Arch NDA# 21-107
HFD-180
HFD-180/HGallo-Torres
HFD-715/DHoberman, TPermutt, DOB2, CAnello, Chron

# Ischemic Colitis

FIGURE 1

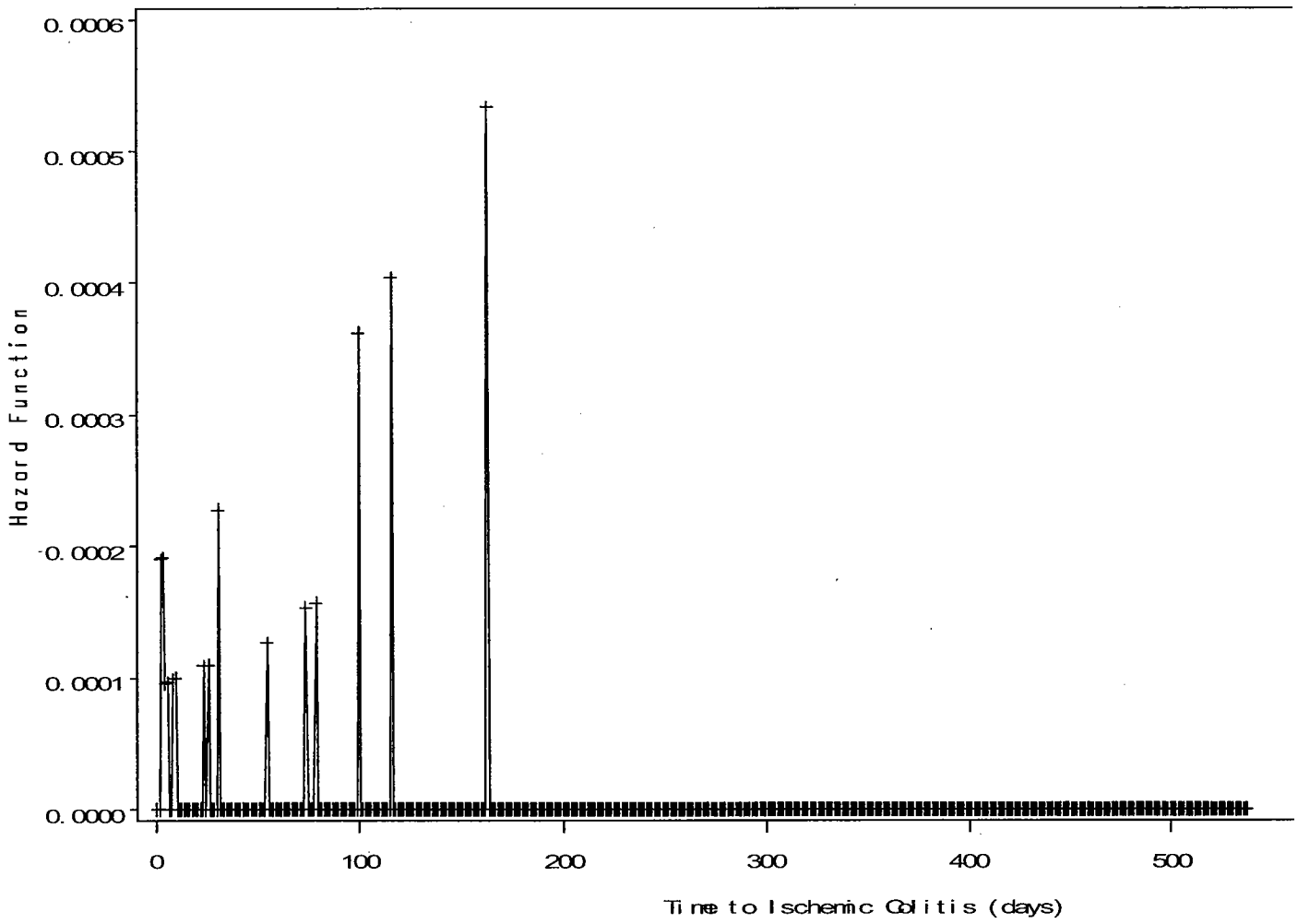

0.0006
0.0005
0.0004
0.0003
0.0002
0.0001
0.0000
Hazard Function
0
100
200
300
400
500
Time to Ischemic Colitis (days)

Table 1

| Study | N | Person-Days | Weeks | IC |
|---|---|---|---|---|
| S3B-P12 | 345 | 24,335 | 12 | - |
| S3B20015 | 239 | 17,432 | 12 | - |
| S3B20023 | 534 | 39,871 | 12 | 1 |
| S3B30006 | 348 | 84,875 | 48 | - |
| S3B30011 | 533 | 40,278 | 12 | 1 |
| S3B30012 | 422 | 45,279 | 12 | 1 |
| S3B30013 | 280 | 19,616 | 12 | 1 |
| S3B30017 | 876 | 53,993 | 20 | - |
| S3B30020 | 1828 | 216,714 | 24 | 10 |
| S3B30025 | 1028 | 94,005 | 24 | - |
| S3B30026 | 957 | 58,240 | 32 | - |
| S3B30031 | 277 | 14,589 | 20 | 1 |
| S3B40031 | 246 | 16,480 | 12 | - |
| S3B40032 | 577 | 38,044 | 12 | - |
| S3BA2001 | 287 | 20,160 | 12 | 1 |
| S3BA3001 | 310 | 22,282 | 12 | 1 |
| S3BA3002 | 324 | 23,209 | 12 | 1 |
| S3BA3003 | 640 | 155,136 | 52 | - |
| S3BB3001 | 318 | 23,442 | 12 | - |
| S3BB3002 | 402 | 29,768 | 12 | - |
| | **10,775** | **1,037,748** | | **18** |

Table 2

| Study | Incidence Density (/per-month) |
|---|---|
| S3B20023 | 1/1329 |
| S3B30011 | 1/1343 |
| S3B30020 | 1/722 |
| S3B30031 | 1/486 |
| S3BA2001 | 1/672 |
| S3BA3001 | 1/743 |
| S3BA3002 | 1/774 |
| S3B30012 | 1/1509 |
| S3B30013 | 1/654 |

Overall- 1/1921 person-months over 20 studies

# Severe Constipation

**FIGURE 2: Percentage of patients with severe constipation in 20 largest studies (N >100)**

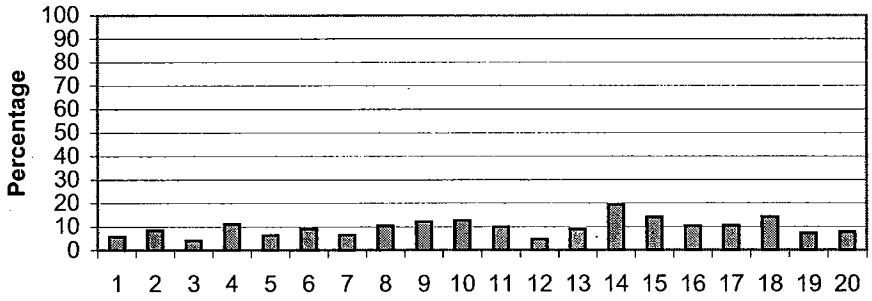


FIGURE 3

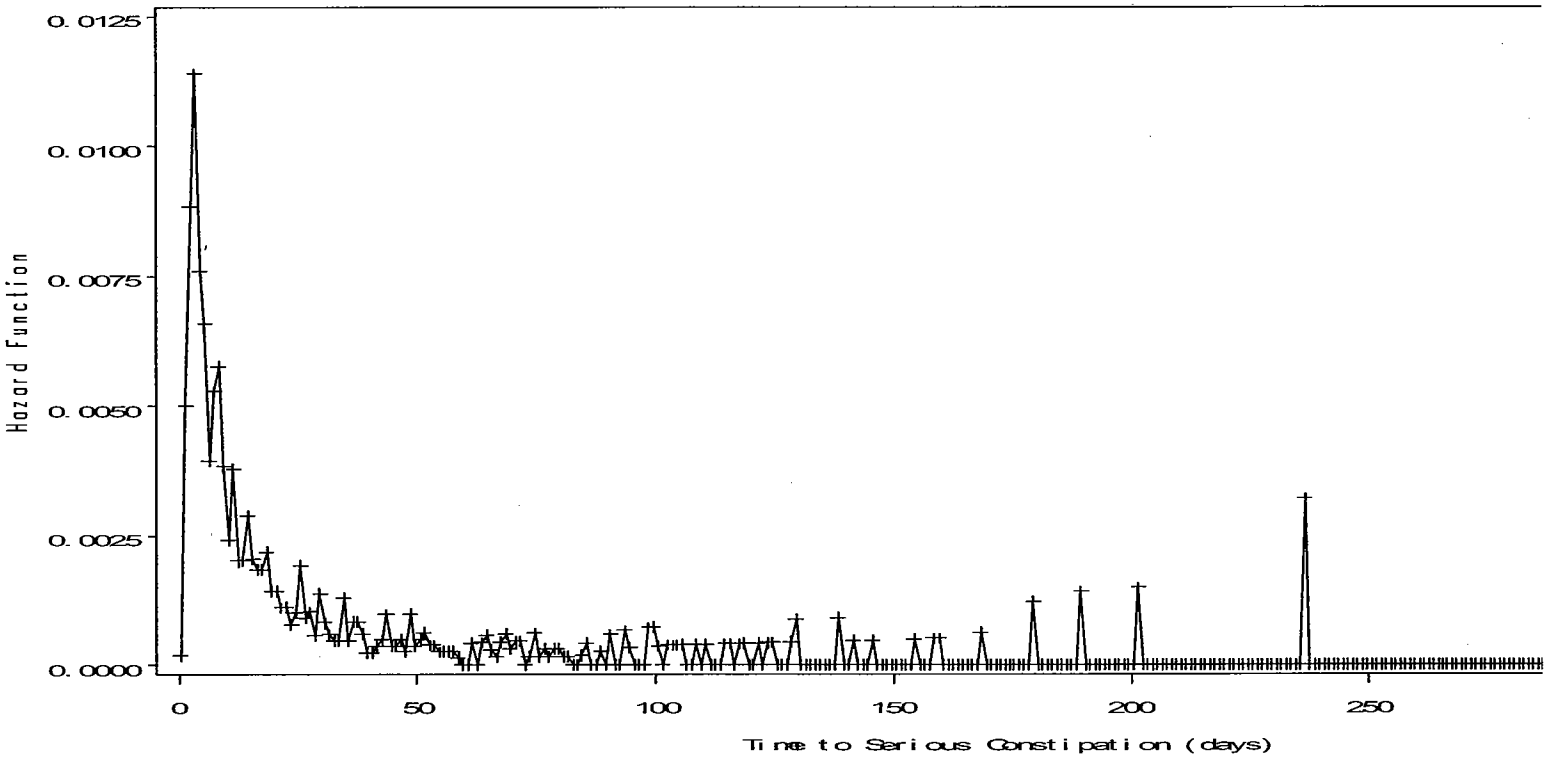
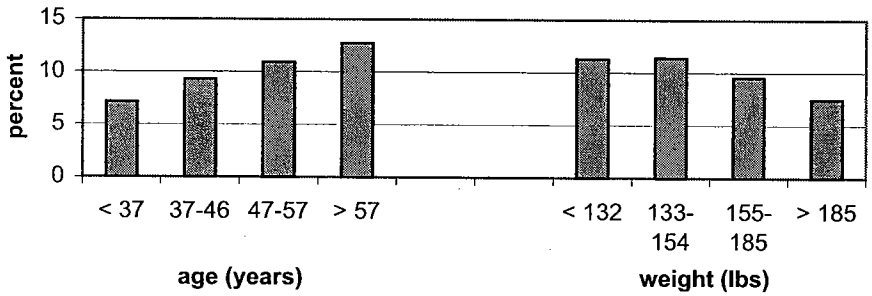

0.0125
0.0100
0.0075
0.0050
0.0025
0.0000
Hazard Function
0
50
100
150
200
250
Time to Serious Constipation (days)

**FIGURE 4: Percent of alosetron patients who had severe constipation as a function of age and weight**



# Urgency

TABLE 3

Percentages of groups who changed from at least 70% of days with urgency at baseline to no more than 15% of days with urgency for selected weeks in each pool of trials: 30011+30012 and 3001+3002.

30011+30012

| | WEEK | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | ... | 12 |
| Pbo | 3.5 | 14 | 16 | 19 | | 29 |
| Lotr | 11.4 | 23 | 33 | 37 | | 50 |

3001+3002

| | WEEK | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | ... | 12 |
| Pbo | 3 | 8 | 9 | 10 | | 19 |
| Lotr | 8 | 20 | 20 | 23 | | 32 |

Although the ratio of percentages of relief from urgency between placebo and Lotronex appears to be constant in the two pooled analyses, the absolute percentages of relief in both groups appear to be substantially greater in the pooling of 30011+30012. An examination of the distribution of baseline percentages in the two pooled analyses reveals that the patients in the 30011+30012 pool had more severe urgency at baseline than those in the 3001+3002 pool. For example, in the former, 40% of the patients had at least 90% urgency at baseline while in the latter, 30% had at least 90% urgency at baseline.

**Figure 5: Percent of Urgency reponders for all 3 months as a function of responder threshold Trials 30011, 30012**

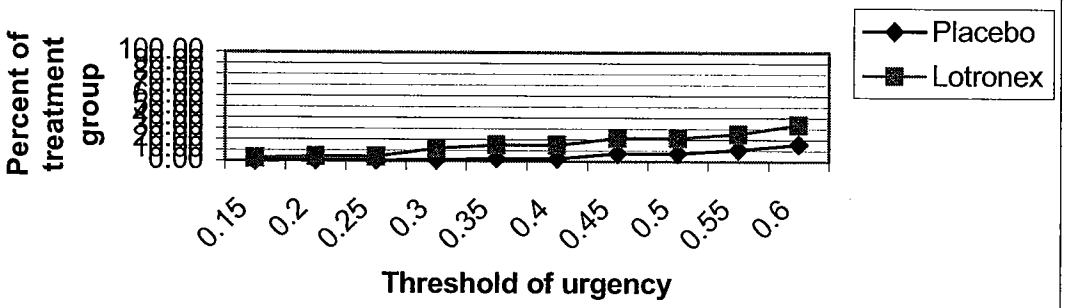
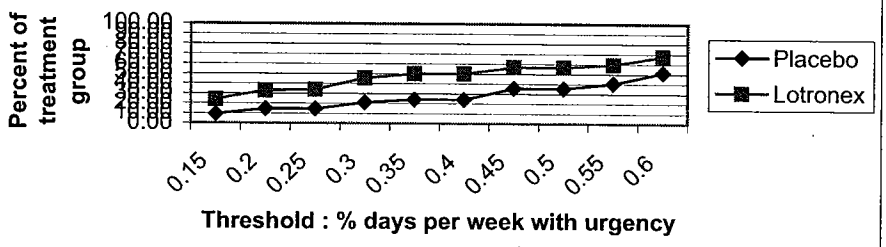


**Figure 6: Percent of urgency responders (any 2 weeks out of a month) for all 3 months as a function of responder threshold**
**Trials 30011, 30012**



# Quality of Life

Introduction

The following information comes from the QOL data collected in the two major NDA trials 3001 and 3002 .*Only patients with diarrhea-predominant IBS are included in this report.* For purposes of descriptive statistics, the trials have been pooled. The 3 QOL data bases were an **IBSQOL** questionnaire, an instrument specifically designed to assess QOL in patients with IBS. The second instrument was a **Resource Utilization** questionnaire which collected information about 1) "the number of days unable to participate in a main activity" such as work or school, 2) "the number of days cut-back on a main activity", 3) "productivity at main activity", and 4) "limitations caused by IBS on ability to work or participate in a main activity". The third instrument was the **SF-36** general QOL questionnaire which measures general daily fitness or symptoms.

This reviewer chose to examine *two scales of the IBSQOL questionnaire (effect on work and effect on social activities)* and then the item on the Resource Utilization questionnaire measuring the *number of days unable to participate in main activities.* These appear to capture the most relevant information available in the trials.

IBSQOL- Social and Work Scales

Attached is the page of the 8 items which comprise the social and work scales of the IBSQOL (4 items/scale). The bar graph labeled "SOCIAL" has 4 sets of 4 bars. Each set of 4 bars corresponds to one of the 4 items on the attachment. The meaning of each of the 4 bars *within* each item is as follows:

First, a subset of all patients was constructed which consists of only who reported that the particular item was a problem either ALWAYS or OFTEN. This was an attempt to isolate the most severely affected patients. Second, the clinical endpoint of interest was whether or not a patient then reported SELDOM or NEVER for the last month of the 3 month trial.

The **bar on the far left** (1) for each item displays the *percentage of **all** patients who were affected either ALWAYS or OFTEN (severely affected).* Thus, this is a measurement of the prevalence in the population of a serious problem.

The next bar to the right (2) displays the *percentage of the severely affected baseline patients in the **placebo** group who answered either SELDOM or NEVER for the last month of the trial.*

The next bar to the right (3) displays the respective percentage for the ***alosetron*** group.

**It is thus the comparison of bars (2) and (3) which indicated a "treatment effect".**

Lastly, the bar on the far right (4) displays **the percentage of ALL alosetron patients** who were severely affected at baseline **AND** who answered SELDOM or NEVER for the last month of the trial. This percentage is a measure of the absolute benefit in the population of people who take alosetron. That is, this is the percentage of all prospective people who take alosetron who are both severely affected AND will, in fact, get the benefit of having the problem SELDOMLY or NEVER after taking alosetron for 3 months. **The difference between (3) and (4) is that the denominator in (3) is the number of alosetron patients who were severely affected at baseline, while the denominator in (4) is ALL alosetron patients at baseline**.

As an example, take the first set of bars indicating 'Avoided Social Situations". The first bar indicates that the prevalence of ALWAYS or OFTEN at baseline was 40%.

The second bar indicates that, among those "ALWAYS or OFTEN" patients at baseline in the placebo group, 21% said SELDOM or NEVER at the end of 3 months .

The third bar indicates that the respective percentage in the alosetron group was 43%.

Lastly, the percentage of all alosetron patients who were severely affected at baseline **and also** responded SELDOM or NEVER at 3 months was 15%. This last figure could be regarded as the true anticipated benefit to be weighed against a risk of severe injury.

The Work Scale bars have exactly the same meaning as the Social Scale bars except "severely affected at baseline" was defined as having responded STRONGLY AGREE while the clinical endpoint at 3 months was DISAGREE or STRONGLY DISAGREE.

Number of Main Activity Days Lost

It should be noted that when the placebo and alosetron distributions of changes in the number of days lost for main activities (the month before baseline versus the last month of the 3 month trial) are compared statistically, there is a significant difference (p=.001). However, when the data are grouped into 4 categories 0-7,8-13,14-20, 21-28, a difference between placebo and alosetron is not apparent: For instance, the tables below display the frequencies of the "before and after" number of days lost to work or school for each treatment group. The rows designate baseline categories and the columns designate endpoint (during the 3rd month or the last month on trial) categories of days lost. Note that the area of the table of interest is the bolded portion to the left of the diagonal line because this area designates "improvement" from baseline.

| | Placebo | | | | Alosetron | | | |
|---|---|---|---|---|---|---|---|---|
| | 0-7 | 8-13 | 14-20 | 21-28 | 0-7 | 8-13 | 14-20 | 21-28 |
| 0-7 | 353 | 13 | 3 | 1 | 383 | 9 | 1 | 0 |
| 8-13 | **13** | 4 | 2 | 0 | **13** | 0 | 2 | 0 |
| 14-20 | **2** | **1** | 5 | 2 | **7** | **0** | 2 | 1 |
| 21-28 | **0** | **0** | **1** | 0 | **3** | **1** | **0** | 0 |

**In the alosetron group, 56% of the patients had *zero* days off due to IBS both in the run-in period and during the 3rd month. In the placebo group, 47% of the patients had zero days off in both the run-in period and during the 3rd month**. Note that fully 95% of the patients in each group changed by 7 or fewer days during the trial. It is clear by comparing the **bolded** regions of the two tables that there is essentially no difference between the drug and placebo groups in the categorical distributions of patients who "improved" from baseline to 3 months.

| Protocol code | Session number | Subject initials | Subject number |
|---|---|---|---|
| S3BA3002 | | | |

## Final Visit

**These questions ask about how often your Irritable Bowel Syndrome (IBS) problems and symptoms affected your usual social activities DURING THE PAST 4 WEEKS. CIRCLE ONLY ONE RESPONSE PER QUESTION.**

12. Because of your IBS, how often did you...

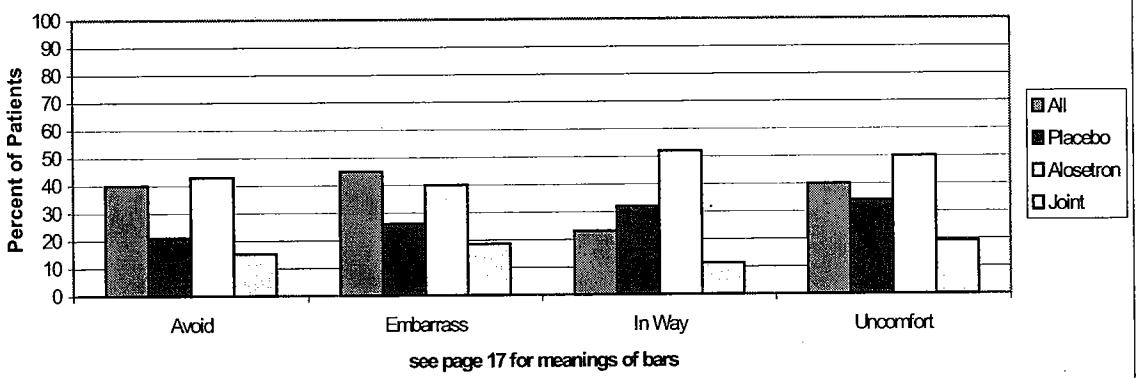
| | DURING THE PAST 4 WEEKS | | | | |
|---|---|---|---|---|---|
| | Always | Often | Sometimes | Seldom | Never |
| 12a. Feel uncomfortable during social or family activities. | 1 | 2 | 3 | 4 | 5 |
| 12b. Avoid certain social activities because there would be no bathroom facilities nearby. | 1 | 2 | 3 | 4 | 5 |
| 12c. Feel concerned that your IBS might embarrass you during social activities. | 1 | 2 | 3 | 4 | 5 |
| 12d. Feel that your IBS got in the way of someone else's social or recreational activities. | 1 | 2 | 3 | 4 | 5 |

**The next questions ask about the effect of IBS on your main activity. Your main activity refers to your job or business, going to school, keeping house or doing chores around the house.**

Please mark your level of agreement to indicate how your Irritable Bowel Syndrome (IBS) problems or symptoms affected the work related to your main activity DURING THE PAST 4 WEEKS. CIRCLE ONLY ONE RESPONSE PER QUESTION.

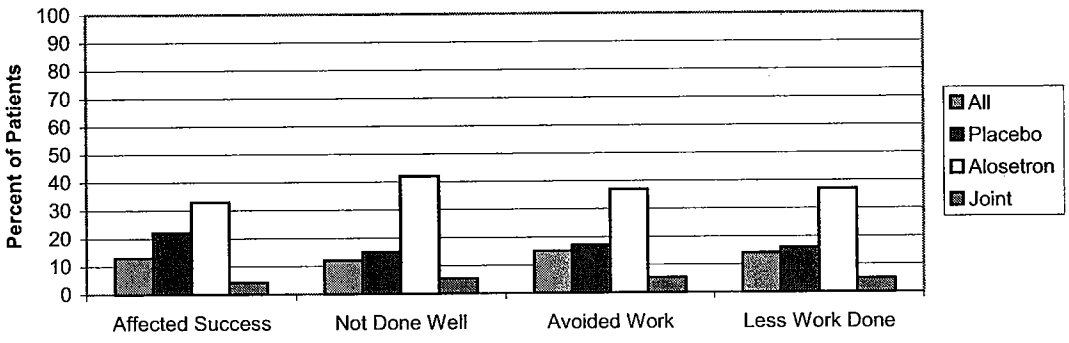
| | DURING THE PAST 4 WEEKS | | | | |
|---|---|---|---|---|---|
| | Strongly Agree | Agree | Neutral | Disagree | Strongly Disagree |
| 13. My IBS affected my ability to succeed at work/main activity. | 1 | 2 | 3 | 4 | 5 |
| 14. I got less work/main activity done because of my IBS. | 1 | 2 | 3 | 4 | 5 |
| 15. There were certain work activities/main activities I avoided because of my IBS. | 1 | 2 | 3 | 4 | 5 |
| 16. My IBS affected how well I did my job/main activity. | 1 | 2 | 3 | 4 | 5 |

**Figure 7: SOCIAL**




see page 17 for meanings of bars

**Figure 8: WORK**




see page 17 for meanings of each bar

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

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/s/
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David Hoberman
3/26/02 02:21:07 PM
BIOMETRICS

Thomas Permutt
3/26/02 02:23:59 PM
BIOMETRICS
concur

S. Edward Nevius
3/26/02 02:30:21 PM
BIOMETRICS
Concur with review.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PID# D020045

DATE: March 26, 2002

FROM: Ann Corken Mackey, R.Ph., M.P.H.
Safety Evaluator
Zili Li, M.D., M.P.H.
Medical Epidemiologist

THROUGH: Julie Beitz, M.D., Director
Division of Drug Risk Evaluation, HFD-430

TO: Victor Raczkowski, M.D., Acting Director
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: Office of Drug Safety (ODS) POSTMARKETING SAFETY REVIEW
Drug: Alosetron (Lotronex)
Reactions: Ischemic colitis, small bowel ischemia, complications of serious constipation

**This document contains information from IMS Health National Prescription Audit Plus and National Disease and Therapeutic Index (on-line) and is not to be used outside of the FDA without prior clearance by IMS Health.**

EXECUTIVE SUMMARY

This memorandum communicates safety concerns identified by ODS associated with alosetron and ischemic colitis, small bowel ischemia, and complications of serious constipation. Alosetron was approved on February 9, 2000 for the treatment of women with diarrhea-predominant irritable bowel syndrome (IBS); the marketing of alosetron was suspended on November 28, 2000. As of August 17, 2001, there were 76 cases of ischemic colitis, 6 cases of small bowel ischemia, and 85 cases of complications of serious constipation reported to the FDA Adverse Event Reporting System (AERS), leading to 2, 3, and 2 deaths, respectively. There were 9, 5, and 28 surgeries, respectively. AERS is a passive surveillance system that is subject to under-reporting, normally only 1 to 10% of adverse events are reported to FDA.[1,2]

Postmarketing data can be used to capture information that clinical trials for alosetron were not able to capture. Of the 3 cases of ischemic colitis that occurred in the clinical trials before alosetron approval, there were no surgeries. During the postmarketing period, however, there were 9 cases of complications of ischemic colitis requiring surgery (colectomy), including 2 cases of death. IBS is usually not life-threatening, yet after treatment with alosetron, serious consequences, such as surgery and death, can result as seen in our case series.

In interpreting these data, we have to be aware that the drug has been used off-label, in contraindicated conditions, and in patients with confounding factors. Of the 161 patients who experienced ischemic colitis or complications of serious constipation as described in this document, 6 (4%) were male, at least 15 (9%) of patients using alosetron had contraindicated conditions, and at least 19 (12%) were using alosetron for conditions other than diarrhea-predominant IBS (e.g., diarrhea, constipation-predominant IBS). Of the 76 patients who developed ischemic colitis, several were taking concomitant medications also known to cause ischemic colitis, such as estrogen 21 (28%), beta blockers 3 (4%), or sumatryptan 2 (3%); the role of the use of concomitant medications in the development of ischemic colitis in these patients has not been determined.

With regard to presenting symptoms or possible early detection of ischemic colitis, postmarketing data found that 47 (62%) of patients with ischemic colitis reported bloody stool, 12 (16%) reported constipation, and 56 (74%) reported abdominal pain. Due to the nonsensitive and nonspecific nature of these symptoms, early detection of ischemic colitis could be challenging; this may be better answered by analyzing ischemic colitis cases that occurred in the clinical trials. At this time, we do not know which patients will develop a more severe form of ischemic colitis and possibly require surgery.

## BACKGROUND/INTRODUCTION

This document provides a summary of adverse events reported for alosetron through AERS and covers the time period of March 13, 2000 (the introduction of alosetron to the marketplace) through August 17, 2001. The sponsor's original cut off date was July 31, 2001, so the August 17 date allows for the sponsor's reports to be received and processed by the agency. (Note that ODS received follow-up information to some of the reports on March 7, 2002; however, the information was not received in sufficient time to review and include in this document before our deadline of March 15, 2002. The follow-up information will be presented at the Lotronex Advisory Committee meeting in April. The sponsor is including the follow-up information in their briefing document.) The marketing of alosetron was suspended on November 28, 2000.

A comprehensive document entitled "NDA 21-107: Lotronex (alosetron) Safety & Risk Management Summary" was prepared by ODS (formerly the Office of Postmarketing Drug Risk Assessment [OPDRA]) on November 16, 2000, before marketing suspension (see Attachement A). The November 16, 2000 document contains the details of individual cases. Please refer to the November 16, 2000 document.

Alosetron is indicated for the treatment of women with diarrhea-predominant IBS based on findings from premarketing clinical trials. Once a drug is on the market, it can be used off-label or in patient populations other than those studied, etc. Postmarketing data can be used to capture information that clinical trials for alosetron were not able to capture, such as use in males, use in contraindicated conditions, uses other than the labeled indication, drug combinations, symptoms with regard to possible early detection of serious outcomes, and the severity of ischemic colitis or complications of serious constipation.

When evaluating spontaneous reports, it is important to keep the following limitations in mind. The main utility of a spontaneous reporting system, such as AERS, is to detect signals of potential drug safety issues that are rare. Hence, when considering these figures, it should be realized that accumulated case reports cannot be used to calculate incidence or estimates of

drug risk for a particular product, as reporting of adverse events is a voluntary process, and underreporting exists. Further, because of the multiple factors which influence reporting, comparisons of drug safety cannot be made from these data. Some of these factors include the length of time a drug is marketed, the market share, size and sophistication of the sales force, publicity about an adverse reaction and regulatory actions. It should also be noted that in some of these cases, the reported clinical data was incomplete, and there is no certainty that these drugs caused the reported reactions. A given reaction may actually have been due to an underlying disease process or to another coincidental factor.

There were a total of 514,000 alosetron prescriptions dispensed by retail pharmacies (chain, independent, food stores, and mail order) in the U.S from March 1, 2000 through December 31, 2000. (Note that alosetron sales were suspended November 28, 2000.) The sponsor determined that there were 534,000 prescriptions dispensed in the same time period using Scott-Levin Source Presciption Audit data (information provided by GlaxoSmithKline, document #RM2001/00173/00). Data from the National Disease and Therapeutic Index (NDTI) from March 1, 2000 to December 31, 2000 indicate that approximately 10% of alosetron use was in males and approximately 16% of female users were 65 years of age and older. The sponsor determined a 95% use of alosetron in females (use in males not provided) and a 13% use in patients 65 years of age and older using Scott-Levin Source Prescription Audit data (information provided by GlaxoSmithKline, document #RM2001/00173/00).

**Selected Adverse Events**

ODS is focusing this review on three areas of special interest, namely ischemic colitis, small bowel ischemia, and complications of serious constipation. Unless otherwise specified, the reports in the ischemic colitis and complications of serious constipation categories are mutually exclusive (i.e., if they coexist, the case would be linked to ischemic colitis). In contrast, the sponsor has classified serious constipation as the primary event and ischemic colitis as secondary and, therefore, has excluded these cases from their ischemic colitis category. However, they discuss these cases in other sections of their document. Any case of injury to the small bowel will be discussed under the Small Bowel Ischemia section of this document, regardless of the reason for injury. The sponsor refers to small bowel cases as Mesenteric Ischemia, Occlusion, or Infarction in their document (GlaxoSmithKline document #RM2001/00173/00).

Reports received through AERS after market suspension of alosetron (November 28, 2000) have come primarily from consumers; therefore the quality and completeness of the data are not as good as reports received before November 28, 2000. In addition, since August, 2001 ODS has been receiving reports from class action lawsuits; the quality and completeness of these data also are not as good. ODS has included these reports in our analysis because the events could not be ruled out. The sponsor has excluded some of these reports from their analysis based on limited documentation; however, they do discuss the events under a separate section of their document (GlaxoSmithKline document #RM2001/00173/00).

It should be pointed out that ODS contacted reporters for additional information, when possible and if needed, for all cases of the above-stated selected events involving death and surgery before market suspension (November 28, 2000). After market suspension ODS was not able to obtain follow up due to a large volume of reports and lack of resources. For reports that were submitted as part of a class action lawsuit, follow up was attempted when the first reports were received, but the lawyer-reporter was not willing to submit additional information; it was then

decided that ODS would not attempt follow up on subsequent class action lawsuit reports. Note that the absence of supporting documentation does not imply that the patient did not have the event, only that documentation was not obtainable.

**Ischemic Colitis**

The case definition used by the FDA ODS for ischemic colitis for epidemiological risk assessment was based on any or a combination of the following: (1) the term "ischemic colitis" is explicitly used in the AERS report as a possible diagnosis, (2) any endoscopic or histologic evidence of ischemic change or necrosis, or (3) any radiological evidence of ischemic colitis. The sponsor selected cases from their database, by reviewing any case with terms possibly representing ischemic colitis, including acute ischemic colitis, ischemic colitis, possible ischemic colitis, ischemic bowel, ischemic necrosis of intestine, possible bowel ischemia, ischemic colonic ulcer, gastrointestinal ischemia, ischemia of colon, possible ischemia of colon, and decreased gastrointestinal blood flow (information provided by GlaxoSmithKline, document #RM2001/00173/00).

As of August 17, 2001, there were 76 cases of ischemic colitis in AERS. This number represents unduplicated patient cases, not individual reports.

*Diagnostic Certainty of Ischemic Colitis Cases* (Categories are mutually exclusive) (N = 76)

Both histologic and endoscopic evidence: 24 (32%)
Endoscopic evidence only: 14 (18%)
Histologic evidence only: 15 (20%)
Radiologic evidence only: 5 (7%)
For 18 (23%) cases, the reporters stated that the patient had ischemic colitis, but did not provide documentation (Note that for one case, the pathology report did not specifically state ischemic colitis, but the clinician made a diagnosis of probable ischemic colitis based on clinical observation).

Among the 54 cases reported before market suspension, there was 1 case (2%) of ischemic colitis reported to AERS by a consumer and no cases reported as part of a lawsuit, compared to 9 cases (41%) and 4 cases (18%), respectively, out of 22 cases reported after market suspension.

*Description of Ischemic Colitis Cases* (N = 76)
(n = number of cases used as the denominator in the calculations because some of the information was missing from the reports)

Gender: Male 1 (1%), Female 73 (96%), Unk 2 (3%)
Age (years): 55 mean; ≥ 65 = 24 (35%) (n = 69), Unk = 7
Indications for use as stated in the report (n = 55), Unk = 21:
IBS-Diarrhea predominant: 19 (35%)
IBS: 29 (53%)
IBS-Alternating: 3 (5%)
Diarrhea: 3 (5%)
Abdominal pain: 1 (2%)

Time to onset (days): 35 mean, 14 median, 1 to 200 range (n = 59), Unk = 17
Presenting symptoms as stated in the report (n = 76):
Bloody stool: 47 (62%)
Constipation: 12 (16%)
Abdominal pain: 56 (74%)

Contraindicated conditions as stated in the report (n = 76):
Ischemic colitis, or history of: 1 (1%)
Constipation, or history of: 1 (1%)
Bowel obstruction, or history of: 2 (2%)
Concomitant medications as stated in the report (n = 76):
Hormone use, including estrogen and oral contraceptives*: 21 (28%)
Beta-blocker use*: 3 (4%)
Sumytryptan use*: 2 (3%)

* Drugs associated with ischemic colitis based on reports submitted to AERS.

*Outcomes* (Categories not mutually exclusive) (n = 76)

Required hospitalization: 52 (68%)
Required surgery for an obstructed, necrotic, ruptured bowel: 9 (12%) (all surgeries involved segmental resection)
Required transfusions: 2 (3%)
Death: 2 (3%)

The sponsor states that there are no deaths from ischemic colitis; they refer to the two deaths as 1) complication of serious constipation and 2) ruptured sigmoid diverticula because they classify those as the primary events and ischemic colitis as secondary. ODS and the review division believe that it cannot determine which event came first, and, therefore, has placed these cases in the ischemic colitis category. Per a telecon with the sponsor on March 11, 2002, we have agreed to disagree on the categorization of these two cases.

**Small Bowel Ischemia**

The case definition used by ODS for small bowel ischemia was any ischemic change of the small bowel documented by endoscopic, surgical, or pathological evidence. As of August 17, 2001, six cases of small bowel ischemia were reported to AERS. All cases have the endoscopic, surgical, or pathological evidence of small bowel ischemia, infarction, or necrosis. In at least three cases, the ischemia also involved other parts of the gastrointestinal system, such as the colon or stomach. All patients were female who ranged in age from 33 to 81 years. In four cases, the onset was within ten days of beginning alosetron treatment; the shortest onset was four hours. Three deaths occurred among these six cases. See attachment B for a summary of these cases. While each case may have an alternative explanation for the small bowel ischemia, in light of the strong association between alosetron and ischemic colitis, ODS believes that the association between alosetron and small bowel ischemia could not be reasonably excluded.

**Complication of Serious Constipation**

The case definition used by ODS for complications of serious constipation for epidemiologic risk assessment was constipation or suspected constipation that was associated with an ER visit, hospitalization, or complications, including but not limited to, fecal impaction, bowel obstruction, necrosis, or rupture. The sponsor identified cases of serious constipation using a multi-step process. First, their database was searched for all cases assessed as serious; from these serious cases, all cases with a reported event of constipation or related term were identified and individually reviewed to determine if constipation was the event that led to the assessment of serious. As stated in their document, the sponsor identified 15 event codes: acute constipation, chronic constipation, complete inability to defecate, constipation, constipation with diarrhea, decreased bowel movements, decreased frequency of bowel movements, exacerbation of constipation, exacerbation of hard stool(s), fecal impaction, feeling of constipation, hard stools, irregular bowel movements, painful constipation, and possible fecal impaction (information provided by GlaxoSmithKline, document #RM2001/00173/00).

As of August 17, 2001, there were 85 cases of complications of serious constipation in AERS. This number represents unduplicated patient cases, not individual reports. (Note that some reports included in this section did not specifically mention "constipation;" however, ODS has included these reports in this section because constipation may have preceded the complicating event. Per telecon with the sponsor on March 11, 2002, they have chosen not to include these reports in their analysis; they discuss these cases in a separate section of their document.)

Among 23 cases reported before market suspension, there were 9 cases (39%) of complications of serious constipation reported to AERS by consumers and no cases reported as part of a lawsuit, compared to 43 cases (69%) and 2 cases (3%), respectively, out of 62 cases reported after market suspension.

*Description of Complications of Serious Constipation Cases* (n = 85)
(n = number of cases used as the denominator in the calculations because some of the information was missing from the reports)

Gender: Male 5 (6%), Female 80 (94%)
Age (years): 55 mean; ≥ 65 = 33 (43%) (n = 77), Unk = 8
Indications for use as stated in the report (n = 55), Unk = 30:
- IBS-Diarrhea predominant: 16 (29%)
- IBS: 27 (49%)
- IBS-Constipation predominant: 2 (4%)
- IBS-Alternating: 3 (5%)
- Diarrhea: 6 (11%)
- Abdominal pain: 1 (2%)

Time to onset (days): 34 mean, 12 median, 1 to 180 range (n = 53), Unk = 32
Presenting symptoms as stated in the report (n = 85):
- Bloody stool: 17 (20%)
- Constipation: 65 (76%)
- Abdominal pain: 53 (62%)

Contraindicated conditions as stated in the report (n = 85):
- Inflammatory bowel disease, or history of: 3 (4%)
- Constipation, or history of: 4 (5%)
- Bowel obstruction, or history of: 4 (5%)

*Outcomes* (Categories not mutually exclusive) (n = 85)

Required hospitalization: 63 (74%)
Required surgery for an obstructed, necrotic, ruptured bowel, rectal surgery (n = 28) (33%):
  Intestinal surgery (large bowel): 21
  Analrectal surgery: 7
Transfusions: 1 (1%)
Death: 2 (2%)

In contrast, the sponsor has chosen not to include one of the deaths in their analysis; they have discussed this case in a separate section of their document because the report did not specifically list constipation (report states that the patient was in the OR for a bowel perforation, but died of cardiac arrest secondary to perforated bowel before surgery began).

**Summary of all death cases**

As of August 17, 2001, there were a total of 13 deaths in patients receiving alosetron; 7 deaths showed a strong association with alosetron (2 cases of ischemic colitis, 3 cases of small bowel ischemia, and 2 cases of complications of serious constipation).[3]

DISCUSSION/CONCLUSION

Alosetron was approved on February 9, 2000 for the treatment of women with diarrhea-predominant irritable bowel syndrome (IBS); the marketing of alosetron was suspended on November 28, 2000. As of August 17, 2001, there were 76 cases of ischemic colitis, 6 cases of small bowel ischemia, and 85 cases of complications of serious constipation reported to the FDA Adverse Event Reporting System (AERS), leading to 2, 3, and 2 deaths, respectively. There were 9, 5, and 28 surgeries, respectively. AERS is a passive surveillance system that is subject to under-reporting, normally only 1 to 10% of adverse events are reported to FDA.[1,2]

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In interpreting these data, we have to be aware that the drug has been used off-label, in contraindicated conditions, and in patients with confounding factors. Of the 161 patients who experienced ischemic colitis or complications of serious constipation as described in this document, 6 (4%) were male, at least 15 (9%) of patients using alosetron had contraindicated conditions, and at least 19 (12%) were using alosetron for conditions other than diarrhea-predominant IBS (e.g., diarrhea, constipation-predominant IBS). Of the 76 patients who developed ischemic colitis, several were taking concomitant medications also known to cause ischemic colitis, such as estrogen 21 (28%), beta blockers 3 (4%), or sumatryptan 2 (3%); the role of the use of concomitant medications in the development of ischemic colitis in these patients has not been determined.

With regard to presenting symptoms or possible early detection of ischemic colitis, postmarketing data found that 47 (62%) of patients with ischemic colitis reported bloody stool, 12 (16%) reported constipation, and 56 (74%) reported abdominal pain. Due to the nonsensitive and nonspecific nature of these symptoms, early detection of ischemic colitis could be challenging; this may be better answered by analyzing ischemic colitis cases that occurred in the clinical trials. At this time, we do not know which patients will develop a more severe form of ischemic colitis and possibly require surgery.

## REFERENCES


1. Rogers AS, Israel E, Smith CR. Physician knowledge, attitudes, and behavior related to reporting of adverse drug events. Arch Intern Med 1998; 148: 1589-92.
2. Scott HD, Rosembaun SE, Waters WJ, et al. Rhode Island physicians' recognition and reporting of adverse drug reactions. R I Med J 1987; 70: 311-6.
3. Gallo-Torres H. Alosetron-associated deaths. NDA 21-107. FDA DFS System, August 31, 2001.


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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

| | |
|---|---|
| NDA: | 21-107/S-005 |
| Date Submitted: | December 7, 2001 |
| Sponsor: | GlaxoSmithKline<br>Research Triangle Park, NC |
| Drug: | LOTRONEX® (alosetron hydrochloride)<br>Tablets for oral administration |
| Pharmacological Category: | 5-$HT_3$ receptor antagonist |
| Material Reviewed: | Proposed Risk Management Plan (RMP) for LOTRONEX® |
| Reviewer: | Hugo E. Gallo-Torres, M.D., Ph.D.<br>Medical Team Leader, GI Drugs<br>HFD-180 |

## EXCUTIVE SUMMARY

### OVERALL CONCLUSION

Through the supplemental New Drug Application (sNDA) GlaxoSmithKline (GSK) is seeking FDA approval of market reintroduction for LOTRONEX ® tablets under a mutually acceptable Risk Management Plan (RMP). The sponsor's proposal consists of 11 components all of which, including the labeling , have been previously discussed with the Agency. However, the newest version of the **modified labeling** contains some new items (wording) which we have not agreed. The opportunities and constraints associated with each of the 11 components of the RMP are succinctly commented on this Executive Summary. The reviewer believes that, with some modifications/ clarifications/adjustments - proposed thro ughout this review - the RMP pr oposed by GSK is appropriate.

Market re-introduction of LOTRONEX ® at the soonest possible time, for this restricted distribution under the provisions of **21 CFR 314 (Subpart H)**, should be vigorously pursued.

### GSK proposed Risk Management Plan (RMP) for LOTRONEX ®

Each of the 11 components of the sponsor's proposed RMP are briefly discussed in this Executive Summary. Further details of the reviewer's appraisal are found within the text of this review.

1. **Objectives**

The reviewer agrees with the sponsor that the overall RMP to address the risk issues of **intestinal vasculopathy (IV), primarily ischemic colitis (IC)** and serious complications of constipation might be acceptable.

The primary approach to control constipation and its complications is **PREVENTION**. A strict, conservative definition of constipation should consider number of daily stools, consistence of the stool and straining associated with the bowel movement. The **challenge** is to inform the patient **when to discontinue the drug** in order to **prevent serious complications** while at the same time allowing for continuation of the medication in those patients who are **deriving benefit**. Although at the present time, risk factors for the development of Lotronex-induced IV/IC remain to be properly characterized, some suggestions for patient experiencing early signs of IV/IC seem appropriate.

2. **Patients for whom benefits outweigh risks**

The reviewer believes that the approach of restricting use of the drug under 21 CRF 314 Subpart H to only those patients with **significant impairment** for whom there is no reasonable therapeutic alternative raises the threshold for acceptance of possible risks. Although no solid scientific su pport for this plan has been developed, this approach is sound.

3. **Appropriate prescribers**

The reviewer does not agree with the sponsor's proposal. The reviewer recommends that appropriate prescribers should be **Gastroenterologists (only)** who are willing to **comply with all required aspects** of the RMP. This includes agreeing to have their records examined to determine if he/she **continues to be qualified**. Examples of reasons for disqualifications of a physician as a Lotronex ® prescriber are listed in the text of this review.

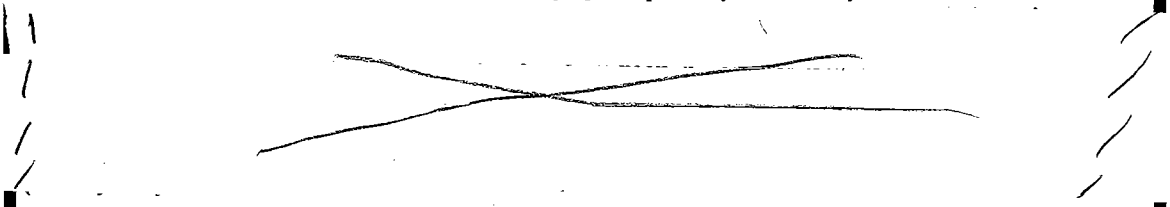
The goal of the program should be to closely monitor each patient taking the drug through a **patient Registry** administered by the sponsor. A gradual expansion should be based on agreed upon stages.

**4. Modified Labeling**

The key elements to the proposed labeling changes and the rationale for these revisions are listed in Table 4 of this review. Although very strict, conservative definition of constipation is now pr oposed, this reviewer believes that the final wording should: a) be negotiated with the sponsor and b) allow for continuation of the drug in those patients who are clearly deriving benefit.

**5. Modified packaging**

This is another area where a refinement to the sponsor's proposed plan may be necessary. The reviewer believes that



**6. Communication of risks**

Although some adjustments are needed, in general, this component of the sponsor's pr oposal appears to be reasonable. In this reviewer's opinion, the sponsor's proposed number of **trained prescribers** is too large.

It is recommended that the **first RMP** consists of the following target for prescribers and distributors:

a. Gastroenterologist **prescribers (ONLY)**
b. Pharmacies to receive an additional page with stocking and dispensing information. This would include hospital pharmacies and retail pharmacies.

Again, a gradual expansion should be based on agreed upon stages.

**7. Definition of risk**

This component of the RMP will require additional clinical trials and Epidemiological research, for which the past year **would have been the optimal timing to conduct these studies** . Now it becomes critical to the start of the Subpart H program: In this reviewer's opinion, a commitment to begin or the actual starting the RCTs is enough to approve re-introduction of Lotronex into the U.S. market. Because **longer periods of time (years?) would be required** if the results of these additional clinical trials are a requisite for market re-introduction, and such approach is not advisable. The reviewer recommends that the Epidemiological Research component in the sponsor's December 7, 2001 sNDA, be evaluated by ODS.

**8. Program evaluation**

Although, among other things, is suggested, the reviewer recommends to assess this component of the RMP in consultation with a **specialist on RM** such as Dr. Holmboe.

to closely evaluate/monitor program compliance is recommended. There is need to have an agreed upon predetermined frequency and severity of SAEs that will trigger **further restriction** of distribution and/or removal from marketing.

**9. Enhancement of safety monitoring**

The sponsor's proposal, apparently based on discussions at the April 3, 2001 meeting between the Agency and GSK, and additional interactions throughout the past year, appears reasonable to this reviewer.

**10. Post-marketing commitments**

The sponsor's proposed approach appears to be reasonable. It is expected that these commitments would be listed as conditions of (re-) approval of the restricted use plan instituted under 21 CFR 314 Subpart H.

**11. Promotional activities**

This component of the sponsor's RMP is acceptable (see text).

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## I. BACKGROUND/INTRODUCTION

NDA 21-107 for LOTRONEX® (alosetron hydrochloride) tablets was received from GlaxoWellcome on June 30, 1999 and given **priority review status** because it was a **new molecular entity** that represented a significant **therapeutic advance** as a first line monotherapy for the significant population of female patients with **non-constipated IBS** (DP-IBS). The Division's multidisciplinary pre-marketing review process successfully identified a potentially serious risk of **ischemic colitis (IC)** associated with the use of Lotronex®. The four cases of IC identified pre-marketing, all of which required hospitalization, were eventually described in the labeling as **mild, self-limiting and resolving without overt sequelae**. Another adverse event identified pre-marketing was **mild to moderate constipation** in about one third of the patients. None of these constipation cases was serious and none required hospitalization, but 10% dropped out of phase III trials because of constipation. The November 16, 1999 Advisory Committee (AC) found the generally understood benefit-risk relationship acceptable and recommended unanimous approval of the drug. Lotronex was approved on February 9, 2000, only when the Agency judged that its benefit for DP-IBS women outweighed the risks for its use in this intended patient population and after seeking independent evaluation of pathology slides of patients with ischemic colitis (IC) and further review of these IC cases.

Soon after marketing a **significant change** was noted related to the seriousness and severity of IC. In addition, cases of serious complications of **severe constipation** ranging from fecal impaction to obstruction, toxic megacolon, perforation and gangrenous colitis were reported. Some of these patients required hospitalization and surgical removal of part or even the entire colon. To a certain extent, the increase in severity of IC and serious complications of constipation seemed **unexpected** in view of a) the previous experience with the drug in randomized clinical trials and b) the at that time thoroughly "adequate" labeling for the intended population and use, which in the final analysis, **proved inadequate**.

The sponsor and the Agency agreed that, because there had been a **major shift** in the balance between benefit and risks, it was appropriate to undertake a formal and mutually agreeable Risk-Management Plan (RMP). The consensus of participants at a second AC (27-June-2000) was that both physicians and patients needed to be made aware of the potentially serious AEs associated with the use of Lotronex®. The need for a **Medication Guide** was discussed and supported by the Committee.[1] The sponsor has since submitted several versions of a RMP, implementing part of the plan which included product re-education initiatives, labeling revisions, the distribution of a Medication Guide and a "Dear Health Care Practitioner" letter. Negotiations with FDA continued for the remaining elements of the RMP, but it was clear that the Agency did not find the sponsor's RMP entirely satisfactory. This situation was compounded because of the significantly increasing use of the drug: during a 9-month period, over —— patients filled over —— prescriptions of the drug.[2]

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[1] Intense negotiations between the sponsor and the GI Team in collaboration with other CDER members, including Drs. Nancy Ostrove and Karen Letcher, culminated in a July 31, 2000 CDER recommendation to the then FDA Commissioner, Dr. Jane Henney, that the proposed patient labeling for Lotronex ® be designed as an official Medication Guide. This recommendation was accepted by the Commissioner. A Patient Medication Guide began to be implemented by the firm on August 23, 2000.

[2] At the time of the drug's withdrawal from the market, the number of prescription may have been more than —— according to data provided by the Sponsor).

At the November 28, 2000 meeting between GW and the Agency, after considering the RMP options presented by the Agency, the sponsor voluntarily withdrew Lotronex® from the market.

Soon after the voluntary withdrawal of Lotronex® from the market, many patients have contacted the Agency seeking access to Lotronex. Many of these patients have described their suffering as well as the **chronic and debilitating** nature of their IBS symptoms. Through their E-mails or telephone conversations these patients have expressed frustration with their inability to control their IBS symptoms successfully with therapies other than Lotronex®, and they have indicated that they are desperate for access to Lotronex®. The need to provide interim access to Lotronex® for these patients in need was once again reiterated in a letter to sponsor. When presented with two possible options, access under an IND or under 21 CFR 314 Subpart H, the sponsor opted for the ultimate access under Subpart H (i.e. marketing approval). The sponsor's restricted distribution Subpart H approach is the main subject matter addressed in the present review.

It needs to be emphasized that, as noted by the sponsor in their sNDA submission of December 7, since January of 2001, representatives of FDA and GSK have held discussions to explore options related to the development of a mutually acceptable RMP. These milestones are briefly summarized below.

| DATE (2001) | EVENT/PROPOSAL |
|---|---|
| **February 14** | • (meeting): FDA and GSK agree that initial efforts for development of a RMP would focus on appropriate product labeling |
| **March 9** | • GSK submit proposed changes to the package insert and Medication Guide. A patient-physician agreement document is proposed. |
| **March 23 and 27** | • FDA facsimiles to GSK |
| **March 29** | • t-con: GSK obtains further input from FDA |
| **April 3** | • (meeting): GSK describes to FDA representatives the RM program. FDA requests specific modifications to the plan. |
| **July 6** | • In letter to FDA, GSK describes the goals of the sNDA and discussion topics for the July 13 meeting |
| **July 12** | • FAX: FDA provides a list of requests for inclusion in the sNDA |
| **July 13** | • sNDA pre-submission meeting |
| **July 18** | • t-con between Dr. Raczkowski and Dr. D. Wheadon concerning a separate meeting to discuss providing access to Lotronex® |

| | |
|---|---|
| **August 9** | • At t-con, the Agency requests GSK facilitate FDA access to patients reporters of AEs |
| **August 23** | • GSK letter, providing a summary of the discussions that occurred at the July 13 pre-submission meeting. The final Clinical Study Reports of 28 of the 40 new studies that will be included in the sNDA are submitted. |
| **September 4** | • FDA sends Patient Access letter to sponsor |
| **October 25** | • GSK submits 40 Reports of Clinical Studies (EDR) |
| **December 7** | • sNDA submission. Supplement contains safety data from 40 trials, revised labeling and revised RMP (EDR) |
| **December 20** | • GSK submits CRFs in response to Medical Officer's requests. |

## II. Review of GSK proposed RMP for LOTRONEX® (sponsor's sNDA of December 7, 2001)

The sponsor's proposal consists of the following 11 components:

1. Objectives
2. Patients for whom Benefits outweigh Risks
3. Appropriate Prescribers
4. Modified Labeling
   - Package Insert and Medication Guide
   - Patient-Physician Agreement
5. Modified Packaging
6. Communication of Risk
7. Definition of Risk
   - Additional Clinical Trials
   - Epidemiological Research
8. Program Evaluation
   - Patient-based monitoring
9. Enhancement of Safety Monitoring
10. Post-Marketing Commitments
11. Promotional Activities

**NOTE:** For simplification purposes, the comments to each of these components will be given in Table form. Additional remarks are included within the text.

**1. Objectives (Table 1)**

(See the Comments section of this Table).

In addition the reviewer wishes to mention that the characterization of Lotronex-induced intestinal **vasculopathy/ischemic colitis (IV/IC)** is incomplete. Although one may suspect that the patient has Lotronex-induced IV/IC by the presence of blood in the stool and presence of abdominal pain (of different character/nature from that denoting IBS), the complication appears to have a varied presentation. Only some of the factors/drugs that appear to predispose to Lotronex-induced IV/IC are known. It does not have a predictable anatomical distribution which is rather variable. It is not always restricted to the colon. It sometimes requires surgery but it is not yet possible to predict with certainty when does it require resection of the involved colon (or small intestine?). It does not appear to have a chronic course or recurrences (but more information is needed). Although it is suspected not to produce permanent damage to the gut, it is not really known if IV/IC is reversible despite continued usage of Lotronex. However, in most instances, it is not very difficult to differentiate Lotronex-induced IV/IC from other colitides.

**2. Patients for whom benefits outweigh risks (Table 2)**

This proposal seems acceptable.

Indeed, the indication for use and population treated are two important factors influencing a benefit/risk assessment. There are anecdotal information originating via E-mail from many patients who claimed that Lotronex was of benefit in circumstances where no other medication worked.

Table 1

## 1. Objectives of the GSK RM P for Lotronex®

| sNDA (December 07, 2001) | COMMENTS |
|---|---|
| • Designed to address the risk issues of IC and serious complications of constipation.<br><br>• GSK believes that serious complications of constipation represent a rare but largely manageable risk.<br><br>• While IC presents a risk for a small number of patients, sequelae may be prevented or mitigated with appropriate medical supervision, patient and prescriber knowledge, immediate cessation of Lotronex, and prompt medical attention.<br><br>• Access to Lotronex would be restricted under the provisions of 21 CFR 314 Subpart H.<br><br>• GSK's RMP will restrict prescribing to only physicians knowledgeable and experienced in the diagnosis of IBS and diagnosis and management of IC and complications of constipation.<br><br>• An initial lower starting dose will be implemented.<br><br>• Physician and patient knowledge will be enhanced with modified labeling including an enhanced Medication Guide, Mandatory patient/physician agreement document, health care provider education, and modified packaging. | Although the overall RMP might be acceptable, the sponsor appears to be overoptimist in two areas:<br>a) At the present time, risk factors for the development of IV/IC have not been identified. Many of the cases presented with no prodromic manifestations. In some, the presence of blood in the stool together with an increase in severity but -- more important -- change in the nature of abdominal pain, may be a signal to discontinue Lotronex.<br><br>b) The reviewer agrees with the sponsor that serious complications of constipation may represent a largely manageable risk. **The primary approach to control constipation and its complications is PREVENTION.**<br><br>c) The reviewer agrees with the sponsor that IV/IC sequelae may be prevented or mitigated with the most adequate medical supervision, patient and prescriber knowledge, immediate discontinuation of Lotronex® and prompt medical attention.<br><br>• There is, however, a challenge in identifying the early signs of complications of constipation in those patients, like the 14 described in the memorandum authored by Dr. Kress indicating that these patients experienced impaction **without even suspecting** that they were constipated. In these patients a very conservative and strict definition of constipation may be needed. A strict, conservative definition of constipation should consider number of daily stools, consistency of the stool and straining associated with the bowel movement. The challenge is to inform the patient when to discontinue the drug in order to prevent serious complications while at the same time allowing for continuation of the medication in those patients who are deriving benefit. |

## Table 2

### 2. Patients from whom benefits outweigh risks

| sNDA (December 07, 2001) | COMMENTS |
|---|---|
| • Indicated for women with DP-IBS who have failed traditional therapy.<br><br>• Patients would be educated about benefits and risks of Lotronex by the prescriber and would be required to review and sign a **patient-physician agreement document** (based on the content of the FDA approved Medication Guide) confirming the delivery of the key messages.<br><br>• The most important safety messages are reinforced by a FDA approved Medication Guide that Pharmacists are required by federal law to provide at the time of dispensing.<br><br>• According to the sponsor, the dispensing of Medication Guides at the pharmacy level will be facilitated by introduction of new packaging. | a) Although the reviewer agrees with the approach of restricting treatment to those patients who have exhausted other treatment options, there are no data - other than anecdotal information - demonstrating that Lotronex is effective in **refractory** patients.<br><br>b) On the other hand, the reviewer agrees that restricting use under 21 CRF 314 Subpart H only to those patients for whom there is no reasonable therapeutic alternative raises the threshold for acceptance of possible risks.<br><br>c) At some point in time the sponsor should be asked to carry out a clinical trial in severly debilitated DP-IBS female patients not responding to other treatments. If using this approach, benefits are shown in this group of patients, the indication for use and population treated would be more adequate/acceptable in view of the known potential AEs. |

3. **Appropriate Prescribers (Table 3)**

Listed in Table 3 are sponsor's proposed measures intended to **restrict** prescribing of Lotronex to only those physicians who are knowledgeable and experienced in the diagnosis and treatment of IBS and able to diagnose and manage IV/IC and serious complications of severe constipation. This **very broad definition** does not seem to meet the definition of "restricted." In this section, GSK does specify who these prescribers would be but in section 6. "Communication of Risks" the sponsor states that target audience will be the following HCP

The reviewer does not agree with the sponsor. Appropriate prescribers should be Gastroenterologists (ONLY) who should be chosen not only on the basis of their professional (specialized) qualifications but also because of their willingness and commitment (by signing appropriate documents) to comply with all other components of the RMP.

- Although the word "qualified" is used, the sponsor needs to specify that these are Physicians (Gastroenterologists) who understand IBS, the drug and the response to the drug (Safety and Efficacy=S+E). Gastroenterologists have training and experience, can provide adequate IBS patient care and most are experienced in the monitoring of S&E in clinical trials. The sponsor should be able to examine physician's records to determine if he/she continues to be qualified as a Lotronex® prescriber.

- Examples for Physician's disqualification are:
  - Fails to keep adequate records
  - Fails to report serious or unexpected AEs
  - Fails to maintain good clinical practice
  - Does not comply with exclusion criteria (labeling)
  - Violates the protocol (major; although the drug is available in the market, the prescribing physicians need to follow a certain "protocol")
  - Prescribes the drug inappropriately: for example to men; women who are already constipated, ignores contraindicated drugs or conditions
  - Uses the drug off-label
  - Delegates authorization of patient care to unqualified individuals

NOTE: One obvious challenge is how to enforce the above-listed requirements to be met by Gastroenterologist participants to this program. Further interaction between FDA and GSK is needed to arrive at mutually agreeable approaches dealing with the **practice of medicine**. In short, the FDA "should not interfere with the practice of medicine". But in this particular case maybe it should.

- A gradual expansion of appropriate Lotronex® prescribers should be based on agreed upon stages.

**Table 3**

**3. Appropriate Prescribers**

| sNDA (December 07, 2001) | COMMENTS |
|---|---|
| • The product labeling will specify that prescribing is restricted to only physicians knowledgeable and experienced in the diagnosis and treatment of IBS and able to diagnose and manage ischemic colitis and complications of constipation.<br>• Prescriptions must be conveyed in writing only.<br><br>**Physicians must:**<br><br>• Sign an attestation statement located on the patient-physician agreement document confirming appropriate experience/training.<br>• Counsel patients on benefits-risks and key safety monitoring issues.<br>• Obtain confirmation of patient education via signed patient-physician agreement.<br>• Provide a copy of the agreement document to the patient and place a copy in the patient's medical record.<br>• Affix a special sticker to the written prescription to provide notice to pharmacists that the prescription was written in accordance with the RMP. | a) The goal of the Program should be to closely monitor each patient taking the drug through a **Patient Registry** administered by the sponsor.<br><br>b) Although the description of "Appropriate prescribes" is adequate, there seems to be an incongruency between such a definition and the total number of physicians/specialists that may participate in the Restricted Distribution Plan.<br><br>c) Appropriate prescribers should be Gastroenterologists **(ONLY).**<br><br>d) A gradual expansion of appropriate Lotronex® prescribers should be based on agreed upon stages. |

4. **Modified Labeling (Table 4)**

The GSK's USPI Key elements of the proposed labeling changes to the existing PI and the Medication Guide are listed in Table 4. As the sponsor states, the proposed changes reflect discussions with FDA that occurred at various times. Included were meetings of February 14 and April 13, 2001, phone conference of March 29, and written input contained in the FDA facsimiles of March 23 and 27 (provided in response to GSK's proposal submitted on March 9, 2001).

In the **Black Box Warning** section information is now included on outcomes, such as visit to the ER, hospitalization, need for transfusion, surgery and even fatal outcomes, not use of the drug in [redacted]; those already constipated and in those who already have underlying conditions that predispose them to IV/IC or [redacted] The same conditions are listed in the **Contraindication** section of the labeling.

[redacted] 1 mg QD appears reasonable, it needs to be clarified that one would be using this approach mainly for safety. This is because in Phase II trials, this regimen of alosetron did not seem to be efficacious. Furthermore, the patients being enrolled in this program are women with DP-IBS who have "severe" IBS and in addition, have failed traditional therapy, It is not inconceivable that - due to the severity of their condition - these patients may eventually need to be treated with the recommended dose/regimen of the drug (1 mg BID). In other words, [redacted] in these patients may show neither IV/IC nor overt constipation or complications of constipation. But at the same time no effects on the abdominal pain, urgency and/or increased frequency being experienced by these patients may be seen (thus no overt safety problems but also no benefit) [see additional comments in Table 4].

This reviewer recommends modifying the **Information for Patients** section of the labeling and the **Medication Guide** to provide the most conservative approach to the definition and effective management of constipation that develops following the administration of the drug. As we have repeatedly stated, constipation is a very subjective manifestation and should be **defined by the patients themselves**. Nonetheless, some important directions to the patient seem important. Constipation can be monitored on the basis of three main manifestations. The presence of each of these manifestations must be a reason to **discontinue the drug**.

i. [redacted]
ii. decrease in consistency: [redacted]

i and ii are of course, a **challenge,** because the DP-IBS patients may have been experiencing diarrhea or liquid stools for a long time and may be rather happy to experience some constipation for a change.

and

iii. [redacted]

But the final wording should allow for continuation of the drug in those patients who are deriving benefit (see Table 4).

**Table 4**
**4. Modified Labeling**

| sNDA (December 07, 2001) | COMMENTS |
|---|---|
| • A **Black Box Warning** has been prominently placed at the beginning of the PI.<br>• The **Indication** section has been modified to reflect that LOTRONEX should be used only in women with DP-IBS who have not received satisfactory control of symptoms with traditional therapy (i.e. second line therapy).<br>• The labeling has been modified to include a warning regarding use in elderly and/or debilitated patients.<br>• The **Warnings** section includes language reflecting additional safety information received since the labeling was approved in August 2000. Specific changes include: Rewording of the warning section further emphasizes the most important safety information; enhanced directions to monitor for constipation; a drug is stopped in patients with non-severe constipation; telephone numbers have been added for GSK and FDA to facilitate prescriber reports of adverse events; and a warning has been added regarding use of concomitant medications that can cause constipation.<br>• The **Information for Patients** section has been enhanced to add detail regarding the patient counseling and agreement process.<br>• The Dosage and Administration section has been modified to include a low-dose initial treatment period (1 mg daily). Only after it has been demonstrated that patients adequately tolerate this trial period of a low dose, would therapy at doses supported by clinical trials be initiated.<br>• The **Medication Guide** has been modified to be consistent with the PI<br><br>**Patient-Physician Agreement**<br><br>• This document will be mandatory component of the RMP.<br>• The P-PA is consistent with the discussion outcomes from the March 29, 2001 teleconference As discussed previously, GSK proposes a combined patient-physician agreement form, to include physician attestation, rather than a patient-physician agreement and a separate document to provide physician attestation. | a) All in all, the proposed labeling revisions are acceptable. For the most part, these revisions are based on FDA's suggestions, which have been incorporated into the various sections of the labeling.<br><br>b) A critical component of the labeling is how to enhance directions to monitor and manage the risk of constipation, especially in that patient in whom a serious complication of severe constipation has occurred and who has not even "noticed" that she is constipated.<br><br>c) It is worth noting that GSK proposes a combined patient-physician agreement form, to include physician attestation, rather than a patient-physician agreement plus a separate document to provide physician attestation. This seems a reasonable approach. |

**5. Modified Packaging**

The packaging configuration previously marketed for Lotronex Tablets, 1 mg is: 60 tablets packed

GSK intends to pursue changes to this configuration as interventions intended to improve safety:

- Unit-of-use dispensing with medication guide and bottle enclosed within a sealed carton
- Changes from 60 to 30 count bottle as soon as practicable.

nt. If the patient tolerates Lotronex® at 1 mg per day, but is not yet deriving benefit, she can then given medication at the dose of 1 mg BID (the usually recommended dose) for 1 month using . If the patient tolerates the 1 mg per day dose **and** is deriving benefit (not very likely in view of existing Phase II information) she may continue on Lotronex® 1 mg per day.

**6. Communication of Risk (Table 5)**

The sponsor states that the communication of risk component of the RMP has been developed in recognition of the intense media attention regarding GW's withdrawal of Lotronex® and potential risks associated with treatment with this drug. The proposed plan provides the following primary features:

- Designed to help ensure Lotronex® is prescribed only to **appropriate, informed patients.**
- GSK will provide substantial **educational opportunities to Health Care Providers (HCPs).**
- Involves **Pharmacists** as a real-time double check to assure that provisions of the program are being followed.
- Medical education to be promoted and posted on-line.

The above-listed primary features of the communication of risk component of the RMP appear adequate. Specific elements of the communication component of the RMP are summarized in Table 5. As previously stated, the reviewer does not agree with the type and number of HCPs and Pharmacies. A smaller (restricted) number is proposed as the **start of the program.** The numbers of HCPs and Pharmacies and the types of Specialists that could be enrolled in the Plan may increase after a reasonable amount of time (ex. 1 year) of restricted distribution has elapsed, and an evaluation of the program **demonstrates success.** The latter is measured by an unequivocal demonstration that the various energetically/forcefully executed interventions work.

That the aggressive Restricted Distribution Program to ensure appropriate use has made these adverse events **manageable**. In other words, this means that serious complications of severe constipation have been largely prevented and that the **severity** of IV/IC cases **(it is unrealistic to expect no cases of IV/IC)** has considerably decreased.

The sponsor states that there are no plans at this time to distribute patient starts (samples) or conduct a Direct to Consumer (DTC) campaign on behalf of Lotronex®. This less intense advertising is acceptable.. However, it seems that if Lotronex® is really re-introduced, the **uniqueness** of this Regulatory Action by FDA will have **a very significant impact in the public** so that no campaign on behalf of the drug may be needed. After all, it would be the **one and only drug re-introduced** into the marketing after withdrawal. To this reviewer's knowledge, no other situation is similar to this, although drugs such as thalidomide, accutane and cisapride - among others - are being used under Restricted Distributions Programs. **Thalidomide** is now approved for the treatment of **erythema leprosum nodosum** (a very rare condition for which it is very effective) but was **never approved** in the U.S. **Accutane** is approved in this country for the treatment of **rosacea** for which clear cut efficacy was demonstrated. Accutane was never withdrawn from the U.S. market. **Cisapride**, removed from the market because of serious cardiac arrhythmias and questionable/inconsistent efficacy in nocturnal heartburn related to GERD, is being made available to selected patients under a **Limited Access Program** but there are no intentions or sound rationale for bringing the drug back into the U.S. market.

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**TABLE 5**

**6. Specific Components of the Communication of Risk Component of the Plan**

| sNDA (December 07, 2001) | COMMENTS |
|---|---|
| • **Dear Healthcare Professional (HCP) Letter**: Announces reintroduction via communication that includes a letter, new PI, new Medication Guide, and a sample copy of the new Patient/Physician Agreement form. Also included will be a sample of a prescription sticker.<br>• Pharmacists will be instructed in their communication materials not to dispense Lotronex unless a sticker is affixed to the written prescription.<br>• **Target audience** will be the following HCP and Pharmacies:<br>- A total of — Pharmacies wil receive an additional ~age with stocking and dispensing information including: — etail pharmacies and — hospital pharmacies<br>• **Re-Introduction Patient Agreement Kit**<br>• The kit will be available to HCPs who request it from 1-800 number, and a website.<br>• **Sales representatives:** will be trained on changes to the Package Insert/Medication guide and on the introduction of the Patient-Physician Agreement Form and stickers.<br>• **Product/IBS Disease Awareness:** Product specific and IBS disease materials will be available via a GSK sales force.<br>• **Product Specific Materials:**<br>- Package Insert/MedGuide/Patient-Physician Agreement Form with stickers<br>- Formulary Kit-Managed Care<br>- Dear HCP Letter<br>- Website: Includes downloadable Package Insert, Medication Guide and instructions on how to order Patient-Physician Agreement Forms and Stickers<br>- Patient Education Brochure: How to use Lotronex as well as IBS information<br>• IBS/GI AGA Disease Materials | a) The use of stickers is important because they will be affixed to the prescription for Lotronex by the physician. In addition, stickers will serve as notice to a pharmacist that the physician has written the prescription in accordance with the RM Program.<br><br>b) The sponsor's proposed number of **trained prescribers** is too large. It is recommended that the **first RMP** consists of the following target for prescribers and distributors:<br>— Gastroenterologist prescribers (ONLY)<br>b. Hospital pharmacies and — retail pharmacies<br><br>c) A gradual expansion should be based on agreed upon stages.<br><br>d) As explained by the sponsor, the Re-Introduction Patient Agreement Kit contains a letter outlining re-introduction program. The kit includes: new package insert, —<br>Form along with prescription stickers outlined above. The kit will also include product specific and IBS Disease Awareness materials list that HCPs can order for their patients. This approach appears reasonable.<br><br>e) The kit will also be delivered by sales representatives to physicians **(Gastroenterologists)** believed to have been among the most frequent prescribers of the drug while it was previously marketed.<br><br>f) DTC/Patient Starters: There are no plans at this time to distribute patient starts (samples) or conduct a DTC campaign on behalf of Lotronex **[see text]**. |

7. **Definition of Risk (Table 6)**

This component of the Risk Management Plan includes Additional Clinical Trials and Epidemiologic Research. Regarding **additional CTs** answer to the three questions listed below is **critical** to the start of the Subpart H program: within a few months [(if YES to a) or b)] vs within a few years [if YES to question c)].

**NOTE: This reviewer strongly recommends the approach listed under a). The other approaches would significantly delay access of the drug to the patients in need.**

a) Should a **commitment** from GSK to **start** these additional clinical trials be acceptable before market re-introduction?

b) Should the actual beginning of these additional clinical studies be enough for the Agency to approve re-introduction of Lotronex into the U.S. market?

c) Should the results of these additional efficacy evaluations be a requisite for market re-introduction?

**Epidemiological Research**

The sponsor states: "Information regarding the epidemiology program was previously described in GlaxoWellcome's presentation at the June 27, 2000 Advisory Committee meeting. Detailed information regarding the protocols and design of the epidemiology trials were previously submitted to NDA 21-107 in letters dated August 31, 2000 and October 11, 2000. Other letters describing the epidemiology studies include those dated: December 22, 1999, May 17, 2000, June 29, 2000, and November 2, 2000. A summary of recently generated data that are pertinent to an understanding of the background incidence of ischemic colitis was submitted with our letter dated May 15, 2001."

This reviewer recommends that this component of the December 07, 2001 sNDA be evaluated by ODS, with active participation of members from the GI Clinical Team.

## TABLE 6

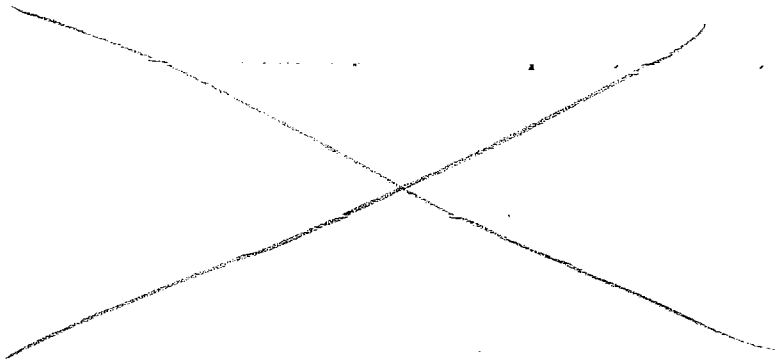
### 7. Definition of Risk

| sNDA (December 07, 2001) | COMMENTS |
|---|---|
| **Additional Clinical Trials**<br><br>a. Dose titration study<br><br>b. A study that evaluates a functional outcome as the primary endpoing with a **randomized withdrawal** component.<br><br>c. Studies to evaluate constipation management options and to explore alternative doses (agreements beyond the original set of Phase 4 commitments).<br><br>**Epidemiologic Research**<br><br>• An extensive program of epidemiologic research is ongoing. These studies are being conducted as part of the Phase 4 commitments agreed at the time of approval.<br>• This research is intended to generate population-based data to quantify the occurrence of IC and complications of constipation in Lotronex users and to evaluate risk factors for those events.<br>• The studies fall into two categories:<br><br>1) Studies specifically designed to evaluate IC and severe constipation in populations including Lotronex users, and<br><br>2) Studies designed to improve our understanding of the background incidence and risk factors for these events. | a) The sNDA includes concept Protocols for the two studies described under CONCLUSION, 5. Need for additional efficacy data ,of the current review.<br><br>b) The sponsor states that substantial FDA input regarding the design of studies planned under c., had already been given [redacted]<br><br>c) The design and proposed execution of the proposed protocols appears acceptable.<br><br>d) The reviewer strongly recommends that a commitment from GSK to start these additional clinical trials is acceptable before marketing re-introduction. Other approaches may significantly delay access of the drug to the patients in need |

**8. Program Evaluation (TABLE 7)**

GSK designed two studies to evaluate program compliance via **physician-monitoring** and **patient-based monitoring**. The key elements of these studies are summarized in Table 7. The aim of the monitoring of prescribing practices seems appropriate: to characterize all patients who receive Lotronex® by "appropriateness for Lotronex® therapy". Also appropriate is the patient-based monitoring since it includes information on whether counseling was provided and Patient-Physician Agreement was signed and whether the Medication Guide was received.

This reviewer proposes to assess this component of the RM Plan in consultation with a specialist on Risk-Management such as Dr. Holmboe. It seems that the following information could be used to assess whether the RMP instituted by GSK is succeeding or failing. Note that for IV/IC, the **frequency** of events in these Epidemiological studies is expected to be the same as in the RCTs (one in 750) whereas the number of cases of increased primary or secondary colonic ischemia is expected to considerably decrease.



NOTE: The Risk Management Program evaluation should be closely monitored by a group of FDA

- There is need to have an agreed upon predetermined frequency and severity of SAEs that will trigger **further restriction of distribution** and/or removal from marketing.

**TABLE 7**
**8. Program Evaluation Component**

| sNDA (December 07, 2001) | COMMENTS |
|---|---|
| **Monitoring of Prescribing Practices**<br><br>Data to be collected to characterize all patients who receive Lotronex by "appropriateness for Lotronex therapy"<br><br>• Demography<br>• Relevant GI medical history in the six months prior to the first dispensing of Lotronex<br>• Whether care was provided by a **gastroenterologist**<br>• Frequency of visits to the **gastroenterologist**<br>• Prescription drug dispensing in the 6 months prior to Lotronex<br>• Safety evaluation<br><br>**Patient-Based Monitoring**<br><br>This is a prescription-based approach to the study of Lotronex in collaboration with the Slone Epidemiology Unit (SEU)[a] and Eckerd Corporation. Within<br><br>• Demography<br>• IBS history and severity<br>• Appropriateness for treatment with Lotronex<br>• Medications used prior to Lotronex<br>• Whether counseling was provided and Patient-Physician Agreement was signed<br>• Receipt of the Medication Guide<br><br>• Safety data will be collected in a follow-up contact | a) The sponsor states that these two studies were discussed during the April 3, 2001 meeting with the Agency.<br><br>b) In addition to the specific data to be collected during the study, safety data will be collected in a follow-up contact in order to conduct a safety evaluation. For patients with selected serious AEs, additional information,<br><br>c) In this reviewer's opinion, the Program Evaluation Component needs to be assessed by a Specialist in Risk-Management. The Division needs to send a Consult to the appropriate individual(s). Meanwhile, the success/failure of the RM Program can be assessed on the basis of certain goals as specified within the text of this review.<br><br>• The RMP evaluation should be closely monitored by an FDA group, from the a<br><br>• There is need to have an agreed upon predetermined frequency and severity of SAEs that will trigger **further restriction of distribution** and/or removal from marketing.. |

[a] Boston University School of Medicine Post Marketing Study of Lotronex

**9. Enhancements for Safety Monitoring**

GSK agrees to voluntarily expedite reporting of "targeted events" by utilizing an Expert Review Board (ERB) to provide an independent expert evaluation of the evolving safety data.

These matters were discussed during the April 3, 2001 meeting between the Agency and GSK. This proposal appears reasonable. The ERB will be comprised of external gastrointestinal experts who will provide GSK with assessments regarding key safety issues including IV/IC, complications of constipation, and other G.I. events. In addition, an initial followed by regular meetings (e.g. quarterly) are needed between GSK and FDA to establish a common understanding of the baseline safety data prior to implementation of the RM Plan intervention and re-introduction of Lotronex under a Subpart H Restricted Distribution Program.

**10. Post-Marketing Commitments**

- A detailed description of the status of the post-marketing commitments was given on pages 367 through 373 of the NDA Annual Report dated April 12, 2001.

- Should Lotronex® be reintroduced, GSK will continue to comply with these prior commitments. However, in view of the product withdrawal, GSK will need to reach agreement with the Agency on the timeframe to complete any outstanding activities as well as any **new requirements**. This approach appears reasonable.

- The sponsor states: "It is expected that these commitments would be listed as conditions of approval of the restricted use plan instituted under 21 CFR 314 Subpart H." Again, the proposal is acceptable.

**11. Promotional Activities**

- GSK states that, in accordance with their plans to seek approval of the modified labeling restrictions for use described under 21 CFR 314 Subpart H promotional activities for Lotronex will be subject to the provisions of 21 CFR 314.550.

- Product specific promotional materials will be submitted to FDA for pre-approval.

- This approach seems reasonable. In addition, please see Section 6. Communication of Risk of this review, for reviewer's opinion on GSK's no plans to distribute patient starts (drug samples) or conduct a DTC (Direct to Consumer) campaign.

## III. OVERALL SUMMARY/CONCLUSIONS/REGULATORY RECOMMENDATIONS

The reviewer believes that the Risk Management Plan proposed by the sponsor, which is based on the agreed on principle modified labeling and on close interactions with the Agency is appropriate, with the modifications/clarifications/adjustments of/on some of the components, as briefly summarized below. It is to be noted that the newest version of the **modified labeling** contain new items (wording) which we have not agreed. Considerations regarding other aspects of the use of the drug are also included.

1. The primary goal to the occurrence of serious complications of constipation should be **PREVENTION**. This should be handled using the most conservative approach which is to discontinue the drug at the earliest sign of this side effect while allowing for continuation of the medication in those patients who are deriving benefit. Efforts toward the elucidation of the risk/predisposing factors for the development of intestinal vasculopathy/ischemic colitis (IV/IC) should continue.

2. Scientific data should be developed in support of the approach of restricting use under 21 CRF 314 Subpart H to only those patients with significant impairment for whom there is no reasonable therapeutic alternative.

3. The appropriate prescribers should be **Gastroenterologists (ONLY)** who are willing to comply with all required aspects of the RMP. One challenge is to develop sound reasons/approaches to disqualify prescribers from continuing participation into this plan. A gradual expansion of appropriate Lotronex® prescribers should be based on agreed upon stages.

- The goal of the Program should be to closely monitor each patient taking the drug through a **Patient Registry** administered by GSK.

4. Significant progress regarding the modified labeling has been made, but further interaction between GSK and FDA is needed to arrive at mutually acceptable changes, and also to incorporate revisions proposed by this reviewer, before FPL.

5. [redacted]

NOTE: If the patient tolerates the 1 mg per day dose [redacted] **and** in deriving benefit [redacted]. If the patient tolerates the 1 mg per day dose [redacted], **but is not deriving benefit,** she may be [redacted]

6. The **first RMP** should be as follows :

   a. [redacted] Gastroenterologist prescribers (ONLY)

b. Hospital Pharmacies and [redacted] retail pharmacies.

- A gradual expansion of the number of participating Gastroenterologists and pharmacies should be based on agreed upon stages.

7. Additional RCTs and Epidemiological Research is needed. In order not to delay access of the drug to the patients in need, marketing reintroduction under the RMP should start once a commitment from GSK to **start** these additional clinical trials has been obtained.

   Additional epidemiological research proposed by GSK should be evaluated by ODS, with active participation of members of the GI Clinical Team.

8. It is recommended to f [redacted], to closely evaluate/monitor program compliance. Tools such as these listed in the tezt under 8. Program Evaluation of this review, should be put in place to assess the success/failure of the proposed Program. Strong participation of individuals that are experts on risk management should be sought.

- There is need to have a preagreed upon predetermined frequency and/or severity of SAEs that will trigger **further restriction of distribution** and/or removal from marketing.

9. The proposed utilization of an Expert Review Board (ERB) is acceptable. This would provide an independent expert evaluation of the evolving safety data. In addition, an initial, followed by regular meetings (e.g. quarterly) between FDA and GSK should be planned.

10. The post-marketing commitments, listed as conditions of approval of the restricted use plan instituted under 21 CFR 314 Subpart H are acceptable. Also, an important re-introduction component should be a commitment to initiate the proposed clinical studies.

11. The sponsor's proposed promotional activities, subject to the provisions of 21 CFR 314.550 (under CFR 314 Subpart H) appear reasonable to this reviewer. This is, however, subject to further considerations by DDMAC.

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/s/

Hugo Gallo Torres
2/14/02 03:17:40 PM
MEDICAL OFFICER

**DIVISION 0F GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS**
MEDICAL OFFICER'S REVIEW

**NDA: 21-107**

SPONSOR: Glaxo Smith Kline, Five Moore Drive, Research Triangle Park, North Carolina, 27709

DRUG: Alosetron hydrochloride (Lotronex™) tablets 1 mg

DATE OF SUBMISSION: 29 June 1999

DATE OF APPROVAL: 9 February 2000

VOLUNTARILY REMOVED FROM THE MARKET: 28 November 2000

INDICATION: Relief of abdominal pain in patients with diarrhea predominant Irritable Bowel Syndrome

SUBJECT UNDER REVIEW: Ischemic Bowel complications associated with Alosetron (Lotronex™) intake

MATERIAL REVIEWED: Medical Officer Review (MOR) (Efficacy), R. Prizont, MD NDA 21-107, Oct. 15, 1999; MOR (Safety), J. Senior, MD, NDA 21-207, Oct. 22, 1999; MOR (Secondary), H. Gallo-Torres, MD, NDA 21-207, Nov. 17, 1999; OPDRA Review, 31 July, 2001; S. Kress, MD et al Review of Deaths 29 Aug 2001; S. Kress, MD Review of Constipation, 9 Oct 2001; S Kress MD, Personal communication, Oct 2001.

MEDICAL REVIEWER: Marcelo A. Barreiro, MD, MSc

**ALOSETRON ASSOCIATED ISCHEMIC BOWEL DISEASE (AAIscBD)**

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## GLOSSARY OF ABBREVIATIONS

| | |
|---|---|
| 5HT3 | 5 Hydroxy Tryptamine 3 (receptor) |
| A/E | Adverse Event |
| AAIscBD | Alosetron Associated Ischemic Bowel Disease |
| AERS | Adverse Event Reporting System |
| ALT | Alanine Amino Transferase (formerly GPT) |
| AMI | Acute Mesenteric Ischemia |
| AST | Aspartate Amino Transferase (formerly GOT) |
| BID | Twice a day |
| CBC | Complete Blood Count |
| CCK | Cholecystokinin |
| CG | Colonic Gangrene |
| CHD | Coronary Heart Disease |
| CHF | Congestive Heart Failure |
| CI | Colonic Ischemia |
| CMI | Chronic Mesenteric Ischemia |
| CRF | Case Review Form |
| CRH | Corticotrophin Releasing Hormone |
| CT | Computer Tomography |
| CYP-450 | Cytochrome P-450 |
| DP-IBS | Diarrhea Predominant Irritable Bowel Syndrome |
| DVT | Deep Vein Thrombosis |
| ENS | Enteric Nervous System |
| ERCP | Endoscopic Retrograde Cholangiopancreatography |
| FSI | Focal Segmental Ischemia |
| GI | Gastrointestinal |
| GSK | Glaxo Smith Kline (Laboratories) |
| GW | Glaxo Wellcome (Laboratories) |
| HCS | Hyper Coagulable State |
| HMO | Health Maintenance Organization |
| HRT | Hormonal Replacement Therapy |
| IBS | Irritable Bowel Syndrome |
| IC | Transient Ulcerated Ischemic Colitis |
| IE | Insufficient Evidence |
| IFFGD | International Foundation for Gastrointestinal Disorders |
| IMA | Inferior Mesenteric Artery |
| INR | International Normalized Ratio |
| IscBD | Ischemic Bowel Disease |
| Ki | The concentration of a drug required for half of the receptors to be occupied |
| LAG | Lotronex Action Group |
| FLT | Liver Function Tests |
| mg | milligram |
| MVT | Mesenteric Vein Thrombosis |

| | |
|---|---|
| NC | No change |
| NS | Not sufficient |
| OPDRA | Office of Post-marketing Drug Risk Assessment |
| PD | Pharmacodynamics |
| PK | Pharmacokinetics |
| PT | Prothrombin Time |
| PTT | Partial Thromboplastin Time |
| RMP | Risk Management Plan |
| S/P | Status Post |
| SA | Strong Association |
| SERM | Selective Estrogen Receptor Modulator |
| SMA | Superior Mesenteric Artery |
| SMV | Superior Mesenteric Vein |
| SSRI | Serum Serotonin Reuptake Inhibitor |
| TE | Thrombo-Embolic |
| TPN | Total Parenteral Nutrition |
| ULN | Upper Limit of Normal |
| VAIP | Vasoactive Intestinal Peptide |
| WBC | White Blood Cell |
| Y/O | Year Old |

## ALOSETRON-ASSOCIATED ISCHEMIC BOWEL DISEASE

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## EXECUTIVE SUMMARY

This review analyzes the data from 78 patients with suspected Ischemic Bowel Disease (IscBD) associated with Alosetron (Lotronex®, Glaxo Wellcome, later Glaxo Smith Kline, GSK) intake. These patients were identified during the course of pre-approval clinical trials or were reported to the Office of Post-marketing Drug Risk Assessment (OPDRA) by physicians, other health care providers and consumers.

The purpose of this review is to assess the clinical significance of these epidemiological data and attempt to identify predisposing risk factors and clinical patterns that could be used in the design and implementation of a Risk Management Plan (RMP), should Alosetron be reintroduced in the market.

This review is addressed to the physicians in management positions at the CDER, and other professionals who may find this information useful for their practice. This review is not intended to be read by the lay public.

**Irritable Bowel Syndrome (IBS)** is the accepted term to identify a group of patients with predominantly colonic symptoms, "without physical or biochemical" evidence of disease that justifies those symptoms. Seventy percent of these patients, in the western world, are female. The cause of IBS is unknown. Recent findings have established that these patients actually have abnormalities in the transmission of impulse at the level of the synapses with a disordered brain-gut regulation, that can be demonstrated by research tests that have not yet been accepted in the clinical practice. The implication of this is that diagnosis and measurement of severity in these patients is carried out by evaluation of symptoms by the attending physician or by the patients' answers to lengthy questionnaires, both of which are poor replacements for a biological marker (for example hemoglobin determination in anemia). This fact complicates the design of clinical trials, the interpretation of results, the measurement of placebo effect, and retrospective reviews like this one.[6,21]

**Alosetron** is a selective 5-$HT_3$ antagonist that was shown to inhibit colonic motility, increase colonic compliance, decrease colonic sensitivity and decrease secretion by the colonic glandular crypt. Alosetron is indicated for the treatment of females with IBS predominant diarrhea in doses of 1 mg BID.

Alosetron was released for sale on February 9, 2000. Because of serious adverse events associated with its use, the sponsor (GW at the time) decided to withdraw the drug from the market on 28 November 2000.

In clinical trials Alosetron produced modest symptomatic improvement in about 40% of the cases.[23] However, after the product was on sale, a subgroup of patients affected with severe diarrhea with urgency identified themselves when the produce was withdrawn from the market. In their communications to the newspapers, to the Agency and through patient advocacy groups like the International Foundation for Functional Gastrointestinal Disorders (IFFGD) and the Lotronex Action Group (LAG), these patients who had been severely disabled almost on lifetime basis stated that this was a nearly miraculous drug that had given them a life back. But this

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benefit came with a risk. During clinical trials, constipation was a common A/E observed in 25 to 30% of approximately 6800 patients receiving the drug. One-third of the patients affected with constipation decided to withdraw from the study. This was a dose-related A/E that resolved without sequelae upon discontinuation of the drug. In addition, three cases of Ischemic Colitis (IC), a form of Ischemic Bowel Disease, were observed during the pre-approval clinical trials. They were transient, reversible forms of the disease, that also resolved without sequelae.[24] The severity of these apparently benign A/E in the RCTs changed during the post-marketing period. Patients with both constipation and "Ischemic Colitis" suffered from perforations, bowel resections and death. Thus, the conflict faced by both the sponsor and the physician regulators at the Agency: Should Alosetron be allowed back in the market? And if so, under what circumstances? How can we best protect the public, and help them make an intelligent, educated choice? The clinical assessment of the post-marketing serious complications of severe constipation has been carried out in a separate document.[29] This review will perform a clinical assessment of the "Ischemic Colitis" epidemiological data and attempt to answer some of the above questions.

**Ischemic bowel Disease (IscBD).** Ischemic injury to the bowel occurs when blood flow is reduced to a level at which delivery of oxygen and other nutrients to the tissue is insufficient to maintain oxidative metabolism and hence cell integrity. The presentation ranges from the transient form of ulcerative ischemic colitis that resolves spontaneously and may go undiagnosed, to the acute mesenteric ischemia, an abdominal catastrophe, with mortality in excess of 70%. The early diagnosis necessitates a high degree of suspicion. There are no non-invasive tests for its detection. The abdominal pain and the physical findings are non-specific. Colonoscopy presents a picture indistinguishable from Crohn's disease, and that is how it is commonly mislabeled in the elderly. The second most common endoscopic appearance is with pseudomembrane formation, resembling *C. Difficile* colitis. The least common endoscopic appearance mimics neoplasia: a distorted, endematous, ulcerated area of the colon with pseudopolyp formation is often confused with a malignancy. Histologically the inflammatory changes are also non-specific. The colonic crypts are affected beginning with its superficial half. When the damage is more severe and prolonged there is total destruction of the crypt and mucosal necrosis. It is the combination of all these factors that establishes the diagnosis in mild and moderately severe cases of IscBD. Depending on the severity of the insult, the transmural ischemic process may heal and lead to stricture or may progress further, and the affected bowel becomes gangrenous and requires surgery.[1,2,3,7,8,12,13]

In this review, a criteria for the retrospective clinical diagnosis of AAIscBD was created, taking into consideration the protean manifestations of IscBD and the difficulties found in establishing a diagnosis with certainty. The 78 cases reported to OPDRA were thus classified into two groups: those in which there was an association between Alosetron intake and the diagnosis of Ischemic Bowel Disease (AAIscBD 46 cases, 59%) and those in which there was insufficient evidence to establish such an association (IE 32 cases, 41%). The 46 cases of AAIscBD were further apportioned according to the classification of D.A. Greenwald and L. Brandt[1], which is universally accepted and is cited in most textbooks of gastroenterology and review articles. This classification considers three main groups of patients with IscBD (Acute and Chronic Mesenteric Ischemia and Colonic Ischemia) and several subgroups, depending on the localization and severity of the ischemic process. Alosetron intake has been associated with all

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clinical forms of Ischemic Bowel Disease, that is why this reviewer considered that perpetuating the epidemiological password "Ischemic Colitis" would be misleading for the purposes of this review. A more detailed discussion of the anatomy of the circulation of the gastrointestinal tract and of the different forms of Ischemic Bowel Disease is part of this review, and I believe it is indispensable reading to understand the clinical classification and the results.

During the clinical trials that preceded approval, four cases of reversible, transient ulcerated ischemic colitis were observed. They all resolved uneventfully. Because of these cases, the Agency requested from the sponsor a list of all cases of blood in the stools observed during the course of those trials, that were not accounted for by hemorrhoids or menstruation. Approximately 40 additional cases were uncovered. The bleeds were mild and resolved spontaneously, thus, they were never investigated. Probably some of these cases represented forms of **reversible ischemic colonopathy**. During the post-marketing period three cases of acute mesenteric ischemia **(mesenteric vein thrombosis)**, two cases of **chronic mesenteric ischemia** complicated by SMA and/or IMA thrombosis, and 37 cases of colonic ischemia (34 of **transient ulcerated ischemic colitis**, one of **colonic stricture** and two of **colonic gangrene**) were identified as occurring in apparent association with alosetron. In 32 additional cases there was insufficient evidence to associate Alosetron with the A/E. Administration of **female sex hormones** (birth control and HRT) and Tamoxifen (one case), as well as **psychotropics**, were the most common medications associated with AAIscBD. In five patients a **hypercoagulable state (HCS)** was suspected. All patients but one were females. These epidemiological data are reviewed under the sub-heading of "Causality" in the Discussion section.

## CONCLUSIONS

1) A total of 78 cases with possible AAIscBD were reported. The CRFs were reviewed manually and compared with a master file of data updated to the beginning of September 2001, provided by Dr. J. Korvick. When available, new data was incorporated in this review. Seventy-four of these cases had previously undergone an epidemiological study and classification by OPDRA. When appropriate, the OPDRA classification was listed next to the clinical classification used in this review.

2) Forty-six of the possible 78 cases (59%) met clinical criteria for AAIscBD as defined elsewhere in this paper, are the subject of this review, and as listed in summary Table 5.

3) Thirty-two cases (41%) had IE for AAIscBD. The reasons for clinical exclusion and the epidemiological classification are listed in Table 11.

4) Thirty-eight cases of AAIscBD (83%) were of reversible, mild forms of IscBD, that resolved spontaneously and without apparent sequelae, upon discontinuation of Alosetron therapy.

5) Eight cases of AAIscBD (17%) represented severe forms of the disease. All eight cases underwent surgery. Three of these eight patients died.

6) In five cases (MVT 3, CG 1, IC 1) there was strong suspicion that a HCS might have played a role in the development of AAIscBD (see Table 12). MVT and CG are amongst the most serious, life-threatening forms of IscBD. Identification of patients with thrombophilia or with risk factors for HCS may prevent the development of the more serious complications of Alosetron therapy.

7) Female sex hormones (estrogen, progesterone, alone or in combination) used in birth control pills and in HRT, and Tamoxifene were used in 37% of the patients. These hormones have known thromboembolic potential. Estrogen has produced Ischemic Bowel Disease in reported cases.

Further, estrogen and progesterone are both extensively metabolized by the liver, known to produce cholestasis and cholestatic jaundice and may interfere with Alosetron metabolism producing abnormally high blood levels of Alosetron or its metabolites. This, in susceptible individuals may increase the risk of thromboembolism, a HCS and IscBD.[1,2,3,7,17]

8) Psychotropics were used by 30% of AAIscBD patients. SSRIs were used by eight patients (17%) alone or in combination with other psychotropic drugs. SSRIs have been reported as causative agents of Ischemic Bowel Disease. Further, they share with Alosetron the same CYP-450 pathways, creating the possibility of drug interaction that, as in the case of estrogen and progesterone, may lead to supratherapeutic levels of Alosetron or its metabolites. The suspicion exists that psychotropics, particularly SSRIs, may have contributed to the development of IscBD.[18,19,20]

9) According to the Bio-Pharmacology report, important data in reference to drug interaction, the effect of enzyme inhibitors and enzyme inducers on Alosetron metabolism and the role of Alosetron metabolites and their receptor binding, are incomplete or missing.[22] These data may help us interpret some of the effects of Alosetron on the splachnic vascular bed and colonic microcirculation.

**RECOMMENDATIONS**

1) A new Risk Management Plan (RMP) should be designed and implemented if Alosetron is allowed back in the
market. This RMP should alert physicians, pharmacists and patients about the risks of AAIscBD.

2) A list of risk factors for AAIscBD should be made (see Table 13) and updated periodically. Patients considered at high risk should not receive Alosetron. Others, at lesser risk, should be given the option, and if willing to take Alosetron should first undergo laboratory tests to rule out a HCS.

3) Consideration should be given to anticoagulation for patients who test positive for HCS and desire to take Alosetron.

4) All patients receiving Alosetron should have close follow-up, more so if belonging to a risk group.
5) The presence of blood in the stools or on the toilet paper in a patient receiving Alosetron should be considered evidence of AAIscBD until proven otherwise. The patient should discontinue Alosetron inmediately, be evaluated, and appropriate testing and close follow-up be instituted. The presentation and evolution of AAIscBD varies greatly and is unpredictable.
6) Natural History Epidemiological Studies by the sponsor should be encouraged and planned along with OPDRA's epidemiologists. Important databases can be found in well organized HMOs [redacted] in the well established multi-specialty medical groups [redacted], and in the case of IBS patients, in IFFGD, a well established patient advocacy group (similar to the Crohn's and Colitis Foundation, the Cystic Fibrosis Foundation).

The epidemiological study submitted by the sponsor (GSK), comparing IscBD in IBS patients with the general population, is a step in the right direction and should be pursued by both the Agency's Gastroenterology Section and OPDRA.

7) [redacted]

## A – INTRODUCTION AND BACKGROUND

### 1) Irritable Bowel Syndrome (IBS)

The IBS is a functional gastrointestinal disorder whose hallmark is abdominal pain or discomfort associated with a change in the consistency or frequency of stools. In the western world, 8% to 23% of adults have IBS and its socioeconomic cost is substantial. Research-generated insights have led to the understanding of IBS as a disorder of brain-gut regulation. Recent advances propose that the experience of symptoms derives from dysregulation of the bidirectional communication system between the gastrointestinal tract and the brain, mediated by neuroendocrine and immunological factors and modulated by psychosocial factors.

The term "irritable bowel syndrome" is in general use and well entrenched in the medical literature and nomenclature. Its literal meaning is in conflict with the rapidly growing understanding of the illness and can be counterproductive in terms of patient education and treatment. When physicians are surveyed on their definition of IBS, their understanding of this condition is that there is a lack of organic disease or that it is a psychiatric condition. These beliefs, coupled with the fact that 60% to 70% of the patients are females (in a profession until recently largely dominated by males), led to the stereotype of the "hysterical females", with the consequent lack of attention to the clinical symptoms, performance of a large number of

unnecessary diagnostic and therapeutic procedures and the lack of interest and funding of research projects.
The re-discovery of the Enteric Nervous System (ENS), the realization of the effect of hormones like estrogen and corticotropin releasing hormone (CRH)[30] on the smooth muscle cell and the stress reaction, and the role of neurotransmitters like serotonin, norepinephrine, dopamine, CCK, motilin, acethylcholine, somatostatin, vasoactive intestinal peptide (VIP), and others, on the conduction of impulse that conveys gut sensitivity and metabolic activity expressed as motility, secretion and circulatory changes, are changing the way that IBS is diagnosed and treated.[14,15,16,30] The fact still remains, however, that in IBS there are no biological markers or physical signs that will identify this condition or gauge its severity. The diagnosis continues to be made on physician's interpretation of a complex of symptoms, or patients' answers to lengthy questionnaires that have been "validated".

**2) Alosetron**

Alosetron (Lotronex®, GSK) was launched into the US market in March 2000. In November of the same year it was voluntarily withdrawn from sale by the sponsor in view of serious adverse events that included Ischemic Bowel Disease and constipation with complications, both leading to surgery and in some cases to death.

Alosetron is indicated for the treatment of IBS predominant diarrhea (DP-IBS) in females. Alosetron is a 5HT3 antagonist. It binds selectively to this receptor site producing a decrease in secretion at the level of the crypt (control of diarrhea), inhibition of motility (increased colonic compliance, control of urgency) and decreased blood flow of the microcirculation. Of all these actions, the effect on motility has received the most attention, probably because of the concept that "IBS is a motility disorder". There is little or no information on the effect of Alosetron on the hemodynamics of the splachnic vascular bed.

Alosetron plasma concentrations are 45% to 100% higher in women than man. Concentrations are also higher in the elderly.[22] This is of clinical significance, because if there is a higher incidence of dose related constipation in older women, a lower efficacy in younger women, or both, due to differences in pharmacokinetics, the risk-benefit profile of this agent would change depending upon the patient subgroup. This type of information should be born in mind when designing an Alosetron risk management plan.

*In vitro*, Alosetron is metabolized by CYP 1A2, 2C9 and 3A4. There is an 11% of drug that is metabolized by non-P450 pathways. *In vivo*, 35% of the dose is metabolized to 6-OH-alosetron and 8.5 % to 7-OH-alosetron, both of which undergo glucuronidation. 6-OH-alosetron is twice as potent as Alosetron, but there seems to be no free 6-OH-alosetron in plasma. The limit of detection of plasma 6-OH Alosetron was 6 fold higher than the Ki (Ki=the concentration required for half of the receptors to be occupied) for this metabolite.

Some important elements of the PK/PD profile of this drug are incomplete or missing:[22]

- Drug interaction studies are conflicting or incomplete.
- There is no information on the ability of Alosetron to induce the metabolism of other drugs.

- The effect of of enzyme inhibitors on Alosetron PK has not been studied.
- The effect of enzyme inducers on Alosetron PK has not been examined. Inducers could either decrease efficacy by decreasing Alosetron exposure or increase efficacy/toxicity by increasing exposure to metabolites.
- The role of metabolites and their receptor binding, PK, and in vitro potential to cause drug interactions have not been adequately examined.

Interpretation of symptoms and A/E caused by Alosetron is difficult in light of the above, which makes design of a risk management plan a challenging task.

**3) Anatomical considerations**

The human gastrointestinal tract can first be recognized in the fourth week of gestation as an endoderm-lined tubular structure extending from the mouth to the cloaca.

During development, the gastrointestinal tract can be divided into foregut, midgut and hindgut, reflecting roughly the structures supplied by the celiac, superior mesenteric (SMA) and inferior mesenteric (IMA) arteries, respectively.[8]

The foregut includes the esophagus, stomach and duodenum up to about the level of the ampula of Vater, liver, pancreas and biliary tract. The midgut extends from the mid-descending duodenum to the transverse colon, near the splenic flexure. The hindgut includes the distalmost transverse colon and the remaining large intestine to the proximal anal canal.

The localization and extent of ischemic lesions is dictated to a great extent by these early processes of embryonic development.

**4) Ischemic bowel disease (IscBD)[1,2,3,7,8]**

a) MESENTERIC CIRCULATION.[8] The intestines are protected from ischemia by an abundant collateral circulation that flows around occlusions of the smaller splachnic arterial branches. In this way, adequate perfusion can be maintained for a variable, but brief, period. Prolonged ischemia leads to vasoconstriction that may persist after the primary cause of mesenteric ischemia has been corrected. Injury progresses from the mucosa to the serosa, depending on the severity of the insult. Reperfusion of the affected bowel may set in motion a cascade of events that will ultimately lead to transmural necrosis, at which point the bowel is no longer viable.

b) CLASSIFICATION[1] Ischemic Bowel Disease can be classified into three broadly defined clinical types (Table 1)

**TABLE 1**
**CLINICAL CLASSIFICATION OF AAIscBD[1]**

1) Acute Mesenteric Ischemia (AMI)

- SMA Embolus
- SMA Thrombosis
- Nonocclusive Mesenteric Ischemia
- SMV Thrombosis
- Focal Segmental Ischemia

2) Chronic mesenteric ischemia (CMI) (intestinal angina)

3) Colonic Ischemia

- Reversible Ischemic Colonopathy
- Transient Ulcerating Ischemic Colitis
- Chronic Ulcerating Ischemic Colitis
- Colonic Stricture
- Colonic Gangrene
- Fulminant Universal Ischemic Colitis

**1) Acute Mesenteric Ischemia.** Regardless of its cause, AMI is an abdominal catastrophe with an average mortality rate of 71%. Early diagnosis depends on the identification of persons at risk and the recognition that the disparity between the severity of the abdominal pain and the absence of significant abdominal findings is characteristic of early AMI.

SMA embolus accounts for approximately 50% of the cases of AMI. Nonocclusive mesenteric ischemia is less frequent now than in the past, probably due to better management of patients' hemodynamics in intensive care units, that prevents hypotension and the resulting mesenteric vasoconstriction. **SMA thrombosis** usually occurs at the origin of the SMA. Symptoms of CMI usually precede the acute attack. The diagnosis of AMI is made by angiography. The treatment depends on when the diagnosis is made: early on, vasodilators (papaverine), thrombolytic therapy and correction of precipitating factors can be attempted. Later on, when peritoneal signs have developed the treatment is surgical.

- **Acute Mesenteric Vein Thromboses (MVT),** represents 5% to 10% of patients with AMI. MVT may be idiopathic (primary) or secondary to a variety of conditions. These include:
-
  - Hematolologic and hypercoagulable states
  - Local venous congestion and stasis
  - Intra-abdominal inflammation and sepsis
  - Parasitic infestation
  - Low-flow states
  - Abdominal trauma

- Decompression sickness
- Abdominal surgery
- Vasopressin infusion
- Estrogens

No cause is identified in 20% to 35% of the cases of MVT.

Abdominal pain is present in more than 90% of patients and, early on, is out of proportion to the physical findings. Unlike SMA thromboses the duration of the pain before admission is usually between 1 to 2 weeks, but may extend up to a month. CT scan diagnoses MVT in more than 90% of the cases, demonstrating thrombi in SMV and portal vein.

The mortality ranges from 20% to 50%, with recurrence rates of 20% to 25%. Postmortem studies demonstrated that almost 50% of patients with MVT have no bowel infarction and most are without symptoms.

- **Focal Segmental Ischemia (FSI)** The clinical picture is varied, resembling Crohn's disease, acute appendicitis or small bowel obstruction, without the life threatening consequences associated with ischemia of more extensive portions of the gut. The most common causes of FSI are collagen-vascular diseases, vasculitis, and oral contraceptive use.

**2) Chronic Mesenteric Ischemia (CMI)** CMI is called **Intestinal Angina**, because the visceral pain has a pattern similar to that observed with chest pain due to coronary heart disease. The picture sometimes resembles that of IBS, but the presence of weight loss (due to food avoidance and malabsorption) should suggest the diagnosis. Acute mesenteric infarction rarely complicates CMI. In good surgical candidates the treatment consists of revascularization or transluminal angioplasty.

Risk factors for CMI are the same as for atherosclerosis: cigarrete smoking, diabetes and hyperlipidemia.

*3)* **Colonic Ischemia (CI).** CI is recognized as the most common ischemic disorder of the gastrointestinal tract. Reversible ischemic colonopathy (submucosal or intramural hemorrhage) is the most frequent form of CI. Sequelae of CI include healed ulcers, strictures, pseudotumors and ischemic ulcerative colitis.

The main differential diagnoses is with AMI. When in doubt, mesenteric angiography is the method of choice.

**In most cases the cause of an episode of CI can not be established with certainty.** Ninety percent of the patients are over 60 years of age. Up to 10% of cases will have an obstructing lesion of the colon, including adenocarcinoma, benign stricture and diverticulitis. When CI is suspected, colonoscopy, with the methodological limitations described above, is the method of choice to establish the diagnosis, because in addition, it offers further diagnostic confirmation by allowing biopsies to be obtained. Abdominal crampy pain, followed in about 24 hours by bloody diarrhea, is the usual presentation. Any part of the colon may be affected: nonocclusive ischemic

injury usually involves the watershed areas of the colon, such as the splenic flexure and the recto-sigmoid junction. Nonocclussive ischemia involves larger segments of the colon than atheromatous emboli. Endoscopic appereance is non-specific. The sequence of submucosal hemorrhage, colitis and finally normal mucosa, evolving over a 10-14 day period, is characteristic.

The factors that may predispose to CI are many, continue to grow and are the same as those listed above for AMI. The colon has an inherently low blood flow, which is less than that of the small intestine. Constipation may exacerbate colonic circulatory inadequacy through the effects of straining at the stool on systemic arterial and venous pressure. **The ultimate cause of an ischemic episode is conjectural in most instances.**

Only 5% of the cases experience a recurrence. The usual outcome is complete resolution of symptoms in 24 to 48 hours followed by radiological or endoscopic healing within 1 to 2 weeks. The rest of the cases can be divided into three about equal groups: gangrene and perforation, chronic ischemic colitis and late (weeks to months) stricture formation.

**B - EVALUATION OF AAIscBD CASES**

***1) Clinical Diagnostic Criteria***

All reported cases of "Ischemic Colitis" suspected of having an association with Alosetron will be classified as follows:

Table 2
CLINICAL DIAGNOSTIC CRITERIA

A – STRONG ASSOCIATION (SA)
Must Have:
- Well documented intake of Alosetron.
  Anyone who took one tablet of Alosetron anytime, is included
- Endoscopic or surgical evidence of Ischemic Bowel Disease supported by histopathological diagnoses or suspicion of diagnoses

B – INSUFFICIENT EVIDENCE (IE)
All others

**2) Materials and Methods**

Seventy eight cases of reported IscBD were reviewed. Four were observed during the pre-approval period. There were 74 cases of IscBD reported in the Adverse Event Reporting System (AERS) database. These cases were the subject of a computerized epidemiological risk assessment. Their inclusion are based on any or a combination of the following: 1) the term "ischemic colitis" was explicitly used in the AERS report as a possible diagnoses, 2) any endoscopic or histologic evidence of ischemia or ischemic changes or necrosis or 3) any

radiological diagnosis of "ischemic colitis". The cases were further **classified from the epidemiological point of view** as follows:[26]

**Diagnostic Certainty of Ischemic Colitis**

- Both histological and endoscopical evidence of ischemic colitis or ischemic change or necrosis
- Endoscopical evidence of ischemic colitis or ischemic change or necrosis
- Histological evidence of ischemic colitis or ischemic change or necrosis
- Radiological evidence of ischemic colitis or ischemic change or necrosis
- Ischemic colitis, without the above evidence.

The clinical and epidemiological inclusion and diagnostic criteria are listed in Tables 3 and 4 For the **clinical review** these 78 cases were evaluated individually, and those that met diagnostic criteria for AAIscBD were classified into appropriate clinical types following the classification listed above. This review did not attempt to "match" the numbers provided by OPDRA. Indeed, it should not match OPDRA's numbers because this is a clinical and not an epidemiological review.

**TABLE 3**

**AAIscBD INCLUSION CRITERIA**

| CLINICAL | EPIDEMIOLOGICAL |
|---|---|
| 1) Well documented intake of Alosetron. Anyone who took one tablet at any time | 1) Mention of "Ischemic Colitis" in the report. |
| 2) Endoscopic or surgical evidence of IscBD supported by histopathological diagnoses or suspicion of diagnoses of IscBD | 2) Any endoscopic or histologic evidence of ischemic or ischemic changes or necrosis. |
| | 3) Any radiological diagnoses of "Ischemic Colitis". |

**TABLE 4**

**DIAGNOSTIC CLASSIFICATION OF AAIscBD**

| CLINICAL | EPIDEMIOLOGICAL (DIAGNOSTIC CERTAINTY OF ISCHEMIC COLITIS) |
|---|---|
| 1) AC Mesenteric ischemia<br>2) Chr. Mesenteric ischemia<br>3) Colonic ischemia | 1) Both histological and endoscopical evidence of ischemic colitis or ischemic change or necrosis<br>2) Endoscopic evidence of *Ibid Above*<br>3) Histologic Evidence of *Ibid Above*<br>4) Radiologic Evidence of *Ibid Above*<br>5) Ischemic colitis without the above evidence |

All 78 cases were compared with an updated Master File of Individual Safety Reports obtained by Dr Joyce Korvick at the beginning of September 2001, and new data, when available, was incorporated into this review.

New knowledge obtained from a literature search performed at the end of August 2001, was used to attempt to define risk factors or patterns of disease that can be subsequently used in formulating a Risk Management Plan (RMP).

**3) Pre-Approval AAIscBD**

**A - COLONIC ISCHEMIA**

The information was obtained from Dr. John Senior's Safety Review of 22 October 1999,[24] Dr. Hugo Gallo-Torres' Secondary, Multidisciplinary Review and Recommendations for Regulatory Action of 17 November 1999 and by review of the individual Case Review Forms (CRF).

There were four cases of Ischemic Colitis (IC) that met the clinical diagnostic criteria established in this report, one in each of four separate studies.

1) Patient # 15687/Study S3BA3001 In this study 309 women were exposed to Alosetron 1 mg BID.

The patient was a 41 year old Caucasian woman who took Alosetron for 54 days. The patient developed a skin rash of three days duration (8/30/98 to 9/2/98) that resolved spontaneously. Subsequently, the patient developed abdominal pain and rectal bleeding and was admitted to the

hospital because of lack of improvement on hyosciamine per os. Stool cultures were not performed. Colonoscopy (9/8/98) revealed severe segmental colitis with inflammatory changes with shallow ulcerations and skip areas of the mucosa extending from about 50 cm from the anal verge (cephalad sigmoid colon) to the transverse colon, immediately past the splenic flexure. The rest of the colon and rectum were unaffected. Biopsy reports confirmed the endoscopic impression of IC. Repeat colonoscopy (11/4/98) revealed complete healing of the ulcers, mild non-specific erythema, in an otherwise normal mucosa. The biopsy was "significantly less abnormal than the previous one". Neither biopsy showed evidence of Crohn's disease. The symptoms resolved without sequelae.

CONCURRENT MEDICATIONS: Prozac, Buspar, Zyrtec.
COMORBIDITIES. Patient's husband underwent vasectomy as contraceptive method on 8/11/98.

*COMMENT This woman had well documented intake of Alosetron, had a clinical picture compatible with CI and endoscopic findings, pathology reports, and prompt resolution of symptoms and signs of disease, supporting the diagnosis of* **Transient Ulcerating Ischemic Colitis**. *What role, if any, played by psychotropic drugs will be discussed later in this review.*

*The fact that the patient's husband underwent a vasectomy may be of interest. Whether this was a personal choice for contraception, or was due to patient's intolerance to birth control pills (phlebitis, etc.).*

2) Patient # 7195/Study S3BA3002 In this study 322 women were exposed to Alosetron 1 mg BID. The patient was a 48 year old Caucasian female who developed rectal bleeding and abdominal crampy pain after 39 days of therapy. Symptoms grew worse despite simple conservative measures and the patient was admitted to the hospital at 3 am. Stool cultures were negative. Colonoscopy revealed a segment of colon extending from 30 to 60 cm from the anus of inflammed, ulcerated mucosa with areas of sloughing. The rest of the colon and rectum were normal. Biopsies confirmed the endoscopic impression IC. The outcome was uneventful.

CONCURRENT MEDICATIONS: Captopril, Procardia XL, Lozol, Micro-K, Prozac.
COMORBIDITIES: History of motor vehicle accident with pulmonary emboli (1976), History of Cushing's disease, status post resection of pituitary tumor (1981), gastric ulcer (1978).

*COMMENT This case is similar to the previous one. The evidence supports the diagnosis of CI, type of* **Transient Ulcerating Ischemic Colitis**. *The patient could very well belong to a high risk group in view of the previous history of pulmonary emboli and concurrent intake of Prozac, a SSRI drug.*

3) Patient 34069/Study S3BA30011 This is a "new study" present only in Dr. Gallo-Torres' report. The patient is a 61 year old woman who had received 7 days of treatment with Alosetron 1 mg bid when she developed abdominal pain and bloody diarrhea. She was hospitalized. An abdominal CT scan revealed mural thickening of the entire transverse colon, descending colon and hepatic flexure. The changes were suggestive of IC but the distribution involving areas in the territories of both SMA and IMA made the attending physicians feel skeptical about that

diagnosis. Stools for O & P and C. Difficile toxin A were negative. Stool cultures were not performed. Colonoscopy showed patchy areas of inflammation with hyperemia and edema involving the descending colon and the adjacent area of transverse colon. The colonic biopsies supported the diagnosis of IC.

CONCURRENT MEDICATIONS: Elavil (for restless legs syndrome), Evista (osteoporosis), Multivitamins.
COMORBIDITIES: Chronic anemia, osteoarthritis of both knees, restless legs syndrome, allergy to sulfa.

*COMMENT CT scanning is a poor method to diagnose CI. CT is most valuable in the detection of SMV and portal vein thromboses. Colonoscopy is the method of choice to establish the diagnosis of CI, it is more sensitive and permits biopsy. The outcome was uneventful.This case, like the preceding ones, has evidence of CI, the type of* **Transient Ulcerating Ischemic Colitis.**
4) Patient 2829/Study S3BA 2001 This was a dose ranging study in which 290 patients (91 men and 199 women) were exposed to Alosetron in doses from 1 mg to 8 mg BID for 12 weeks. The patient was a 33 year old Caucasian woman who, after taking Alosetron 2 mg bid for 2 days, developed severe abdominal pain and watery diarrhea. She reported to the emergency room where she was prescribed Levsin (an anticholinergic). Her symptoms became worse and she developed peritoneal signs, reasons for which she was admitted. Stool cultures failed to identify a pathogen (including E. coli 0157:H7). No C. Difficile toxin was detected. Colonoscopy revealed a diseased segment of the colon extending from 40 cm to 80 cm from the anus, showing edema, friability and ulceration of the mucosa. The biopsy showed mild inflammatory changes, but failed to support the endoscopic and clinical impression of ischemic colitis. The patient's evolution was favorable and she was discharged without any apparent sequelae.

CONCURRENT MEDICATIONS: Transderm estradiol, Pepcid AC, Tums.
COMORBIDITIES: Heartburn, esophageal spasm, urinary stress incontinence, cholecystectomy (1984), total abdominal hysterectomy with partial left salpingo-oophorectomy (1995).

*COMMENT. The overall clinical picture and endoscopic findings on this patient are very much like the previous three cases, indicating a strong possibility that this was an ischemic episode. The biopsy report did not support this impression. As stated by Drs Senior and Gallo-Torres, in general, in inflammatory processes of the bowel, there is a poor correlation between endoscopic appearance and histologic findings. It is also a well known fact, dating back to the original studies by Truelove and others in the 1960's, that the poor correlation extends to symptoms and x-ray findings, that is, the severity of the clinical picture does not parallel x-rays, endoscopy and histology. It is because of these reasons, that despite a negative biopsy report, I have decided to include this case in the group of patients with CI, of the type of* **Transient Ulcerating Ischemic Colitis**. *Estrogen therapy is a risk factor for thromboembolism.*

**B – INSUFFICIENT EVIDENCE**

These were a group of patients who had unexplained rectal bleeding, while on Alosetron therapy, but were lacking some elements of the clinical diagnostic criteria for AAIscBD. When the initial four cases of CI listed above were observed, the Agency requested from the sponsor to search for

patients who had had blood in the stools unexplained by menstruation or the presence of hemorrhoids while participating in the clinical trials. Approximately 40 cases were uncovered (H. Gallo-Torres, MD personal communication). The bleeding was apparently mild, the patients did not look sick and the rectal bleeding was never investigated.

*COMMENT Drs Gallo-Torres and Senior have both commented, and I agree, that some of these patients might have been cases of CI, sub-type of* **Reversible Ischemic Colonopathy**. *About this particular sub group of patients, D. A Greenwald et al in their monograph on Ischemic Bowel Disease in the Elderly state "...many cases of transient or reversible ischemia still are missed because diagnostic studies are not performed early enough in the course of the disease or patients do not seek medical advice because the disease is self-limited and often confused with other diseases such as inflammatory bowel disease". One wonders if these patients with unexplained rectal bleeding shouldn't be the subject of a separate study, looking for clues or patterns of disease that may be risk factors or very early symptoms of the disease.*

There is one additional case that deserves to be discussed separately:

Patient 4595/Study S3BA3001 This was one of the two pivotal studies that followed the dose ranging studies conducted in the USA and Europe, designed with identical protocols, to be carried out in women only with the chosen dosage of 1 mg BID. The patient was a 33 year old Caucasian with a previous history of asthma, obesity, depression and hypothyroidism. Concomitant medications were Prozac, synthroid, estrogen, albuterol, norfloxacin (2/27/98 to 3/19/98), prednisone in tapering doses (4/16/98), omeprazole, zafirlukast and sulfasalazine (5/22/98). The patient was randomized to Alosetron on 2/9/98. On 3/30/98 the patient had a two day episode of rectal bleeding. On or about 4/7/98 the patient underwent a colonoscopy and was diagnosed as with Crohn's disease. The patient was observed to have abnormal function tests with maximal values of ALT of 131, AST of 111 and alkaline phosphatase of 174 on 4/17/98. The total bilirrubin that day reached its peak at 2.1 mg/dl. These are all modest elevations: ALT x 3.85, AST x 3.26, alkaline phosphatase x 1.58 and total bilirrubin x 1.75 their respectives ULN. There apparently was no pruritus or jaundice. Alosetron was discontinued on 4/20/98. All LFTs improved by 4/22/98 and returned to normal on 5/1/98. On 5/15/98 the patient underwent an ERCP with normal results, with an episode of pulmonary edema complicating the procedure, which required an 8 day hospitalization. A liver biopsy was never performed. The ultimate outcome on this patient was favourable.

*COMMENT This is a difficult case to interpret because of the numerous confounding factors. The patient was on several medications, some of which are known to have potential hepato-toxicity: estrogen, norfloxacin, prednisone, omeprazole and azulfidine. We can only speculate about the potential drug-drug interactions.*

*The patient also had several risk factors for Ischemic Bowel Disease: obesity, estrogens and Prozac, a SSRI antidepresant.*

*This patient had well known Crohn's colitis of many years duration (information recently available). This was an exclusion criteria in this clinical trial, and she should have never been entered into this study.*

*The episode of pulmonary edema was ascribed to "a reaction to general anesthesia". This, again, is an unusual occurrence. Intravenous conscious sedation is generally used for endoscopic procedures. General anesthesia is reserved for severely anxious and/or uncooperative patients. The pulmonary edema was probably related to the effect of general anesthesia on this patient's bronchial asthma.*

*In summary, Alosetron could have played a role on both the rectal bleeding and hepato-toxicity, only one of them, or neither one of them. But Alosetron is being used inappropiately because this drug was not intended to be used for the management of Crohn's disease.*

**4) Post-Marketing AAIscBD**

Alosetron was approved on 8 February 2000 and was voluntarily withdrawn from the market by the sponsor on 28 November 2000. A total of 74 cases of "Ischemic Colitis" were recorded in the AERS database until 31 July 2001. There have been no new reports since 30 June 2001. "Ischemic Colitis" is the epidemiological pass-word that has to be mentioned to be part of this database, although the whole spectrum of Ischemic Bowel Disease (CI and deaths) is included in these reports. Any endoscopic or histological evidence of ischemia or necrosis or any radiological evidence of ischemic colitis are also qualifiers. These are unduplicated patient cases, not individual reports.

Forty-six (59%) of the 78 cases reported meet criteria (as defined above) for AAIscBD. These cases have been reviewed manually and classified from a clinical point of view following the criteria of D. Greenwald and L. Brandt in their writings.

The purpose of this evaluation is to look for risk factors or clinical patterns that may be more unique to AAIscBD than other forms of bowel ischemia, and that can be used to alert patients and physicians alike about the proper use of Alosetron.

The cases will be identified by two sets of numbers: the first one, assigned by OPDRA, the second, the manufacturer's (Glaxo/Smith Kline) report number.

**a) – ACUTE MESENTERIC ISCHEMIA** There were three cases, all of Mesenteric Vein Thromboses (MVT)

Case # 68 – A0125536 A physician reported that a 33 y/o caucasian female was precribed Alosetron 1 mg bid for treatment of IBS. Two days later the patient discontinued the medication on her own, due either to no improvement or to worsening of her abdominal pain.

The patient presented herself to the emergency room, probably one or two days later, because of continuing abdominal pain. Chest x-ray and abdominal CT scan were unremarkable. Leukocytosis was noted. A repeat abdominal CT scan demonstrated fluid. She was taken to surgery and a small bowel resection was performed. The pathology report states that two segments of intestine measuring 10 cm and 105 cm long were submitted. The most severe changes were in the larger segment, where in two-thirds of its length there was hemorrhagic gangrenous necrosis secondary to mesenteric vein thromboses. Sections from the mesentery

showed intact mesenteric arteries. At the time of reporting the patient was improved but still hospitalized.

CONCOMITANT MEDICATIONS: None
COMORBIDITIES: 1) Obesity. The patient's weight was in excess of 300 lbs. 2) Personal history of deep vein thromboses (DVT) at age 20, when placed on birth control pills. 3) Hypercoagulable state, Factor V Leiden mutation positive.

*COMMENT. This is a fairly typical case of MVT. This patient had comorbidities that made her a high risk for thromboembolic disease. From the physician's report it is unclear why she was prescribed Alosetron. If it was because of abdominal pain, perharps the MVT process had begun before the first tablet of medication was taken. There seems to be a direct relationship between the aggravation of her abdominal pain and the intake of Alosetron, although, again, this could have been the natural evolution of the MVT. The presentation of MVT is less acute than that of SMA occlusion. In a reported series the mean duration of pain before hospitalization was 5 to 14 days. These characteristics make the early diagnosis of MVT very difficult, to a time when anticoagulation is no longer effective and surgery becomes necessary. Perhaps in the future, a history of thromboembolism should be a contraindication of Alosetron intake.*

Case 152 – (no mfr. Report number) This 45 y/o Caucasian female reported to the emergency room of her local hospital on 10/2/2000 because of an aggravation of abdominal pain for the last two days. On August 29 the patient visited her family doctor because of lower abdominal pain and dysuria. She was given a prescription for Ciprofloxacin and an antifungal medication, probably fluconazole. She felt better, but 3 weeks later developed "soreness" in the upper abdomen and a sinus infection, treated with an unknown antibiotic. About one week later the patient developed futher tenderness in the upper abdomen and loose, bloodless stools two or three times a day. Her doctor checked the stools for C. Difficile and placed her on Flagyl. The stool was reported as C. Difficile toxin negative. She developed further cramping and was given Lotronex by her family doctor. This was ineffective, the cramps worsened, she began to have dry heaves and reported to the emergency room. The physical examination describes the patient as in distress requiring morphine sulfate 4 mg. The abdomen was soft, diffusely tender, bowel sounds were present. Rectal exanination and bimanual pelvic examinations were nondiagnostic. Laboratory work on admission to the emergency room showed a WBC of 14,000, normal RBC series and a platelet count of 520,000 with large platelets seen on the smear. Abdominal x-rays were nondiagnostic. A repeat CBC later on the same day showed a WBC of 45,000. That evening she underwent surgery. The postoperative diagnosis was that of a thrombosis in the distribution of the mesenteric vein with necrosis of the entire jejunum and ileum.
A hematology consult on 10/4/00 failed to elicit any risk factors in her personal or family history that may account for a hypercoagulable state. Coagulation factors that are not affected by an acute setting were tested with negative results.

The patient had an uneventful postop until the morning of 10/8/00 when she worsened, the WBC rose to 24,000. Abdominal CT scan demonstrated a portal vein thrombosis, splenic vein thrombosis, splenic infarction, ascites and intra-abdominal hematoma. She was transferred to [redacted] for further treatment, where she stayed from 10/8/00 to 12/13/00.

While at [redacted] she developed a subclavian deep vein thromboses (secondary to the TPN catheter), underwent exploratory laparoscopy on 10/26 and 10/28/00. Attempts to switch the patient from heparin to oral Coumadin were unsuccessful. The progress notes (2/7/2001) document that despite increasing doses of Coumadin the INR was not affected and the patient had to continue anticoagulation with heparin at home.

COMORBIDITIES Allergy to Penicillin, Zithromax and Keflex. Oophorectomy in the distant past because of benign disease. Tubal ligation.
*CONCOMITANT MEDICATIONS Flagyl, Lotronex and Bentyl.*

*COMMENT. The role of Alosetron in the overall picture is again, difficult to establish. Mild abdominal pains of unclear etiology had preceded the intake of Alosetron. The indications for Alosetron were equivocal at best. There seemed to be a rather sudden aggravation of symptoms after Alosetron intake.*

*Of note, is the indirect evidence of a hypercoagulable state, manifested by the development of axillary, portal and splenic vein thromboses, after the MVT, and Coumadin resistance, that forced the patient to continue with injectable heparin at home. There were no detectable risk factors in this case.*

Case 157 – A0133921A This 46 y/o Caucasian female smoker received Alosetron for five days because of diarrhea and stomach flu. The patient had coronary heart disease, with a history of three heart attacks and coronary angioplasty in October 1996. The patient was receiving concurrently hydroxyzine, metoprolol, warfarine and injectable Depo-Estradiol. The following day she called her physician stating that hydroxyzine was not working and Lomotil was added to her medications. Two days later she was noted to be pale, she was passing tarry stools. Blood pressure was 110/60. Laboratory work on 20 April 2000 revealed a hemoglobin of 7.7 grams, hematocrit 23.7 %, PT greater than 50 seconds and PTT greater than 95 seconds. Warfarine was interrupted for two days and she was placed on dicyclomine. Alosetron had been discontinued on 21 April 2000, after five days of therapy. On 25 April 2000 (four days after alosetron was discontinued) she was seen at the office. Her color had improved, she was feeling better. She was instructed to resume warfarin at the same doses of 5 mg daily, and to continue dicyclomine. She was started on "ferosulfate". There were telephone contacts over the next two weeks for medication refills (dicyclomine). On 9 May 2000 she was seen by a physician and she stated that had continued to have diarrhea. Later on the same day, the patient called the office stating that she continued to have bloody diarrhea. There is apparently no record that the patient had previously indicated that her diarrhea had blood in it. She was referred to a specialist but the same day she reported to the emergency room and was admitted. She complained of abdominal pain. Colonoscopy on 11 May 2000 revealed serpiginous ulcerations of the ileum, cecum and ascending colon. Biopsies were reported with superficial erosive acute inflammation, suggestive of an ischemic pattern. The interpretetion of these findings was that of infectious enteritis. On 14 May 2000 her blood pressure was reported "out of control". She was transferred to the intensive care unit, she was stabilized. Her abdominal pains persisted. The patient underwent surgery on 14 May 2000. The small bowel was necrotic from the terminal ileum to near the ligament of Treitz. The right colon was not involved. Resection of the small bowel except 2 to 3 inches of proximal jejunum and the right colon was performed, with end-to-end anastomosis of the

jejunum to the transverse colon. All visualized vessels were thrombosed. There was pulse in the mesentery. There was no pulse in the region of the superior mesenteric. The pathology report indicated that there was small bowel and proximal colon with extensive hemorrhagic necrosis. Microscopic examination disclosed extensive hemorrhagic mucosal necrosis with focal extension into the muscularis. Sections of the mesentery revealed the vessels "at that examined level" to be patent and free of inflammation. The post-operative diagnosis was a necrotic small bowel presumably from a superior mesenteric vein occlusion. The patient was placed on total parenteral nutrition (TPN) and discharged home in one week. Subsequently she had abnormal liver function tests, secondary to her TPN (18 September 2000) and an episode of urinary tract infection (21 September 2000). She was able to return to work. The patient died eight months after surgery of unknown cause.

Relevant laboratory data shows anemia and prolonged PT and PTT to critical levels at the time of the upper GI bleed, secondary to warfarin administration. One consultant mentioned that the patient was also taking Advil at the time. The bleeding arrested upon discontinuation of both medications, on 20 April. On 25 April her PT was 16.7 seconds, her PTT was 30.7 seconds, and warfarin 5 mg daily was resumed. On 9 May 2000 PT was 12.7 seconds with an INR of 1.2 and PTT 27 seconds. On 10 May, in the emergency room, her PT was 13.2 seconds, the INR was 1.3 Normal values for the laboratory are: PT 9.5 to 13. 5 seconds; INR therapeutic range for anticoagulation: moderate intensity 2.0-3.0, high intensity anticoagulation 2.5-3.5; PTT therapeutic range (0.2-0.5 U/ml heparin) 45-100 seconds. Of note, the INR was not affected by warfarin administration at doses that previously, although possibly influenced by concomitant administration of Advil, had produced critically elevated INR values and an UGI bleed.

COMORBIDITIES. Severe coronary heart disease, three myocardial infarctions, coronary angioplasty 1996, hysterectomy, itchy skin rash prior to 2 Mar 2000 treated with hydroxyzine and Medrol dose pack. A normal colonoscopy in 1996. Drug seeking behaviour (Lortab, Percocet).
CONCOMITANT MEDICATIONS. Warfarin, estrogen cypionate, hydroxyzine, metoprolol, iron (for the anemia, after the UGI bleed), doxycycline (when it was thought she had an infectious enteritis).

*COMMENT This case, like previous ones, has confounders, like the severe atherosclerotic coronary heart disease, cigarrete smoking, and estrogen administration. This patient went on to develop MVT. The clinical picture was a protracted one, as it happens with venous occlusions and not a catastrophic one as with arterial occlusions. There is also the suggestion of a hypercoagulable state, when the patient's INR remained unaffected by the administration of warfarin and MVT subsequently developed. The development of this warfarin resistance seems to coincide with the administration of Alosetron, since the same doses of warfarin had prevented venous occlusions, and induced critical INR levels and an UGI bleeding in the recent past.*

**b) CHRONIC MESENTERIC ISCHEMIA (CMI)** There were two cases that will be reported separately and commented together, at the end of this section.

Case # 66 – A0123214 This 59 y/o female with well documented pre-existing Ischemic Bowel Disease and other risk factors as listed below (see Comorbities) developed frequent loose

bloodless stools and was diagnosed as with IBS in November 1999. She was treated with Librax. By March 2000 she had lost 25 lbs and was hospitalized. There is no information about this hospitalization. On 12 April 2000 she was readmitted because of nausea, vomiting, hematochezia and uncontrolled hypertension with values of 200/110. She was treated with clonidine. A consultant gastroenterologist suspected IBS, with the rectal bleeding secondary to hemorrhoids, and placed the patient on Alosetron 1 mg bid, which she took until 27 April 2000. The following day, 13 April, the patient became febrile and developed leukocytosis of 16,900. She was given Cipro and Flagyl orally on empiric bases. She was discharged on 17 April 2000. One week later she was readmitted with profound watery diarrhea, worse postprandially, and constant epigastric pain with a belt-like radiation. She had lost 40 lbs of weight. Abdominal CT scan showed possible portal and splenic veins occlusion. On 28 April 2000 an angiogram revealed total occlusion of the celiac artery and SMA. The same day she underwent surgery. There was occlusion of both arteries due to atherosclerotic plaque. There were early signs of mesenteric ischemia in the bowel. A supraceliac aorta to celiac and SMA bypass was performed. There were poor Doppler signals in the mesentery after the bypass. The following day she was re-explored. Both grafts were occluded and total infarction of the small bowel and most of the colon had occurred. The patient expired one hour post-op.

COMORBIDITIES.Hypertension, Ischemic Bowel Disease: post-prandial cramping abdominal pain, severe weight loss, urgency and constipation. Cholecystectomy November 1999. Depression with anxiety. Melanoma, basal cell carcinoma.
CONCOMITANT MEDICATIONS. Prempro, Provera, Paxil, Librax.

Case # 149 – A0141438A This 63 y/o female with significant comorbidities as listed below, developed abdominal crampy pain, nausea vomiting, diarrhea and 13 lbs weight loss of one month duration. This was interpreted as IBS following a viral illness and was started on Alosetron. After initial improvement for a few weeks, the abdominal pain worsened and she developed bloody diarrhea. On 24 April 2000, she was admitted, became febrile and developed a leukocytosis of 20,000, treated empirically with Cipro and Flagyl. A colonoscopy on admission revealed a normal colon with an ischemic small bowel mucosa. Biopsy reported necrotizing ischemic changes consistent with ischemic injury. An angiogram the same day demonstrated occlusion of the celiac and SMA arteries and a high grade stenosis of the IMA. She underwent a SMA bypass that night. Her post-op was complicated by CHF with bilateral pleural effusions, which had been present before surgery. On 3 May 2000 an abdominal CT scan demonstrated a patent bypass. The patient was discharged on 11 May 2000.

COMORBIDITIES. Hypertension, hyperlipedemia, cigarrette smoking, SMA angioplasty 1994, Renal Artery stenosis treated by angioplasty, IDDM, laparoscopic sigmoid colon resection complicated by a pelvic abscess October 1999, hypothyroidism.
CONCURRENT MEDICATIONS. Human Insulin, Bentyl, Cipro, Lorazepan.

*COMMENT. These two cases of CMI followed a clinical pattern similar to that of CHD. The pain originally triggered by metabolic activity of the affected organ, becomes constant as the disease progresses. Alosetron seems to precede the aggravation of disease and the development of fever and leukcocytosis in both cases. It is difficult to determine the role of Alosetron in either case, due to the severity of the pre-existing disease and to the fact that in both cases there*

*seemed to be a continuous progression of the clinical picture independent of Alosetron. Whether Alosetron accelerated the progression or not is impossible to say. Ischemic Bowel Disease with CMI unlike CHD, does not usually evolve into infarction.*

**c) COLONIC ISCHEMIA (CI)** Thirty-seven cases (80 %) met criteria of AAIscBD. As had been the pre-marketing experience, there were no deaths in this group. All but one were females. The average age was 53.7 years. Sixteen patients (44%) were in the fifth decade. Six patients each (11%) were in their 40's and 60's. The youngest patient was 25 years of age. The oldest was 71. Two patients (cases # 9 and #25) required surgey and they are discussed below.

- **Transient Ulcerated Ischemic Colitis (IC)** This was the largest group with 34 cases (94 %), that are listed in Master Table 6. Twenty-seven cases (79%) required **hospitalization**. Five cases (14%) were treated on out patient bases and in two instances the issue was not clear.

**MASTER TABLE 6**

**34 CASES OF TRANSIENT ULCERATED ISCHEMIC COLITIS EPIDEMIOLOGICAL DIAGNOSTIC CLASSIFICATION**

| OPDRA # | AGE | LOCALIZATION | HOSPITAL. | OPDRA CLASSIF.. |
|---|---|---|---|---|
| 1 | 55 | Spl.Flx./Desc.C | Yes | Colo w/biopsy |
| 2 | 50 | Desc. Colon | No | Colo w/biopsy |
| 3 | 53 | Spl. Flexure | Yes | Scope w/biopsy |
| 4 | 46 | Desc/Sigm C | Yes | Scope w/biopsy |
| 5 | 51 | Desc. Colon | Yes | Scope w/biopsy |
| 6 | 46 | Recto/sigmoid | Yes | Scope w/biopsy |
| 8 | 42 | Spl. Flx. | Yes | Scope only |
| 10 | 56 | Left Colon/Sigm | Yes | Pathology only |
| 13 | 25 | Sigmoid | Yes | Pathology only |
| 14 | 37 | Rectum | Yes | Scope w/biopsy |
| 15 | 71 | Desc/Sigm C | Yes | Scope w/biopsy |
| 17 | 61 | Sigmoid Colon | Unclear | Scope only |
| 22 | 59 | Sigmoid Colon | Yes | Scope w/biopsy |
| 26 | 53 | Left sided colitis | Unclear | Scope w/biopsy |
| 27 | 49 | Spl Flx/Desc C. | No | Scope w/biopsy |
| 28 | 37 | Rectum | No | Path only |
| 30 | 60 | Unknown | No | Scope w/biopsy |
| 31 | 50 | Desc Colon | Yes | Scope w/biopsy |
| 34 | 50 | Spl Flexure | Yes | Scope w/biopsy |
| 35 | 64 | Unknown | Yes | Scope w/biopsy |
| 36 | 47 | Desc/Sigm C | No | Scope w/biopsy |
| 42 | 68 | Pancolitis | Yes | Path only |
| 63 | 56 | Spl Flx | Yes | Path only |
| 70 | 58 | Spl Flx | Yes | Path only |
| 79 | 70 | Recto/Sigmoid | Yes | Scope w/biopsy |
| 80 | 70 | Pancolitis | Yes | Scope w/biopsy |
| 84 | 52 | Spl Flx | Yes | Scope w/biopsy |
| 86 | Adult | Spl Flx | Yes | Scope w/biopsy |
| 92 | 55 | Left Colon | Yes | Scope w/biopsy |
| 112 | 53 | Left Colon | Yes | Scope w/biopsy |
| 127 | 67 | Sigmoid | Yes | Path only |
| 138 | 59 | Cecum | Yes | Scope w/biopsy |
| 150 | 49 | Desc/Sigm C | Yes | Scope w/biopsy |
| 151 | 39 | Desc Colon | Yes | Scope w/biopsy |

The **chief complaint** was rectal bleeding in 27 patients (79%), which ranged from blood on the toilet tissue only, to frank hematochezia. Constipation preceded the bleed in seven cases (21%), although sometimes it was difficult to determine whether this decreased motility was part of a mild ileus associated with the ischemic episode, or constipation due to drug effect (Table 7)

**TABLE 7**

**CONSTIPATION PRECEDING ALOSETRON ASSOCIATED ISCHEMIC COLITIS**
(n=8 patients)

**PRECEDING RECTAL BLEEDING**

| | |
|---|---|
| 1 | Constipation at 5th day - omitted PM dose - pain and bleeding in AM |
| 1 | Wrong indication: IBS w/constipation |
| 1 | Constipation after "a few weeks". Treated for 6½ weeks with laxatives. Pain and bleeding |
| 1 | After weeks of $R_x$ constipation for weeks then IC |
| 1 | Constipation after 9 days of Alosetron. "Subsequently" bleeding |
| 1 | One week of treatment - obstipation - blood in the rectum |
| 1 | Constipation followed in 24 hours by bloody diarrhea |

**NO RECTAL BLEEDING**

| | |
|---|---|
| 1 | Had a previous course of Alosetron without difficulties. Constipation for 2 weeks then IC |

**Concurrent medications** were studied separately. Hormonal replacement therapy was used by 10 patients. The effect of such hormones on coagulation factors is outlined in Table 8. Psychotropic drugs were taken by 14 patients. They are itemized in Table 9 These were the two most commonly used drugs by these group of patients. Sumatriptan, an antimigraine medication known to cause CI was taken by only three patients, and in one of those, the last tablet was taken

seven weeks before Alosetron treatment started. Other miscellaneous medications consumed by these patients with IC are listed in Table 10. Six patients took more than one medication and those drug combinations are listed in Table 14. Two patients were on no medications and in eight cases concurrent medications were unknown.

**TABLE 8**

**Changes in Coagulation Factors Produced by Hormone Replacement, Tamoxifen, and Raloxifene Therapies**

| Coagulation Factor | Hormone Replacement Therapy (HRT) | Tamoxifen Therapy (20 mg/day) |
|---|---|---|
| Antithrombin III | ↓5% | ↓15% |
| Protein C | NS | ↓20% |
| Protein S | NS | ↓20% |
| Fibrinogen | ↓10% | ↓18% |
| Homocysteine | ↓10% | ↓15% |
| C-reactive protein | ↑75% | |
| Plasminogen activator inhibitor 1 | ↓20% | ↓15% |
| In vivo coagulation markers* | NC | NC |

* Prothrombin segments 1 and 2, fibrinopeptide A, and thrombin-antithrombin.

NC=no charge NS=not significant

**TABLE 9**

**PSYCHOTROPIC DRUGS IN ALOSETRON ASSOCIATED ISCHEMIC COLITIS**
**(n=14 patients)**

| | |
|---|---|
| 2 | Effexor* |
| 2 | Xanax |
| 1 | Buspar/nortryptilline |
| 2 | Paxil* |
| 1 | Desipramine - Valium |
| 1 | Tranxene |
| 2 | Neuroleptin - Lorazepan |
| 1 | Buspar - Trazodone - Luvox* |
| 3 | Prozac - Librax |

* SSRIs

**TABLE 10**

**MISCELLANEOUS MEDICATIONS IN ALOSETRON ASSOCIATED ISCHEMIC COLITIS**
**(n=13 patients)**

**PPIs**

4 Omeprazole
3 Lansoprazole

**Beta Blockers**

1 Lopressor
1 Lotensin

**Thyroid** 2

**Statins**

1 Simuastatin
1 Pravastatin

**TABLE 14**

**MULTIPLE CONCOMITANT MEDICATIONS IN ALOSETRON ASSOCIATED ISCHEMIC COLITIS**
(n=6 patients)

1 Buspar - Trazodone - :Luvox - Estrog/Prog.
1 Estrogen - Effexor
1 Estrogen Paxil
1 Estrogen - Desipramine
1 Tamoxifen - Effexor
1 Estrogen - Sumatriptan

The **duration of treatment** before the diagnosis of CI was looked at in detail. Two-third of the patients developed CI during the first two weeks of treatment.

- **Colonic Stricture (CS)** This is a more severe form of CI, an intermediate stage between the benign, reversible forms and colonic gangrene which requires emergency surgery. In CS the clinical course is more protracted, and the symptoms of partial bowel obstruction develop

weeks or months later. The following single case observed of AAIscBD is a good example of that.

Case # 9 – A0121632A. This 69 y/o female was prescribed Alosetron because of diarrhea predominant IBS. After about one week of treatment, while vacationing in ——— .he patient developed diffuse crampy abdominal pain, vomiting, fever and leukocytosis. Colonoscopy with biopsies performed in Hawaii demonstrated IC of the transverse colon. Alosetron was discontinued and the patient recovered. One month later she visited her family doctor and was observed to have a maculo-papular skin rash across the upper abdomen and two skin ulcers in the right hip area. She was still complaining of diarrhea. This clinical picture was interpreted as Crohn's disease with pyoderma gangrenosum and the patient was placed on oral corticosteroids. One week later the diarrhea had improved, the skin rash was gone, the right hip ulcers had developed eschar formation and two new ulcers had developed localized in the skin of the right abdomen and the lower lip. Biopsies of the right hip ulcerations failed to demonstrate vasculitis or any other specific pathology. Two months later the patient developed symptoms of a bowel obstruction and underwent an exploratory laparotomy with right hemicolectomy. The surgical specimen showed a stricture of the transverse colon, a 12x4 cm circumferential ulcer at the margin of resection and microscopic evidence of IC.

COMORBIDITIES. Hypertension, peripheral neuropathy, hypothyroidism.
CONCOMITANT MEDICATIONS Medroxyprogesterone, Gabapentin, multivitamins.

*COMMENT. There seems to be a fairly clear temporal association between the intake of Alosetron and the development of CI. In this case, there was transmural involvement of the colon by the inflammatory process, with the resultant colonic stricture which necessitated surgical treatment. The skin ulcers are of interest, since in retrospect they seemed to have been ischemic ulcers, and one is tempted to speculate that this is an extra-intestinal manifestation of Alosetron effect. One also wonders about the role of hypertension and medroxyprogesterone in this case.*

- **Colonic Gangrene (CG)** There were two cases of CG. These cases are reported below.

Case # 25 (A0127417A) This 54 y/o female was treated with Alosetron by a physician other than the reporter for an unknown time because of IBS alternating diarrhea with constipation. Alosetron was discontinued because of lack of effect. Several months later the physician reporter, a gastroenterologist, performed a colonoscopy which was normal and recommended the patient try Alosetron again. According to the records, patient's symptoms improved, but two weeks later the patient developed severe abdominal pain and constipation. Alosetron had been discontinued three days prior to admission. Gastrografin barium enema revealed feces in the colon, but no obstruction or perforation. Her clinical picture deteriorated, peritoneal signs and leukocytosis developed and the patient was taken to surgery. The operative report states that "the patient had an obviously gangrenous right colon and proximal transverse colon". The pathology report states that the bowel wall was "thinned to the point of translucency with areas of hyperemia and gross ischemia...perforation is not grossly demonstrable". The final microscopic diagnosis was "changes consistent with ischemic colitis". There is no indication other than that the ultimate outcome was favorable.

COMORBIDITIES S/P Cholecystectomy, appendectomy, transabdominal hysterectomy with bilateral salpingo-oophorectomy, bladder suspension, arthorscopic surgery of the right knee, constipation due to Alosetron reason for which Alosetron was discontinued three days prior to admission. Also GERD, reactive airway disease, labile hypertension untreated, deep vein thrombophlebitis of the right leg.
CONCOMITANT MEDICATIONS Levbid, Prilosec, Vioxx, Proventil, Beconase, Atrovent inhaler.

*COMMENT This case has many interesting points: 1) The patient received Alosetron once before without effects. Several months later she was PLACED ON Alosetron again and developed CI after two weeks of therapy. The information available does not allow for an explanation of this phenomenon. It would be of interest to know if both times she received medication from the same batch of drug. 2) As so many of these patients, she had a previous appendectomy, cholecystectomy and hysterectomy, and one wonders how much were her IBS symptoms a determinant to recommend surgery (for example, were the appendectomy and cholecystectomy emergency surgeries?), and the influence of multiple abdominal surgeries in the subsequent development of CI. 3) The patient had a history of deep vein thrombophlebitis of the right leg that preceded the right knee arthroscopic surgery. 4) There is a history of vasospastic syndrome "like a Raynaud's". 5) The surgeon's description of the affected bowel and the pathologist's are almost identical. At the microscopic level, in the segments studied, there was no true gangrene, but there were very severe ischemic changes that led the patient to surgery and to the surgeon's "obviously gangrenous" statement. One can hypothesize that this most severe picture developed on someone who had coexisting risk factors producing independently DVT and a vasospastic Raynaud's-like syndrome*

Case # 64 – A0130853A This 67 y/o female, resident of a long term care facility, affected with Alzheimer's was treated with Alosetron 1 mg bid because of recurrent diarrhea. After five days of therapy the dose was reduced to Alosetron 1 mg daily. The patient had a tendency to fall. After one her falls, about two months later, she became ill, had difficulty swallowing and breathing, and was taken to the emergency room where she was placed on a ventilator. Because of a gas pattern compatible with a bowel obstruction at abdominal x-rays, she was taken to surgery. Operative findings were that of a massively distended colon from the ileocecal valve to the rectum, with a necrotic sigmoid colon. A tube cecostomy, sigmoid resection with end colostomy and Hartman pouch was performed. Pathology report stated that there was acute inflammation suggestive of ischemic colitis, transmural chronic inflammation, and diverticulosis. No perforation was identified. The segment of colon resected measured 36 cm in length, and the pathologist commented that over three-fourths of its length, the bowel was "somewhat dilated". Postoperatively she didn't do well and expired four days later.

COMORBIDITIES: Alzheimer's: the patient was mobile but unable to speak. Depression. Constipation, last, two and a half years before.
CONCURRENT MEDICATIONS: Buspar, Luvox, Prozac, Medroxyprogesterone, Estrogen, Iron, loperamide before Alosetron therapy.

*COMMENT. The fact that this patient was non-verbal probably delayed the diagnosis of CI. There is a strong temporal relationship between Alosetron intake and the development of symptoms. Estrogen, progesterone, Prozac and Luvox are each, capable of producing CI.*

**d) INSUFFICIENT EVIDENCE** There were 32 cases (41%) that did not meet diagnostic criteria for AAIscBD. These cases are summarized in Table 11. Most of the cases were easily eliminated, but others, as it happens with retrospective reviews (see below under Causality), were a judgement call, and another reviewer may have classified it differently. Sixteen cases were reported by physicians, seven by consumers and in nine it was unclear who was the reporter: a sales representative (employer not specified), a physician, or other. The average age of this group was 57.5 years (the age was not stated in five cases), not significantly different than the cases of CI (53.2 years). The localization of the disease was not stated in 23 cases. The reasons for exclusion were mostly related to the poor quality of the information: in 12 cases (38%) the reports were pending, or the tests were not done; 13 cases (41%) were classified as "scope only" by OPDRA. Of those, in 11 instances (85%) there were no reports, in one the endoscopy and biopsies had been performed weeks after the event, after all symptoms had resolved (untimely test) and in another case, information received a posteriori, proved that no CT scans, endoscopies or biopsies had been performed. Four cases had been labeled by OPDRA as "CT only": in three of these cases no endoscopies or biopsies had been performed (elements necessary for inclusion in the clinical classification) and in one the endoscopy was performed untimely. OPDRA labeled one case as "unknown status". There were no reports on this case and apparently no endoscopy or biopsies had been performed. One case classified as "scope with biopsies" by OPDRA had an alternative etiology (microscopic colitis).

## D - DISCUSSION

### 1) Determination of Causality

Causality is the assessment of a cause-and-effect relationship between two associated events. The likelihood of the cause-and-effect relationship is usually expressed in such terms as definite, probable, possible, unlikely and definitely not. Causality assessments may be viewed at different levels: individual patients (for example: is one particular medicine the cause of the A/E and thus, should be discontinued?), or individual clinical trials (should this trial be prematurely terminated?). For large postmarketing surveillance studies, and adverse event evaluations, the assessment of causality is not relevant for interpreting the data. This is because it is usually not possible to obtain sufficient information on reported A/Es to determine if they are caused by the medicine. As demonstrated in this series, information obtained is usually fragmentary, unverified, and of variable quality. It is often impossible to obtain sufficient additional data to answer important questions. The interpretation of such data is subject to substantial error if the data are analyzed too finely (i.e., to assess causality). Causality is a critical tool for Phase I studies, but it is less valuable, and sometimes even counterproductive, to evaluate causality in post-marketing studies.

**MASTER TABLE 11**

**32 CASES OF INSUFFICIENT EVIDENCE FOR AAIscBD EPIDEMIOLOGICAL DIAGNOSTIC CLASSIFICATION CLINICAL REASON FOR EXCLUSION**

| OPDRA # | AGE | LOCAL | HOSPIT. | EPIDEM. DIAGN. CLASSIF. | CLIN. REASON FOR EXCLUS. |
|---|---|---|---|---|---|
| 7 | 51 | UNKNOWN | UNKNOWN | REP PEND | REP PEND |
| 12 | 73 | UNKNOWN | UNKNOWN | SCOPE ONLY | NO EVID OF SCOP/BX/CT |
| 18 | 37 | UNKNOWN | YES | REP PEND | REP PEND |
| 19 | 44 | SEE NEXT | YES | REP PEND | ALL REP R IN NO EVID |
| 23 | 44 | SUG.DESC C | NO | SCOPE ONLY | UNTIMELY TEST- PATH NEG |
| 24 | UNKNOWN | UNKNOWN | UNKNOWN | REP PEND | REP PEND |
| 32 | UNKNOWN | UNKNOWN | UNKNOWN | SCOPE ONLY | REP PEND |
| 37 | 60 | LEFT COLON | YES | CT EVIDENCE | NO SCOPE OR PATH |
| 39 | 52 | UNKNOWN | YES | CT EVIDENCE | NO SCOPE/PATH NO REPORTS |
| 40 | 56 | SIGMOID | YES | UNKNOWN STATUS | NO BX/NO REPORTS |
| 41 | 44 | UNKNOWN | NO | REP PENDING | TESTS NEVER DONE |
| 62 | 69 | UNSTATED | YES | SCOPE W/BX | ALTERNAT. ETIOLOGIES |
| 71 | UNKNOWN | UNKNOWN | YES | SCOPE ONLY | NO REPORTS |
| 74 | 48 | SIGMOID | YES | REP PEND | ALT ETIOL |
| 75 | 66 | UNSTATED | UNKNOWN | PATH ONLY | NO REPORTS |
| 77 | UNKNOWN | UNKNOWN | YES | REP PEND | NO REPORTS |
| 82 | 59 | TRANSV C. | YES | REP PEND | NO SCOP/BX |
| 83 | 56 | UNKNOWN | UNKNOWN | CI EVID | NO SCOP/BX |
| 87 | 64 | UNKNOWN | UNKNOWN | REP PEND | NO REPORTS |
| 88 | 41 | UNKNOWN | YES | SCOPE ONLY | NO REPORTS |
| 90 | 54 | RIGHT C. | YES | CT EVID | UNTIMELY SCOPE/BX |
| 91 | 72 | PANCOLITIS | YES | SCOPE ONLY | NO REPORTS |
| 93 | 70'S | UNKNOWN | UNKNOWN | SCOPE ONLY | NO REPORTS |
| 94 | 33 | UNKNOWN | UNKNOWN | SCOPE ONLY | NO REPORTS |
| 100 | 69 | RIGHT C. | YES | REP PEND | NO REPORTS |
| 103 | 65 | UNKNOWN | YES | SCOPE ONLY | NO REPORTS |
| 104 | 74 | UNKNOWN | YES | SCOPE ONLY | NO REPORTS |
| 108 | 64 | UNKNOWN | YES | REP PEND | NO REPORTS |
| 110 | UNKNOWN | UNKNOWN | YES | REP PEND | NO REPORTS |
| 118 | 80 | UNKNOWN | NO | PATH ONLY | NO REPORTS |
| 123 | 61 | UNKNOWN | YES | REP PEND | NO REPORTS |
| 155 | 47 | UNKNOWN | YES | REP PEND | NO REPORTS |

For post-marketing surveillance studies there will be an increased demand for **natural history epidemiology**. This means that registries of the natural history of diseases will be used more in the future to establish the background rate(s) of A/Es in patients with the disease. This information will be compared with medicine-induced rates. The determination of background rates, will be more important for post-marketing surveillance evaluations than focusing on the attribution of individual A/Es with the medicine.

All these considerations related to causality are further compounded when we deal with a condition like IBS, for which there are no biological markers to establish a diagnosis or to measure its severity. All assessments are based on the interpretation of symptoms with the inherent biases from the part of the patient and the recording physician

In addition, the A/E under study, Ischemic Bowel Disease, demands a great deal of clinical suspicion to be diagnosed early, accurately, and in its milder forms. There are no accepted diagnostic criteria for other than the most severe, surgical sub-types. Its drug-induced etiology is multiple and varied, with apparently unrelated families of drugs associated with its occurrence. As a consequence of all this, trying to determine risk factors or population sub-sets at higher risk in AAIscBD becomes a daunting task.

**2) Potential drug interactions** Two patients of the 46 with AAIscBD were on no concurrent medications. In another eight patients (17%) there was no information ("unknown") about concurrent medications.

Seventeen patients (31%) were on HRT: 11 on estrogen, 4 on progesterone, one on estrogen/progesterone combination and one on "HRT". One patient was on Tamoxifen. **The female sex hormones** drug group was by far, the more commonly associated with Alosetron therapy. Estrogens and Selective Estrogen Modulators (SERMs) therapy are both associated with an increased risk of thromboembolic events in general, and Ischemic Bowel Disease in particular.[17] Contributors to these tendencies are a decrease in the level of anti-thrombin III and, to a lesser extent, protein S, leading to a hypercoagulable state.[4]

The second most common drug group were the **psychotropics** of which the Serum Serotonin Reuptake Inhibitors (SSRIs) were the most frequently prescribed (8 cases, 17%). Fourteen CI patients (30%) were on one or more of these drugs, as follows: Prozac (3), Paxil (3), Effexor (2), Buspar (2), Luvox (1), Elavil (1), Librax (chlordiazepoxide) (1), Lorazepan (1), Promethazine (1), Tranxene (1), Xanax (1) (Table 9).

IBS patients frequently have symptoms of anxiety and depression (fatigue, pain, sleep disturbances, irritability, anhedonia) and are treated, and respond, to antidepressants, particularly drugs of the SSRI family. Most of the effects of antidepressants in the body, whether therapeutic or adverse, occur at the level of the synapse: the site where one neuron communicates with another neuron or another cell like, for example, a smooth muscle cell. By blocking uptake of neurotransmitters (serotonin, dopamine, noerpinephrine), blocking some neurotransmitter receptors, or inhibiting the mitochondrial enzyme monoamino oxidase, antidepressants alter the magnitude of the effects of neurotransmitters at these synapses. The vast majority of available antidepressants block predominantly the transport of serotonin over norepinephrine and other neurotransmitters, back into the cells from which they were released. The mood elevating effect of these drugs usually begins one to two weeks after initiation of therapy and the full effect is appreciated after six weeks. **The synaptic effects of antidepressants occur within hours** after the patient ingests the drug. Most of the adverse effects of antidepressants can be explained by their synaptic effects.[18,19] Anorexia, nausea and diarrhea/constipation are the most common gastrointestinal symptoms associated with antidepressant therapy. Serotonin is also a potent vasoactive substance, that in SSRI treated patients is now present in larger amounts due to the

inhibition of the reuptake system, affecting motility (diarrhea) and inducing cardiovascular symptoms. This latter effect has been implicated in the etiology of CI in some patients. How these complex pharmacodynamic mechanisms will interplay with another serotonin receptor antagonist like Alosetron is difficult to tell. One can however hypothesize that the microcirculation of the colon, among other factors, may be affected. SSRIs, further, have known pharmacokinetic interactions due to their inhibitory effect on microsomal enzymes of the CYP-450 system. Of note is the fact that Alosetron shares with fluoxetine, paroxetine, fluvoxamine, sertraline and venlafaxine the CYP2D6 metabolic pathway. Fluoxetine (Prozac), and norfluoxetine, its main metabolite in the human, are among the most potent inhibitors of CYP2D6.[20] This is known to have clinical consequences, producing toxic blood levels of other drugs that share the same chemical pathway. Other enzymes inhibited by SSRIs are CYP3A4, CYP1A2 and CYP2C9. Finally, pharmacogenetics may be playing a role in the interaction between Alosetron and SSRIs since we now know that response to medication (for example determination of serotonin transporter) is predicted by the genotype of the patient. SSRIs may interfere with Alosetron metabolism and produce, in some patients, supratherapeutic levels of Alosetron, or one of its metabolites (we don't yet know whether they are biologically active) and induce sustained vasoconstriction of the microcirculation.

**3) A hypercoagulable state (HCS)** Five cases (#7195, # 68, # 152, # 157, # 25) raise the possibility that the patients might have had a pre-existing hypercoagulable state or that they developed one after intake of Alosetron.

**SUMMARY TABLE 12**
**FIVE CASES OF HCS IN AAIscBD**

| CASE # | AAIscBD TYPE | HCS | CONC MEDS COMORB. |
|---|---|---|---|
| 7195 | TRANS ULC IC | MVA WITH PE | PROZAC HYPOPHYSEC |
| 68 | MVT | FACTOR V MUTATION | MORBID OBES DVT AGE 20 |
| 152 | MVT | AXILL/PORT/ SPL VEINS TH. . COUMAD RES. | |
| 157 | MVT | COUMADIN RESISTANCE | SEV CHD ESTROGEN |
| 25 | COL GANGRENE | DVT RIGHT LEG | RAYNAUD'S |

HCS predominates in venous thrombosis. HCS can be inherited or acquired. The increased clinical relevance of the inherited forms of HCS became apparent with the identification of the mutations in factor V (Leiden), the G20210A mutation in the prothrombin gene (factor II) and the homozygous C6771 mutation in the methylenetehydrofolate reductase gene, that are present in an estimated 8-10% of the population.[4] These genetic causes interact with acquired forms due, among other reasons, to the use of contraceptives or HRT, older age, prolonged immobilization, pregnancy and puerperium, clinical and sub-clinical forms of myeloproliferative disorders and previous history of thrombosis. Koutrobakis et al.[10] recently reviewed the role of acquired and hereditary thrombotic risk factors in colon ischemia in ambulatory patients. In their report, 36 patients identified with non-occlusive colon ischemia by clinical, endoscopic and histological criteria consented to return to the clinic to undergo a physical examination and a

battery of laboratory tests, from at least one month to several years after discharge from the hospital. These patients were matched with 18 patients with diverticulitis and 52 healthy controls. The prevalence of acquired and hereditary thrombotic risk factors was found significantly higher compared with the prevalence of these factors in matched controls. Antiphospholipid antibodies were found in 19.4 % of CI patients as opposed to 0 % and 1.9 % in the control groups. Factor V Leiden was present in 22 % of CI patients and in 0 % of diverticulitis and 3.8 % of healthy controls. Combinations of multiple prothrombotic risk factors were found in 9 CI cases (25 %). In an editorial comment L. J. Brandt analyzes the data with a dose of healthy skepticism, but **accepts the possibility that underlying coagulation disorders may increase the risk for irreversible types of CI.**[3]

The use of oral contraceptives increases the risk of venous thrombosis by a factor of 3.8 in normal women and by a factor of 34.7 in women who are hetererozygous for factor V Leiden. HRT likewise produces an increase in the risk of venous thrombosis in both healthy women and those with an inherited HCS. **This HCS is not a systemic disorder. Each vascular bed is qualitatively unique in maintaining its hemostatic balance.**[5] The molecular mechanisms that underlie these vascular-bed-specific differences are found in complex signaling networks that have evolved in the endothelial-cell lining of the vascular tree. The endothelium integrates and transduces multiple signals that vary in both time and space. In patients with congenital or acquired HCS, signaling pathways are differentially affected in different segments of the vascular tree, leading to characteristic thrombotic phenotypes.

Alosetron with its selectivity for 5HT3 receptor sites in the colon could disrupt this balance between procoagulants and anticoagulants called hemostasis, and trigger vascular events in the splachnic vascular bed. This effect can be due to Alosetron, to one of its metabolites or to drug interactions with estrogens, SSRIs, or other drugs that may compete for the same metabolic pathways.

Should we subscribe to this hypothesis, Alosetron use should be withheld in patients who have risk factors for HCS, like for example, previous history of DVT, thromboembolism, use of contraceptives or HRT, older age, cancer, fetal loss, or family history of venous thrombosis. SSRIs, contraceptives, HRT should be dicouraged in patients on Alosetron therapy. Patients considered at high risk for AAIscBD should be screened for congenital or acquired HCS, by means of appropriate laboratory determinations.

### *4)* AAIscBD Syndrome

From the foregoing a clinical syndrome of Ischemic Bowel Disease in association with Alosetron intake emerges that can be summarized as follows:

- The patient is usually a female who has been taking Alosetron for some time, ranging from one day to weeks or months, continually or intermittently. The patient might have taken Alosetron without difficulty in the past. This could be a second (or third, or more) course of Alosetron therapy.

- Worsening of abdominal pain and blood per rectum, in any amount, without initially other positive findings at physical examination.

- Risk factors for AAIscBD and predisposing drugs are listed in Table 13. Previous history of thromboembolic disease, a hypercoagulable state, concomitant therapy with female sex hormones and psychotropics, seem to predispose to more severe forms of the disease leading to surgery.

- AAIscBD is not different than other forms of IscBD. A high degree of suspicion and familiarity with the multiple presentations of IscBD should dictate the physician's course of action. If AMI is suspected, emergent CT scanning and angiography are indicated. If rectal bleeding predominates in the picture, colonoscopy with biopsies should be performed to rule out other etiologies and firm up the diagnosis.

- It is recommended that a surgical consult be requested early during the course of the diagnostic work up, preferably with a vascular surgeon or a surgeon with experience in IscBD. AAIscBD usually follows a benign, self limited course restricted to the colon. There is a 15 to 20 % of cases in which ischemic necrosis of the bowel and gangrene develop in the small intestine and/or colon, requiring bowel resection that may be extensive. The initial symptomatology of both, the benign and the severe forms of the disease, is most of the times identical. An experienced physician would use those initial hours to aggresively conduct diagnostic tests and therapeutic procedures that may be surgery-sparing and life-saving, rather than wait for peritoneal signs to develop.

- In a small percentage of cases (2 % in this series) small bowel or colonic strictures may develop weeks or months after the initial acute episode of AAIscBD has subsided, the correction of which may necessitate surgery. In those cases, the symptomatology is indistinguishable from other forms of partial bowel obstructions.

- There is nothing specific or pathognomonic about AAIscBD. The best way to confirm that the acute episode was indeed IscBD is to repeat some of the tests, particularly abdominal CT scanning and colonoscopy with biopsies, and demonstrate the normalcy of the affected organ(s).

- Alosetron should be discontinued immediately at the first symptom compatible with IscBD. This, however, does not assure that the clinical picture will reverse itself.

- There is no experience with re-challenge of Alosetron after an episode of AAIscBD. Therefore, it is not advisable to resume Alosetron therapy after an attack of AAIscBD.

**TABLE 13**

**RISK FACTORS THAT MAY CONTRIBUTE TO AAIscBD**

| **Predisposing Factors** History of: | **Predisposing Drugs** |
|---|---|
| Thrombotic event before age 45 | Female sex hormones |
| Recurrent venous thrombosis | Tamoxifen |
| Fetal loss | Steroids |
| | Vasocostrictors |
| Fetal growth retardation | Ergot |
| Preclampsia | Pseudoepinephrine |
| Abruptio placentae or stillbirth | NSAIDs |
| | Digitalis |
| Three unexplained abortions | Cocaine |
| Paroxysmal nocturnal hemoglobinuria | Psychotropics |
| Myeloproliferative disorder | SSRIs |
| | TCAs |
| Elderly | Flutamide |
| Tobacco Atherosclerosis | 5 HT - 1 Agonists |
| Congestive Heart Failure | Sumatriptan |
| Vasculitides | $\alpha$ Interferon |
| Constipation | |
| Infections: Pathogenic E Coli | |
| Hypoperfusion states | |
| | |
| Hypercoagulable states: | |
| | |
| Factor V Leiden | |
| Protein C deficiency* | |
| Protein S deficiency* | |
| Antithrombin III* | |
| Prothrombin 20210 mutation | |
| Increased Factor VIII | |
| Factor XII deficiency | |
| Anti phospholipid antibodies | |
| Dysfibrinogenemia | |
| Lupus anticoagulants | |
| Protein Z | |
| Protein-Z dependent Protease inhibitor | |

* Test not reliable during acute TE events or critically ill

## E – CONCLUSIONS

1) Seventy- eight cases were reported with possible AAIscBD. Of those, 46 (59%) met clinical criteria as defined in Table 2.

2) Thirty-two cases had IE of AAIscBD. The reasons for exclusion and their epidemiological classification are listed in Table 11.

3) Thirty-eight cases in the group of AAIscBD (83%) were of reversible, mild forms of the disease, that resolved spontaneously upon discontinuation of Alosetron therapy.

4) Eight cases of AAIscBD (17%) represented severe forms of the disease. These include: three cases of MVT, two cases of CMI complicated by SMA and/or IMA thrombosis, two cases of CG and one case of CS. All eight cases underwent surgery. Three cases (38%) died.

5) In five cases of AAIscBD (11%) (MVT 3, CG 1, IC 1) there was strong suspicion that HCS might have played a role in the pathogenesis of AAIscBD.

6) Female sex hormones (birth control and HRT) and Tamoxifene were used in 37% of the patients. These hormones have known thromboembolic potential. Estrogen per se has been reported to induce CI.

7) Psychotropics were used by 30% of the patients. SSRIs, alone or in combination with other psychotropics were taken by 17% of AAIscBD patients. SSRIs have been implicated in cases of IscBD and, in addition, share with Alosetron important CYP P-450 metabolic pathways. This latter phenomenon could interfere with Alosetron metabolism and produce supratherapeutic levels of Alosetron or its metabolites in blood.

8) Based on these data and the review of the literature one can conclude that IscBD is a multifactorial disease. Arterial disease is platelet-centered and atherosclerotic in nature, whereas venous thromboembolism is based on defects in the coagulation/anticoagulation pathways. Arterial disease was present in this series in only two patients with AAIscBD (4%), MVT in three patients (7%) and HCS was suspected in five patients (11%). Alosetron or its metabolites may tilt the scale against the patient by affecting coagulation or selectively affecting the endothelium of the splachnic vascular bed. By concentrating in the prevention of the 17% of patients with serious forms of AAIscBD, we may be able to also decrease the prevalence and manage the other 87% of the cases with milder forms of CI, and the other unknown number of patients with even milder forms of the disease, who go undiagnosed.

Marcelo Barreiro, M.D.

cc:
HFD-103/FHoun
HFD-180/VRaczkowski
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**AAIscBD – BIBLIOGRAPHY**

1) Greenwald David A. et al. Ischemic Bowel Disease in the Elderly. Gastroenterology Clinics of North America, 30:2, June 2001, 445-473.
2) Greenwald D. A. and Brandt L. J. Colonic Ischemia. J. Clin Gastroenterol 1998;27(2):122-128.
3) Brandt L. J. Intestinal Ischemic Disorders. DDW 2000. Handout on file.
4) Seligsohn U. and Lubetsky A. Genetic Susceptibility to venous thrombosis. NEJM vol 344:1222-1231 April 19, 2001.
5) Rosenberg R. D. and Aird W. C. Vascular-bed–Specific Hemostasis and Hypercoagulable States. Review Article: Mechanisms of Disease. NEJM vol 340:1555-1564. May 20, 1999
6) Ringel Y., Sperber A. D. and Drossman D. A. Irritable Bowel Syndrome. Annual Reviews Medicine 2001.52:319-338
7) Mesenteric Ischemia. Chapter 114. Vol 2. Pages 2583-2604. Textbook of Gastroenterology. Editor T. Yamada. Lipincott Williams & Wilkins © 1999.
8) Gastrointestinal Blood Flow. Chapter 23. Vol 1 Pages 519-546. Textbook of Gastroenterology. Editor T. Yamada. Lipincott Williams & Wilkins © 1999.
9) Concept of Cause and Effect. Guide to Clinical Trials. B. Spilker. Raven Press © 1991.
10) Koutroubakis I. E. et al. Role of Acquired and Hereditary Thrombotic Risk Factors in Colon Ischemia of Ambulatory Patients. Gastroenterology 2001;121:561-565.
11) Brandt L. J. Editorial. Gastroenerology 2001;121:724-726.
12) American Gastroenterological Association Medical Position Statement: Guidelines on Intestinal Ischemia. Gastroenterology 2000;118:951-953.
13) AGA Technical Review on Intestinal Ischemia. Gastroenterology 2000;118:954-968.
14) Smith D. S. and Mertz H. The Enteric Nervous System in Health and Disease. Clinical Perspectives in Gastroenterology July/August 2001 Pages 225-234.
15) Furness J. B. et al. Memory in the enteric nervous system. Gut 2000;47(Suppl 4):iv60-iv62 (December).
16) Kunze W. A. A. and Furness J. B. The enteric nervous system and regulation of intestinal motility. Annual Reviews Physiology 1999.61:117-142.
17) A special report. An update on the effects of SERMS on women's health. Postgraduate Medicine. March 2001.
18) Cadieux R. J. Antidepressant drug interactions in the elderly. Understanding the P-450 system is half the battle in reducing risks. Postgraduate Medicine vol 106/No 6/November 1999.
19) Richelson E. Pharmacology of Antidepressants. Mayo Clinic Proceedings 2001;76:511-527
20) Ball S. E. et al. Venlafaxine: *in vitro* inhibition of CYP2D6 dependent imipramine and desipramine metabolism; comparative studies with selected SSRIs, and effects on human hepatic CYP3A4, CYP2C9 and CYP1A2. Br J Clin Pharmacol 1997;43:619-626.
21) Talley N. J. Methodological Issues in Irritable Bowel Syndrome Clinical Trials: Practical Relevance for the Clinician. Practical Gastroenterology. August 2001 Vol XXV No 8 Pages 16-23.

22) Clinical Pharmacology and Biopharmaceuticals Review by R. E. Kavanagh, Pharm.D., Ph D. NDA 21-107 September 21, 1999.
23) Medical Officer Review (Efficacy) by R. Prizont, MD. NDA 21-107. October 15, 1999.
24) Medical Officer Review (Safety) by J. Senior, MD. NDA 21-107. October 22, 1999.
25) Secondary, Multidisciplinary Review and Recommendations for Regulatory Action by H. Gallo-Torres, MD, Ph D. NDA 21-107. November 17, 1999.
26) OPDRA Postmarketing Safety Review. Ischemic Colitis and Complications of Serious Constipation Events as of July 31, 2001
27) S. Kress, Personal Communication
28) S. Kress, M. Barreiro, H. Gallo-Torres. Review of Alosetron-Associated Deaths Reported Post-marketing 29 August, 2001
29) S. Kress. Review of Lotronex (Alosetron)-Associated Serious Complications of Severe Constipation Reported Post-Marketing. 9 October 2001
30) Mayer E.A. The Neurobiology of Stress and Gastrointestinal Disease. Gut 2000; 47(6):861-869

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**DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS**

**To: Hugo Gallo-Torres M.D., Ph.D., Medical Team Leader**

**From: Scheldon Kress, M.D., Medical Officer**

**NDA 21-107 REVIEW of LOTRONEX (ALOSETRON)-ASSOCIATED SERIOUS COMPLICATIONS OF SEVERE CONSTIPATION REPORTED POST-MARKETING**

## Executive Summary


Lotronex (alosetron) was approved February 9, 2000 for the palliative treatment of irritable bowel syndrome (IBS) in women whose predominant symptom is diarrhea (D-IBS). Two major adverse events were noted during pre-marketing review of Lotronex: ischemic colitis (being addressed separately) and dose-related constipation. The latter occurred in about one third of the patients, was mild to moderate in severity, was not serious, and no patient needed to be hospitalized for treatment of complications of constipation.

Post-marketing use of alosetron for treatment of IBS was associated with cases of serious complications of constipation, ranging from fecal impaction (prolonged retention of fecal material in the rectosigmoid region and even more proximal regions of the colon) to obstruction, toxic megacolon, and perforation necessitating surgery.

Whereas constipation was the most frequently observed AE experienced by alosetron users in clinical trials, fecal impaction exaggerated constipation, contributed to 29/77 (38%) of the constipation-related SAEs experienced post-marketing by alosetron users. These epidemiological data revealed varying degrees of bowel obstruction which made up 18/77 (23%) and colon perforation which made up 11/77 (14%) of the serious complications of severe constipation observed among alosetron users. Major abdominal surgery, unknown to occur among D-IBS patients, was required in 23/77 (30%) of patients to treat the serious complications occurring among this group of alosetron users. These SAEs placed these patients at substantial operative risk by the necessity for emergent surgical treatment to repair 12 intestinal obstructions and 11 colon perforations with resultant 9 colostomies, and 1 colectomy. Even two deaths subsequent to colon perforation occurred following this sequence of events among alosetron users.

To deal with these serious adverse events and deaths reported in association with its use, the Agency requested implementation of a Restricted Distribution Plan-Risk Management Program (RDP-RMP). The Agency met with Glaxo Wellcome on November 28, 2000 to discuss options proposed by FDA that included:

a) voluntary withdrawal with limited access under an IND study program;
b) temporary suspension of drug marketing pending an Advisory Committee Meeting ;
c) restricted distribution to patients already receiving Lotronex, with informed consent, under 21 CFR 314 Subpart H.

After considering these options, GW decided to withdraw alosetron from the marketplace.

The main goal of this detailed clinical analysis of the epidemiological data is to characterize the alosetron-associated SAEs of severe constipation as much as possible from the spontaneous reporting information. As a consequence of the analyzed information, labeling revisions, modifications to the Medication Guide, and additional intervention to the RDP-RMP are proposed.

As of August 22, 2001 (the date of OPDRA's latest memorandum), 77 cases of alosetron-associated serious complications of severe constipation have been reported to OPDRA. The majority, 86% (66/77), of these patients required hospitalization and 30% (23/77) required surgery. Whereas, constipation was a presenting complaint in 63 patients and was not in the additional 14 patients, this review analyzes these cases of alosetron-associated serious complications of severe constipation both separately and together. Identification of a set of patients who apparently did not report constipation even though they already were impacted, represents a further challenge to the management of alosetron-induced complications of constipation. In these individuals the slight benefit (end of diarrhea) may be indistinguishable from the risk (development of impaction).

Analysis of the data suggested that those patients who experienced serious complications of severe "unreported" constipation required hospitalization in 100% (14/14) and surgical procedures in 57% (8/14) of cases, higher than those with serious complications of severe symptomatic constipation among alosetron users. If this newly identified group actually represents patients who experienced serious complications of constipation without prodromal manifestations, prevention and treatment of this SAE among some alosetron users may be even more difficult to achieve than previously suspected.

The Agency's Benefit-Risk Evaluation and recommendations for regulatory action, and expectations and limitations of possible actions are reviewed. The single most important recommendation of the GI Division has remained: *days without bowel movements must become days without this medication* if the severity of these constipation –related SAEs is to be significantly reduced and prevented.

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## 1. Introduction to Review of Alosetron-Associated Serious Complications of Severe Constipation Reported Post-Marketing

NDA 21-107 for Alosetron for the treatment of D-IBS (diarrhea–predominant irritable bowel syndrome) submitted on July 1, 1999, was granted priority review because of the lack of effective treatment for this form of IBS. In the two clinical trials of approximately 2800 patients, alosetron demonstrated *adequate relief of pain and discomfort* (primary endpoint) by showing a 12% to 15% therapeutic gain over the placebo response rate of 26% and 29% for the combined 3 months of study treatment.

Constipation refers to reduced frequency of stools, the passage of a hard stool, or straining at stool. A more strict definition is the passage of less than 3 stools per week. Constipation is quite prevalent. Symptoms of constipation are reported by 14.7% of Americans ages 18 and older. 5.5% are attributed to constipation-predominant IBS (C-IBS). Whereas many patients consume drugs that have anti-motility effects, drug-induced constipation is quite common.

In the pre-approval clinical trials of alosetron, constipation was found to be 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 (1 in 3 of those experiencing constipation) to withdraw from clinical studies. In spite of this, serious complications associated with constipation were not observed in the pre-approval studies.

This review analyzes the 77 cases of alosetron-associated serious complications of severe constipation occurring post-marketing that have been reported to the Office of Post-Marketing Drug Risk Assessment (OPDRA) as of August 22, 2001. In 63 patients, severe constipation was a major component of the patient's presenting complaint. **In the additional 14 patients, constipation was not apparent among the presenting complaints**. However, as the subsequent clinical syndrome evolved, severe constipation played a major role in the evolution of the serious complications associated with alosetron usage. Therefore, these cases were analyzed separately.

The occurrence of serious complications of severe constipation such as fecal impaction, intestinal obstruction, ischemic ulceration, and perforation, without patients being aware that they are constipated, has been repeatedly observed. It is speculated that these patients may have not been aware of the degree of constipation present or liquid stool may have seeped around fecal impactions and prevented the patient from recognizing the presence of constipation or its impending serious constipation-induced sequelae. Furthermore, patients who have been experiencing troublesome diarrhea and are now "happy" to be diarrhea-free, may be unaware that the drug's benefit has been replaced by an adverse event.

Information for each case report was provided by physicians, patients, their relatives, or other incidental witnesses (sales representatives, office staff, nurses) to the OPDRA. Where ever possible OPDRA has followed up with requests for office and hospital records in order to clarify the actual role of alosetron in each case. Despite repeated requests, often no further information has been made available. Thus, assessment of each case has to be based on whatever information is available, understanding that it often is incomplete.

**Alosetron**

Alosetron is a selective 5-$HT_3$ receptor antagonist and was the first of a new class of drugs that have evolved based on new knowledge of the key role of serotonin in the function of the Enteric Nervous System (ENS). Serotonin, a potent vasoactive neuropeptide, plays an important role in the transmission of impulses at the level of the synapse and is instrumental in triggering events related to intestinal motility and secretion. 5-$HT_3$ receptors normally stimulated by serotonin binding, increase intestinal motility, increase intestinal secretion from the mucosal crypts, and increase blood flow within the microcirculation. Alosetron, by binding to this receptor site, produces the opposite effect: decreased motility and secretion (its therapeutic properties) and an effect on the microcirculation that has not been fully characterized.

Lotronex (alosetron) was approved February 9, 2000 for the treatment of D-IBS in females. Safety concerns by the Agency at the time of the November 16, 1999 GI Advisory Committee based on the NDA study data included:

**Lotronex–Associated Serious Adverse Events Pre-Approval**

| Ischemic Colitis | Serious Complications of Constipation |
|---|---|
| 3 | 0 |

Post-marketing use of alosetron was associated with several unique, incapacitating and potentially serious gastrointestinal adverse events i.e., serious complications of severe constipation, ischemic colitis, and small bowel ischemia associated with arterial or venous thrombotic occlusions of the mesenteric vessels.

To deal with these serious adverse events and deaths reported in association with its use, the Agency requested implementation of a Restricted Distribution Plan-Risk Management Program (RDP-RMP). The Agency met with Glaxo Wellcome on November 28, 2000 to discuss options proposed by FDA that included:

1) voluntary withdrawal with limited access under an IND study program;
2) temporary suspension of drug marketing pending an Advisory Committee Meeting ;
3) restricted distribution to patients already receiving Lotronex, with informed consent, under 21 CFR 314 Subpart H.

After considering these options, GW on November 28, 2000 decided to withdraw alosetron from the marketplace. During that 9 month period of time the drug was marketed, over 300,000 patients filled over 450,000 prescriptions for alosetron.

**Irritable Bowel Syndrome (IBS)**

IBS is the most common functional gastrointestinal disorder affecting about 15 % of the population. Of those seeking medical care, in the Western world, 65-70% are women. Beside its frequent occurrence, IBS affects public health by its physical and emotional impact on the QOL of patients with severe disease.

The symptoms of IBS are abdominal pain, usually crampy and relieved by expelling flatus and/or stool, abnormal elimination in the form of constipation, diarrhea or alternating periods of constipation and diarrhea, bloating, urgency and the feeling of incomplete elimination. Although these symptoms can be long standing, and are usually not life-threatening. IBS patients often undergo unsuccessful surgical procedures to alleviate their persistent and difficult to manage symptoms, but usually they do not develop pathological processes that require surgical intervention. IBS is frequently associated with other disorders of unknown etiology that can severely affect quality of life and are difficult to treat, such as fibromyalgia, migraine, PMS, depression, anxiety, and dyspareunia.

**2. Post-Marketing Experience-**
**Recognition of Serious Enteropathies Associated with Alosetron Usage**

Post-marketing use of alosetron for treatment of IBS was associated with several unique, incapacitating and potentially serious gastrointestinal adverse events i.e., serious complications of constipation, ischemic colitis, and small bowel ischemia associated with arterial or venous thrombotic occlusions of the mesenteric vessels.

Reports of **serious complications associated with severe constipation** were described in patients taking alosetron. The constipation occurred generally, but not always, within the first months of therapy, and was associated with abdominal pain and occasionally rectal bleeding. The majority (66/77) of these patients required hospitalization, 30% (23/77) required surgery, and only 6/77 were treated in an Emergency Room without admission to the hospital. Several known serious complications of constipation occurred necessitating hospitalization: fecal impaction requiring disimpaction and/or surgery, intestinal obstruction requiring intubation and/or surgery, and ischemic (stercoral - hard feces induced) ulceration requiring surgery. Surgery was required for perforation and complications of obstruction. Even two deaths occurred following this sequence of events among alosetron users.

**Ischemic colitis** was a clinical colonopathic syndrome that occurred in association with alosetron usage in pre-marketing clinical studies. As described in the labeling, this ischemic colitis appeared to be nonthrombotic, mild, self-limited and reversible upon discontinuation of the drug. It consisted of abdominal pain (usually crampy and severe), diarrhea, bloody diarrhea and rectal bleeding. Post-marketing more severe cases were recognized.

Post-marketing, a third type of SAEs was reported among patients taking alosetron, **small bowel ischemia**. These patients experienced severe ischemia of the small bowel alone or in combination with the colon and, developed necrosis of small segments or the entire intestinal tract. Most of these patients demonstrated arterial or venous thrombotic occlusions of the mesenteric vessels. All of these patients were critically ill and required surgery. One patient died.

These cases of alosetron-associated ischemic colitis and small bowel ischemia will be analyzed in a separate review in progress (Drs. M. Barreiro and Hugo E. Gallo-Torres).

**<u>CONSTIPATION:</u> Serious Adverse Events Associated with Lotronex Usage**

A total of 77 cases of alosetron-associated serious complications of severe constipation. were reported in patients who received alosetron. All patients had documentation of alosetron intake of variable duration, as little as 12 hours to as long as 180+ days. In many instances, alosetron was prescribed "off label." "Off-label" indications included: non-IBS diarrhea, post-operative diarrhea, acute diarrhea, chronic pancreatitis-associated diarrhea, and diarrhea type-IBS among men. (The drug has yet to be shown to be effective in male patients.) In most cases, evaluation of causality was difficult to classify because of insufficient and even conflicting information. Therefore, all cases were conservatively considered as possibly cases of alosetron-associated serious complications of severe constipation. Guidelines for determining causality are shown in Appendix 1.

**Sixty-three of the MedWatch case reports (82%) included descriptions of the severe constipation experienced by each patient. In the additional fourteen MedWatch case reports (18%), there was no mention of constipation**. Among the possible explanations for these omissions are: patients were too ill to report constipation, not aware that they were actually constipated, or were so sick and the reporter inadvertently omitted the symptom constipation from the report. For this review, we have chosen to refer to this group as patients with serious complications of severe "unreported" constipation. This group experienced significantly more serious adverse events, all sequelae of severe constipation. All fourteen required hospitalization, eight (57%) required major abdominal surgery, six (43%) had colon perforations, and one may have possibly died from the serious complications of severe "unreported" constipation. Since these patients may have experienced serious complications without prodromal manifestations, this group was analyzed both separately as well as together with the symptomatic group.

Table 1 summarizes the incidence of severe complications, experienced by these two groups of patients, symptomatic and "unreported" severe constipation probably associated with alosetron–associated severe constipation.

**Table 1**

**Summary of Incidence of Hospitalization and Surgery Among the Two Groups of Patients With Serious Complications of Symptomatic and "Unreported" Severe Constipation**

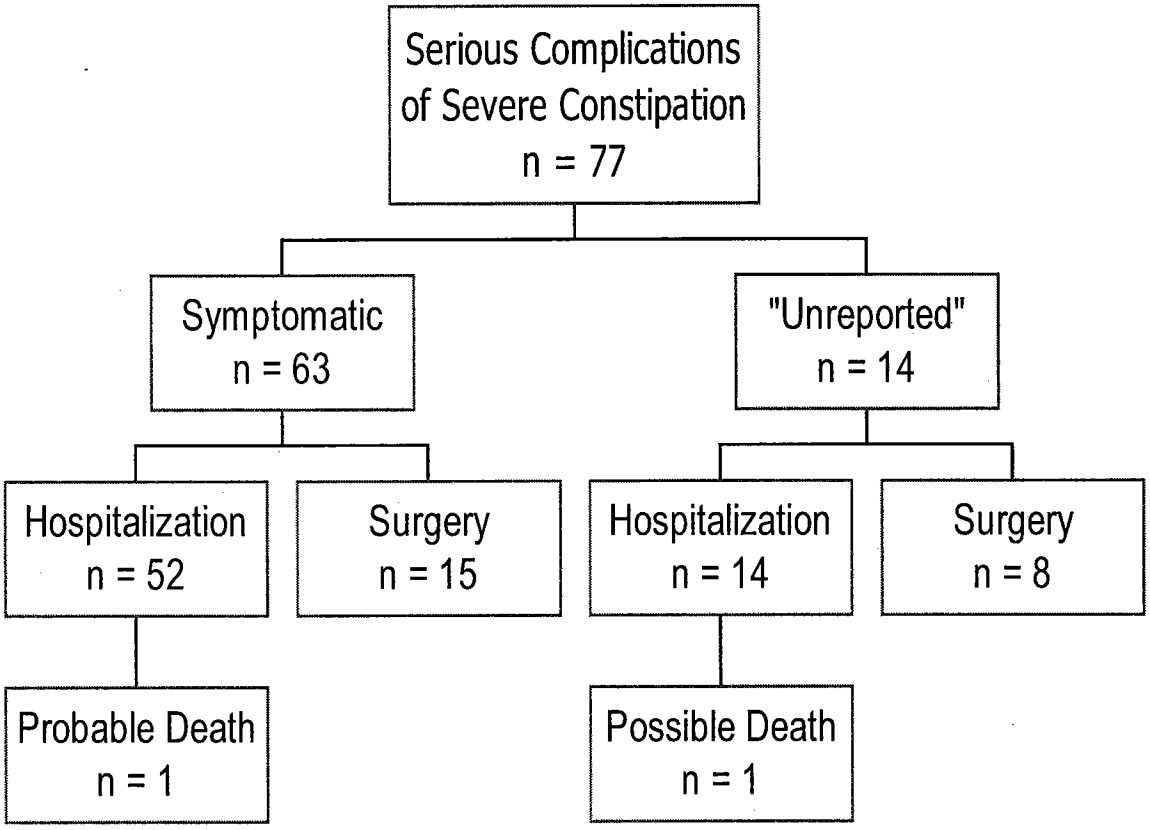
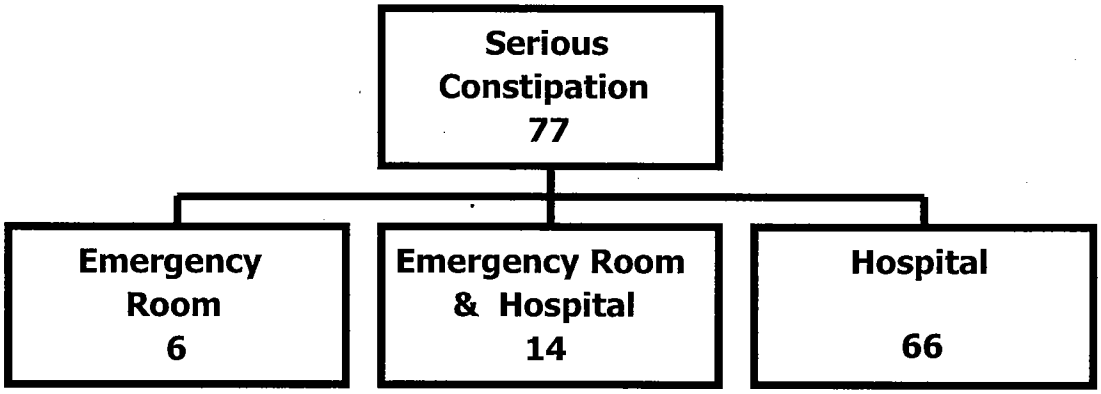


Table 2 classifies the reported cases by the site (local) where the more serious cases were treated. It should be immediately apparent, that these data lack complete accuracy. Whereas, practically all patients admitted to the hospital are admitted after evaluation in an Emergency Room, these data suggest that 52 patients (the 66 hospitalizations less the 14 patients treated in the Emergency Room prior to hospitalization), or the majority of the 66 patients hospitalized did not receive prior evaluation in an Emergency Room (no mention of Emergency Room treatment can be found in these reports). Unfortunately, prior evaluation in an E R can not be assumed. The obvious omission of this information from the medical records reinforces the need for greater completeness of data.

**Table 2**

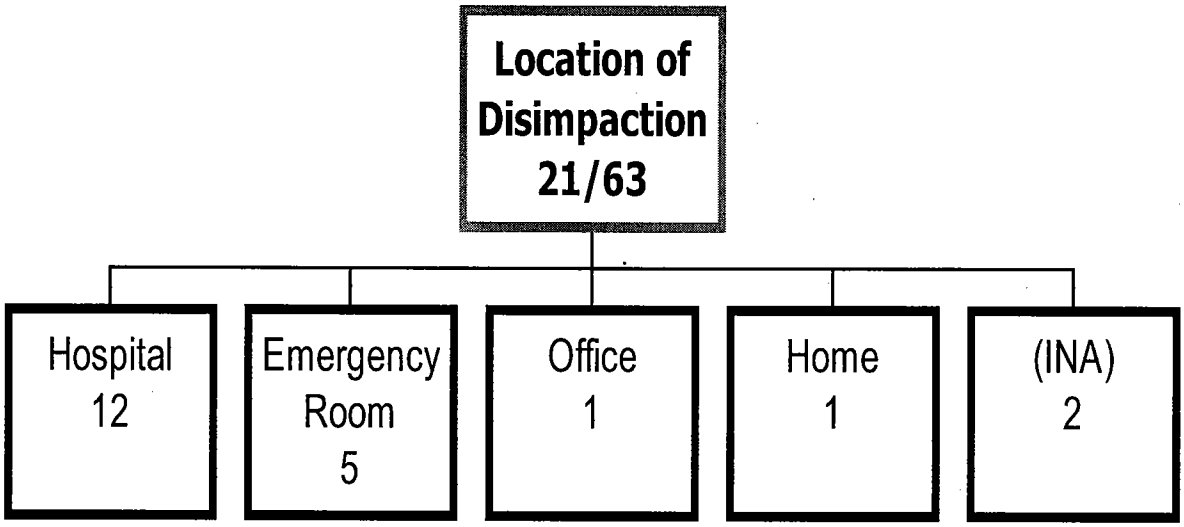
## Serious Complications of Severe Constipation By Treatment Site



Twenty-one patients experienced fecal **impaction**, a serious complication of severe constipation associated with alosetron usage. Fecal impaction was severe enough to require hospitalization and disimpaction (an intervention needed) in 33% (21/63) of the patients in the severe symptomatic group. The site (local) where disimpactions took place is presented in Table 3.

## Table 3

**Location of Disimpaction In Patients with Severe Symptomatic Constipation (Fecal Impaction) Associated with Alosetron Usage**




INA = Information not available

### 3. Analysis of Patients with Lotronex (alosetron)-Associated Serious Complications of Severe Constipation With Symptomatic Constipation

This section of the review evaluates epidemiologic data from the 63 patients with severe symptomatic constipation that played a major role in the evolution of the serious complications reported in association with alosetron usage.

In this group of patients, 83% (52/63) required hospitalization, and 24% (15/63) required surgery. The major medical diagnoses requiring hospitalization occurring in these 52 patients are displayed in Table 4.

## Table 4

## Medical Diagnoses Requiring Hospitalization Occurring In Patients with Severe Symptomatic Constipation Associated with Alosetron Usage

| Major Medical Diagnoses Recorded in MedWatch Report | Number (s) |
|---|---|
| Abdominal pain | 8 |
| Fecal impaction | 7 |
| Partial obstruction | 6 |
| Bowel obstruction | 5 |
| Diverticulitis | 3 |
| Diverticulitis and perforation | 3 |
| Rectal bleeding | 2 |
| Colon perforation | 2 |
| Dehydration | 1 |
| Stercoral (focal ischemia) ulcer | 1 |
| Colitis with stricture | 1 |
| Colitis (type not specified) | 1 |
| Bowel paralysis | 1 |
| Hemorrhage with blood transfusion | 1 |
| Small bowel obstruction | 1 |
| Rectocoele | 1 |
| Anal ulcer and fissure | 1 |
| Rectal polyp and hemorrhage | 1 |
| Obstipation | 1 |
| Prolapsed colon | 1 |
| Toxic megacolon | 1 |
| None stated | 3 |
| **TOTAL** | **52** |

Table 5 displays the surgical procedures the fifteen patients with severe symptomatic constipation associated with alosetron usage required.

**Table 5**
**Surgical Procedures Required During Hospitalization**
**In Patients with Severe Symptomatic Constipation**
**Associated with Alosetron Usage**

| Surgical Procedure Recorded in MedWatch Report | Number (s) |
|---|---|
| Colostomy for perforated diverticulitis | 2 |
| Repair anal tear and/or fissure | 2 |
| Segmental resection with colostomy for perforated diverticulitis | 1 |
| Segmental resection with colostomy for perforation | 1 |
| Colostomy for perforation | 1 |
| Temporary colostomy for colitis with sigmoid stricture | 1 |
| Segmental resection for diverticulitis | 1 |
| Segmental resection | 1 |
| Bowel obstruction | 1 |
| Laparoscopy for abdominal pain | 1 |
| Repair rectocoele | 1 |
| Repair prolapsed colon | 1 |
| Cholecystectomy | 1 |
| **TOTAL** | **15** |

The information in Tables 4 and 5 reveals a large assortment of medical conditions resulting from severe constipation and the procedures required for their surgical correction. They ranged from abdominal pain (8) and fecal impaction (7) to bowel obstruction (11) and colon perforation (5). Among the 15 surgical procedures required by this group of patients, 5 were repairs of perforations and 6 consisted of colostomies.

**4. Analysis of Patients with Lotronex (alosetron)-Associated Serious Complications of Severe Constipation with "Unreported" Constipation**

This section of the review evaluates the group of 14 patients with sequelae of severe constipation whose medical records lacked mention of constipation (Table 1). In all of these patients, it seems that **severe asymptomatic and silent constipation** played a important role in the evolution of the serious complications reported in association with alosetron usage.

In this group of patients with serious complications of severe "unreported" constipation, 14/14 (100%) required hospitalization, 8/14 (57%) required surgery, and 1/14 (7%) died (Table 1). None of the patients in this group were able to be treated in the Emergency Room and then released. Even though this group is smaller, the proportion of patients requiring hospitalization and surgery was much higher. Table 6 displays the major medical diagnoses requiring hospitalization occurring in these 14 patients with severe "unreported" constipation associated with alosetron usage.

## Table 6

## Medical Diagnoses Requiring Hospitalization Occurring In Patients with "Unreported" Severe Constipation Associated with Alosetron Usage

| Major Medical Diagnoses Recorded in MedWatch Report | Number (s) |
|---|---|
| Colon perforation | 4 |
| Partial obstruction | 3 |
| Bowel obstruction | 3 |
| Stercoral (focal ischemia) ulcer with perforation | 2 |
| Fecal impaction | 1 |
| None stated | 1 |
| **TOTAL** | **14** |

Table 7 displays the surgical procedures required for these patients with serious complications of severe "unreported" constipation associated with alosetron usage.

**Table 7**
**Surgical Procedures Required During Hospitalization**
**In Patients with "Unreported" Severe Constipation**
**Associated with Alosetron Usage**

| Surgical Procedure Recorded in MedWatch Report | Number (s) |
|---|---|
| Colectomy for bowel obstruction | 1 |
| Colostomy for perforation colon | 1 |
| Colostomy for perforation of stercoral ulcer | 1 |
| Hemicolectomy and colostomy for perforation of stercoral ulcer | 1 |
| Segmental resection colon | 1 |
| Laparotomy for sigmoid perforation | 1 |
| Drainage right colon perforation | 1 |
| Bowel perforation | 1 |
| **TOTAL** | **8** |

Tables 6 and 7 display the medical conditions resulting from serious complications of severe "unreported" constipation and the procedures required for their surgical correction in this group of patients. The medical conditions ranged from fecal impaction to bowel obstruction (6) and colon perforation (6). Among the 8 surgical procedures required (Table 7), 6 were for repair of perforations (one patient died on the operating table), 3 patients consisted of colostomies, and 1 patient required a colectomy.

## 5. Summary of All Patients Reported to Have Serious Complications of Severe Constipation

The following Tables, 8A, 8B, 8C, and 8D, provide a detailed list that summarizes information on the 63 patients with Lotronex (alosetron)-associated serious complications of severe **symptomatic constipation**.

Table 9 provides a detailed list that summarizes data from the 14 patients with Lotronex (alosetron)-associated serious complications of severe **"unreported" constipation**.

A detailed list summarizing the duration of therapy prior to onset of the SAEs and a list of the concomitant medications of the 14 patients with Lotronex (alosetron)-associated serious complications of severe "unreported" constipation is provided in Table 10.

Table 11 provides a detailed list that summarizes data from the 5 patients suspected of having Lotronex (alosetron)-associated serious complications of severe constipation, but who were determined to have alternative diagnoses that could explain their medical conditions. They were found to have alternative explanations for their presenting symptoms that included Crohn's disease, intestinal adhesions, and hyperparathyroidism. Therefore, they were not included in the case calculations, nor will these cases be discussed further.

**Table 8A List of patients with Lotronex (alosetron)-Associated Serious Complications of Severe Constipation**

| I D | AERS # | Mfr # | M/F | Age | Constipation | Death | Surgery | ER Visit | Reason for Hospitalization | Disimpaction (where) |
|---|---|---|---|---|---|---|---|---|---|---|
| 44 | 3541955 | A0126874A | F | 52 | X | | | | F. impaction | Hospital |
| 45 | 3541961 | A0126710A | F | 68 | X | | | | | Office |
| 46 | 3539989 | A0131969A | F | 78 | X | | | | | Home |
| 47 | 3535290 | A0127144A | F | 38 | X | | | | X | |
| 48 | 3532321 | A0127032A | F | 41 | X | | | X | F. impaction | Hospital |
| 49 | 3533547 | direct | F | 68 | X | | | | F. impaction | Hospital |
| 50 | 3527782 | direct | F | 27 | X | | | | X | |
| 51 | 3529162 | A0126751A | F | 61 | X | | | | F. impaction | Hospital |
| 52 | 3523843 | A0131970A | F | 60 | X | | | X | F. impaction | Hospital ?? |
| 53 | 3521996 | A0125896A | F | 48 | X | | | | | |
| 54 | 3523844 | A0131878A | F | 44 | X | | | F. impaction | | E R |
| 55 | 3515834 | A0125873A | F | ? | X | | | X | Bowel blockage | |
| 57 | 3484530 | A0117776A | F | 32 | X | | | | | X |
| 58 | 3470487 | A0118883A | F | 68 | X | | Temp. colostomy | | Sigmoid stricture Colitis | |
| 59 | 3458712 | A0117431A | F | 48 | X | | | | Stercoral (focal ischemic) ulcer | Hospital |
| 60 | 3459462 | A0117392A | F | 50 | X | | | | Small bowel obstruction | Hospital |
| 69 | 3549407 | A0129291A | F | 82 | X | X | Segmental resection colostomy | X | Diverticulitis perforation | Hospital |
| 72 | 3538702 | A0127146A | F | 30 | X | | Laparoscopy | | Abd pain | |
| 73 | 3541558 | direct | F | ? | X | | | | Hemorrhaging Transfusions 4 U | |
| 85 | 3566655 | direct | F | ? | X | | colostomy | | Perf diverticulitis | |

X denotes presence reported without further details

**Table 8B List of patients with Lotronex (alosetron)-Associated Serious Complications of Severe Constipation**

| I D | AERS # | Mfr # | M/F | Age | Constipation | Death | Surgery | ER Visit | Reason for Hospitalization | Disimpaction (where) |
|---|---|---|---|---|---|---|---|---|---|---|
| 89 | 3567599 | A0131674A | F | 44 | X | | | | Bowel obstruction | Hospital |
| 95 | 3576078 | A0133164A | F | 71 | X | | Colostomy | | Perf diverticulitis | |
| 98 | 3575301 | A0133365A | F | 72 | X | | | | B. paralysis | Hospital |
| 99 | 3573910 | direct | F | 40 | X | | | Rectal tear | | E R |
| 102 | 3577129 | A0133950A | F | 72 | X | | | | Fecal impaction | Hospital |
| 106 | 3576642 | A0133142A | F | 57 | X | | | | Abd. pain | |
| 107 | 3575304 | A0133446A | F | 55 | X | | | | Diverticulitis | |
| 111 | 3578582 | A0134064A | F | 25 | X | | Repair anal tear, fistula | | | |
| 113 | 3578571 | A0133209A | F | 52 | X | | Resection, colostomy | | C. perforation | |
| 114 | 3583073 | direct | F | 45 | X | | Colostomy | | C. perforation | |
| 117 | 3581005 | A0134395A | F | 59 | X | | | F. impaction | F. impaction | Hospital |
| 119 | 3578583 | A09134087A | F | 52 | X | | Colon resection | | Diverticulitis | |
| 122 | 3583088 | A0134937A | F | 41 | X | | | | Partial obstruction | |
| 124 | 3581566 | A0134539A | F | 69 | X | | Repair anal hemorrhoids, ulcer, fissure | | hemorrhoids, anal ulcer, fissure | |
| 125 | 3589130 | A0138204A | F | 37 | X | | Bowel obstruction, ileus | X | Bowel obstruction, ileus | X |
| 126 | 3590988 | direct | F | 72 | X | | | Abd. Pain | | |
| 128 | 3580995 | A0133097A | F | 54 | X | | | ? impaction | | |
| 131 | 358959 | A0135987A | F | 36 | X | | | Partial bowel obstruction | Partial bowel obstruction | |
| 133 | 3588804 | A0135822A | F | 68 | X | | Repair Rectocoele | | Rectocoele | |
| 134 | 3593991 | A0137469A | F | 64 | X | | Repair Prolapsed colon | | Prolapsed colon | |

X denotes presence reported without further details

**Table 8C List of patients with Lotronex (alosetron)-Associated Serious Complications of Severe Constipation**

| I D | AERS # | Mfr # | M/F | Age | Constipation | Death | Surgery | ER Visit | Reason for Hospitalization | Disimpaction (where) |
|---|---|---|---|---|---|---|---|---|---|---|
| **135** | 3590704 | A0136357A | **F** | **31** | **X** | | (2) Cholecystectomy Normal gall bladder | | (1) Bowel obstruction | |
| **136** | 3603984 | direct | **F** | **39** | **X** | | | | Colitis | |
| **137** | 3597836 | A0137761A | **F** | **58** | **X** | | | | Diverticulitis | |
| **139** | 3590096 | A0135986A | **F** | **57** | X | | | | Rectal polyps hemorrhage | |
| **140** | 3597832 | A0136570A | **F** | 74 | **X** | | | | NG intubation | |
| **142** | 3547477 | A0123178A | **F** | 59 | X | | | F. impaction | Dehydration | E R |
| **143** | 3610097 | A0133184A | **F** | 40 | **X** | | | Rectal tear, bleeding | | E R |
| **144** | 3603435 | A0138707A | **F** | 64 | X | | | F. impaction | | E R |
| **146** | 3605313 | A0130764A | **M** | 59 | **X** | | | | B. obsruction NG intubation | |
| **147** | 3607370 | A0135362A | **F** | 40 | **X** | | | | Abdominal pain | |
| **153** | 3639939 | direct | **F** | 40 | X | | | | Abdominal pain | |
| **154** | 3617960 | A0141627A | **F** | 68 | **X** | | | | Abdominal pain | |
| **156** | 3647796 | direct | **F** | 69 | X | | | Abd. pain | Abdominal pain | |
| **161** | 3577902 | A0126653A | **F** | 31 | **X** | | | | Abdominal pain | |
| **162** | 3577904 | A0127138A | **F** | 69 | X | | | | Abdominal pain | |
| **163** | 3571105 | A0128319A | **F** | ? | X | | | | Obstipation | |
| **164** | 3616862 | A0133143A | **F** | 53 | **X** | | | | "Bowel blockage" | |
| **165** | 361042 | A0138395A | **F** | 42 | **X** | | | | B. obsruction NG intubation | |
| **166** | 3616863 | A0133035A | **F** | 29 | **X** | | | | Rectal bleeding | |
| **167** | 3617053 | A0134876A | **F** | 74 | X | | | | B. blockage IV fluids | |

X denotes presence reported without further details

**Table 8D List of patients with Lotronex (alosetron)-Associated Serious Complications of Severe Constipation**

| I D | AERS # | Mfr # | M/F | Age | Constipation | Death | Surgery | ER Visit | Reason for Hospitalization | Disimpaction (where) |
|---|---|---|---|---|---|---|---|---|---|---|
| 168 | 3617056 | A0134176A | M | 48 | X | | | | Toxic megacolon | |
| 169 | 3617060 | A0134070A | F | 24 | X | | | | Rectal bleeding | |
| 170 | 3617066 | A0133457A | F | 63 | X | | Segmental resection | | ? | |
| **Total** | | | **M - 2** | | **Constipation** | **Total Deaths** | **Total Surgery Cases** | **Total E R Visits** | **Total Hospitalization** | **Total Disimpactions** |
| **63** | | | **F-58** | | **63** | **1** | **15** | **15** | **52** | **21** |

X denotes presence reported without further details
? denotes understood to have taken place without documentation (surgery requires hospitalization)

**Table 9 List of patients with Alosetron-Associated Serious Complications of Constipation With "Unreported" Constipation**

| I D | AERS # | Mfr # | M/F | Age | Constipation or History | ER Visit | Reason for Hospitalization | Surgery | Death | Impaction |
|---|---|---|---|---|---|---|---|---|---|---|
| **61** | 3477404 | A0120067A | **F** | **72** | **0** | **X** | Sigmoid perforation Fecal peritonitis | Laporotomy | | |
| **65** | 3545380 | A0128810A | **F** | **57** | **0** | **X** | Stercoral ulcer, sigmoid perforation | Hemicolectomy, colostomy | | X |
| **78** | 3494250 | A0122865A | **F** | **39** | **0** | **X** | Stercoral ulcer, sigmoid perforation | Diversion colostomy | | X |
| **96** | 3575294 | A0133194A | **F** | **45** | **0** | | Bowel obstruction | Bowel resection | | |
| **97** | 3576646 | A0133339A | **F** | **79** | **0** | | Fecal impaction | | | X |
| **105** | 3575295 | A0133203A | **F** | **70** | **0** | | Bowel perforation | **Attempted repair** | **X** | |
| **109** | 3571720 | A0132472A | **F** | **47** | **0** | | Rt. colon perforation | Drainage | | |
| **116** | 3586222 | A0139795A | **F** | **47** | **0** | | Bowel obstruction Blood transfusion | Colectomy | | X |
| **121** | 3588401 | direct | **F** | **71** | **0** | | Colon perforation | colostomy | | X |
| **129** | 3583090 | A0134971A | **F** | **?** | **0** | | Partial bowel obstruction, ileus | | | **X** |
| **130** | 3590705 | A0136569A | **F** | **?** | **0** | | Colon obstruction | | | |
| **145** | 3607261 | A0139265A | **F** | **25** | | **X** | Partial bowel obstruction | | | **X** |
| **148** | 3609576 | A0140484A | **F** | **63** | **0** | | Recurrent partial bowel obstruction | | | |
| **158** | 3648872 | direct | **F** | **50** | **0** | **X** | Disimpaction | | | **X** |
| **Total 14** | | | | | **0** | **5** | **14** | **7** | **1** | **8** |

X denotes presence reported without further details

**Table 10 Duration of Therapy Prior to SAE and Concomitant Medications of Patients with Alosetron-Associated Serious Complications of Constipation with "Unreported" Constipation**

| I D | M/F | Age | Duration of therapy prior to SAE | Reason for Hospitalization | Surgery | Death | Concomitant medications |
|---|---|---|---|---|---|---|---|
| 61 | F | 72 | 2.5 weeks | Sigmoid perforation Fecal peritonitis | Laparotomy | | Citalopram, hydrocodeine |
| 65 | F | 57 | 4 weeks | Stercoral ulcer, sigmoid perforation | Hemicolectomy ,colostomy | | Cetirizine, Alprazolam, Rofecoxib, thyroxin |
| 78 | F | 39 | 2 weeks | Stercoral ulcer, sigmoid perforation | Diversion colostomy | | Cyanocobalamine, amitriptyline, Zolpidem, Methocarbamol, Nefazodone, Atorvastatin, Omeprazole, Buspirone,, Compazine, morphine |
| 96 | F | 45 | 4 weeks | Bowel obstruction | Bowel resection | | Unknown |
| 97 | F | 79 | ? | Fecal impaction | | | Amlodipine, Lorazepam, rabeprazole, codeine, triamcinolone, atenolol |
| 105 | F | 70 | 8 weeks | Bowel perforation | | X | Unknown |
| 109 | F | 47 | < 8 weeks | Rt. colon perforation | Drainage | | Liotrex, retinol, potassium chloride |
| 116 | F | 47 | 8 weeks | Bowel obstruction Blood transfusion | Colectomy | | Omeprazole, estrogens |
| 121 | F | 71 | ? | Colon perforation | colostomy | | Unknown |
| 129 | F | ? | ? | Partial bowel obstruction, ileus | | | Unknown |
| 130 | F | ? | 3.5 weeks | Colon obstruction | | | Unknown |
| 145 | F | 25 | 6 months | Partial bowel obstruction | | | Oral contraceptive, allopurinol, spironolactone, lansoprazole, potassium chloride |
| 148 | F | 63 | | Recurrent partial bowel obstruction | | | Metoprolol, spironolactone, cholestyramine, antihypertensives |
| 158 | F | 50 | 6 days | Disimpaction | | | Unknown |
| Total 14 | | | | | | | |

**Table 11 List of patients with Suspect SAE Probably Not Attributable to Lotronex (alosetron)**

| I D | AERS # | Mfr # | M/F | Age | Constipation | Reason for Hospitalization | Surgery | Diagnosis |
|---|---|---|---|---|---|---|---|---|
| 76 | 3557813 | A0129965A | F | ? | 0 | X | Small bowel resection | Adhesions |
| 101 | 3574643 | A0133173A | F | 69 | X | X | Blockage | "Not related to alosetron usage" |
| 115 | 3576649 | A0133640A | M | 48 | 0 | X | Bowel obstruction | Crohn's Dz |
| 120 | 3580998 | A0134167A | M | 48 | 0 | X | Small bowel resection | Crohn's Dz |
| 132 | 3588515 | A0133430A | F | 49 | X | Hypercalcemia, renal failure | | Hyperparathyroidism |
| **Total** | | | **M - 2** | | **Constipation** | **Total Hospitalization** | **Total Surgery Cases** | **Total Diagnoses** |
| **5** | | | **F- 4** | | **2** | **5** | **4** | **5** |

X denotes presence reported without further details

**6. Clinical Summaries from Case Reports of Serious Complications of Severe Constipation Associated with Alosetron Usage With Resultant Death**

**A. The following patient demonstrated <u>Probable Evidence</u> of Certainty of Alosetron-Causality of Serious Complication of Severe Constipation and Death.**

**<u>Case # 69</u> (Mfr. # A0129291A)**

A gastroenterologist reported that an 82 y/o/f with history of IBS for many years, received alosetron for D-IBS. The patient's primary physician reported that about 10 days later the patient developed constipation and sudden onset nausea and diffuse abdominal pain without rectal bleeding. She reported to the emergency room with lower abdominal pain and was found to be diaphoretic, septic, dehydrated, and oliguric. One emergency room physician suspected ischemic bowel, and a consultant suspected diverticulitis with possible perforation. She vomited occasionally, the emesis initially was partially digested food, and later became darker coffee-ground like. She was critically ill and was admitted to the ICU for stabilization and dialysis prior to surgery. The second abdominal CT scan demonstrated **extensive diverticulosis of the sigmoid colon** with a small amount of fluid in the dependent pelvis. Exploratory laparotomy the next day while shocky, confirmed a **ruptured diverticulum** in the sigmoid colon and a Hartman diverting colostomy was performed. The entire colon was packed with solid stool, feeling like a rock. **A couple of pieces of this rock-solid stool were free in the abdominal cavity**. The distal sigmoid colon was markedly inflamed. She experienced atrial fibrillation with hemodynamic deterioration and responded to D/C shock cardioversion . The next day she experienced cardiac asystole and died (on the 4$^{th}$ day of hospitalization). Pathologic examination of the resected colon demonstrated diverticulosis and diverticulitis with perforation. No autopsy was performed.

Colonoscopy with biopsy of the sigmoid and descending colon 18 months earlier, showed **twisted spastic colon, multiple left colonic diverticula**, and irritable colon. Patient had no prior history of diverticulitis or rectal bleeding. Hospital admission note stated a past history of **diverticulitis**. She did have a previous admission with vomiting at which time small bowel obstruction and hiatal hernia were ruled out.

Concomitant medications: Maxzide, Glibenclamide, Loratadine, Lansoprazole

Death occurred Aug. 28, 2000, was reported to manufacturer Oct 5, 2000, and reported to FDA Oct 10, 2000.

**Conclusion**: There was a temporal relationship between the intake of alosetron and the onset of the patient's terminal illness. The pathology report of the resected bowel confirmed the diagnosis of severe obstipation, diverticulosis and diverticulitis with perforation of the sigmoid colon, and spillage of rock hard stool into the peritoneal cavity. This led to overwhelming sepsis, hemodynamic collapse, hypoxia, renal failure, and death. Therefore, **the GI clinical reviewers determined that alosetron was probably causative of this patient's death.**

**B. The following patient demonstrated Possible Evidence of Certainty of Alosetron-Causality of Serious Complication of Severe Constipation and Death.**

**Case 105 (Mfr. A0133203A)**
A consumer reported that her 70 y/o mother took alosetron for treatment of diarrhea for approximately two (2) months. The patient developed abdominal pain and was hospitalized. CT scan of the abdomen showed **bowel perforation**. The patient died in the operating room before surgery began. Autopsy was not performed. No office, hospital or physician records have been obtained.

Death occurred Nov. 26, 2000, was reported to manufacturer Nov. 30, 2000, and reported to FDA Dec. 5, 2000.

**Conclusion**: While there is no confirmation of these statements via hospital records or autopsy report, CT scan evidence of perforation would be strong evidence. More detailed facts would be helpful. However, it is now known that perforation has occurred with both severe constipation and ischemic colitis, and more often with severe constipation. Therefore, **the GI clinical reviewers determined that alosetron was possibly causative of this patient's death. Perforation possibly resulted from severe constipation, but additional information is needed.**

## 7. Summary and Comparison of SAEs Among Two Groups of Patients With Serious Complications of Severe Constipation – Symptomatic and "Unreported"

This review analyzed the 77 cases of alosetron-associated serious complications of severe constipation occurring post-marketing that have been reported to OPDRA as of August 22, 2001. In 63 patients, severe constipation was a major component of the patient's presenting complaint. In the additional 14 patients, constipation was not among the presenting complaints. However, as the subsequent clinical syndrome evolved, severe constipation, "silent" and "unreported" , played a major role in the evolution of the serious complications associated with alosetron usage.

Among this group of patients, severe constipation with impaction was not discovered or recorded in the MedWatch report. The relationship to severe constipation was not recognized until the patient was examined radiologically and determined to have a colon full of rock hard stool or the abdomen was surgically explored and rock hard stool was found to fill the colon or found to have entered the abdominal cavity following colonic perforation.

The separate analysis of these two groups of patients with serious complications of severe symptomatic constipation and the severe "unreported" constipation associated with alosetron usage has previously been presented in this review. A summary review and comparison review of these two groups follows.

The frequency of medical diagnoses among patients with serious complications of severe symptomatic constipation and the severe "unreported" constipation associated with alosetron usage is displayed in Table 12.

## Table 12

## Medical Diagnoses Requiring Hospitalization Among Patients with Serious Complications of Severe Constipation Associated with Alosetron Usage (All Cases)

| Major Medical Diagnoses Recorded in MedWatch Report | Symptomatic Severe Constipation n=63 | 'Unreported" Severe Constipation n=14 | TOTAL Combined Groups n=77 |
|---|---|---|---|
| Fecal impaction | 7 (21) ♦ | 1 (8) ♦ | 8 (29) ♦ |
| Abdominal pain | 8 | | 8 |
| Partial obstruction | 6 | 3 | 9 |
| Bowel obstruction | 5 | 3 | 8 |
| Diverticulitis | 3 | | 3 |
| Diverticulitis and perforation | 3 | | 3 |
| Rectal bleeding | 2 | | 2 |
| Colon perforation | 2 | 4 | 6 |
| Stercoral (focal ischemia) ulcer / perforation | | 2 | 2 |
| Dehydration | 1 | | 1 |
| Stercoral (focal ischemia) ulcer | 1 | | 1 |
| Colitis with stricture | 1 | | 1 |
| Colitis | 1 | | 1 |
| Bowel paralysis | 1 | | 1 |
| Hemorrhage with blood transfusion | 1 | | 1 |
| Small bowel obstruction | 1 | | 1 |
| Rectocoele | 1 | | 1 |
| Anal ulcer and fissure | 1 | | 1 |
| Rectal polyp and hemorrhage | 1 | | 1 |
| Obstipation | 1 | | 1 |
| Prolapsed colon | 1 | | 1 |
| Toxic megacolon | 1 | | 1 |
| None stated | 3 | 1 | 4 |
| TOTALS | **52** | **14** | **66** |

♦ First number represents the number of patients for which the major initial clinical diagnosis was fecal impaction.

The number in parenthesis ( ) represents the total fecal impactions discovered initially and later in the course of the diagnostic evaluation of the patient. Therefore, it also includes all those cases discovered both radiologically and at the time of surgery.

Fecal impaction both symptomatic and "unreported" occurred in 29/77 (38%) of patients and was a major contributor to the severity of the SAEs experienced by these alosetron users. Constipation, the most frequently observed AE within clinical trials, if allowed to progress results in fecal impaction. Some of the saliently occurring medical diagnoses were: *(NOTE: totaling these numbers is without meaning, as patients are frequently included in multiple categories)*

29 – fecal impactions
18 - varying degrees of bowel obstruction
11 - colon perforation
8 – abdominal pain
3 – stercoral ulcer
3 – rectal bleeding
1 – hemorrhage requiring transfusion
1 – toxic megacolon

Table 13 summarizes and compares the surgical procedures required for patients with serious complications of severe constipation associated with alosetron usage. The required surgical procedures for serious complications were compared among the severe symptomatic constipation group and the severe "unreported" constipation group.

## Table 13
## Surgical Procedures Required During Hospitalization For Patients with Serious Complications of Severe Constipation Associated with Alosetron Usage (All Cases)

| Surgical Procedure Recorded in MedWatch Report | Symptomatic Severe Constipation n=63 | Unreported" Severe Constipation n=14 | TOTAL Combined Groups n=77 |
|---|---|---|---|
| Colostomy for perforated diverticulitis | 2 | | 2 |
| Repair anal tear and/or fissure | 2 | | 2 |
| Colectomy for colon obstruction | | 1 | 1 |
| Colostomy for perforation of stercoral ulcer | | 1 | 1 |
| Hemicolectomy and colostomy for perforation of stercoral ulcer | | 1 | 1 |
| Segmental resection with colostomy for perforated diverticulitis | 1 | | 1 |
| Segmental resection with colostomy for perforation | 1 | | 1 |
| Colostomy for perforation colon | 1 | 1 | 2 |
| Temporary colostomy for colitis with sigmoid stricture | 1 | | 1 |
| Segmental resection for diverticulitis | 1 | | 1 |
| Segmental resection colon | 1 | 1 | 2 |
| Bowel obstruction | 1 | | 1 |
| Laparoscopy for abdominal pain | 1 | | 1 |
| Laparotomy for sigmoid perforation | | 1 | 1 |
| Drainage right colon perforation | | 1 | 1 |
| Repair rectocoele | 1 | | 1 |
| Repair prolapsed colon | 1 | | 1 |
| Cholecystectomy | 1 | | 1 |
| Bowel perforation (died in operating room) | | 1 | 1 |
| **TOTAL** | **15/63** | **8/14** | **23/77** |

Major abdominal surgery, unheard of as occurring among D-IBS patients, was required in 23/77 (30%) of patients to treat serious complications occurring among this group of alosetron users. These patients with SAEs were placed at substantial operative risk by the necessity for emergent surgery such as: surgical treatment of 12 obstructions and 11 colon perforations with resultant 9 colostomies, and 1 colectomy. Some of the saliently occurring surgical treatments were: *(*NOTE: *totaling these numbers is without meaning, as patients are frequently included in multiple categories)*

12 – repair of obstructions
11 – repair colon perforations
9 – colostomies
4 – repair tear, fissure, rectocoele, prolapse
3 – segmental resections
1 - colectomy

**8. Summary and Conclusions**

Comparison of the treatment required and the deaths that occurred among patients with serious complications of severe symptomatic and "unreported" constipation is shown in Table 14. The data suggest that developing "silent" serious complications of severe constipation associated with alosetron usage carries a higher risk for hospitalization and surgery than patients experiencing symptomatic severe constipation. If this impression is substantiated by additional data, that a group of patients exist who have silent fecal impactions, then to achieve more favorable outcomes, early recognition of constipation is essential for the prevention and treatment of such serious complications. Thus, becoming constipated while on alosetron without recognizing its existence can result in grave consequences and make early recognition more difficult. *((*NOTE: *Totaling these numbers vertically is without meaning, as by necessity, patients are frequently included in multiple categories)*

Among the symptomatic severely constipated patients, 83% (52/63) required hospitalization and 24% (15/63) required surgery. Among the "unreported" severely constipated patients, 100% (14/14) required hospitalization and 57% (8/14) required surgery. One death occurred in each group. Thus, overall only 8% (6/77) could be treated in the Emergency Room without hospitalization. Almost all, 86% (66/77) required hospitalization and 30% (23/77) required major surgery. Surprisingly, the serious complications of severe constipation have required a higher proportion of hospitalizations and surgical treatments than did those with ischemic colitis. It was the Agency's impression that we could reduce the severity of the SAEs associated with constipation better than we could those associated with ischemic colitis. To date, the evidence supports the opposite.

## Table 14

### Comparison of Treatment Required and Deaths Occurring Among Patients Using Alosetron With Severe Symptomatic and "Unreported" Constipation Experiencing Serious Complications

| Treatment Required for Serious Complications of Severe Constipation | Symptomatic Severe Constipation n=63 | "Unreported" Severe Constipation n=14 | TOTALS Patients n=77 |
|---|---|---|---|
| Treatment in Emergency Room only (not hospitalized) | 6 (10%) | 0 (0%) | 6 (8%) |
| Hospitalization | 52 (83%) | 14 (100%) | 66(86%) |
| Surgery | 15 (24%) | 8 (57%) | 23(30%) |
| Patients with Fecal Impactions | 21 (33%) | 8 ( 57 %) | 29 (38%) |
| Disimpactions | 21 (33%) | 1 (7%) | 22 (29%) |
| SAE with Death | Case # 69<br>1 Probable<br>2% | Case # 105<br>1 Possible<br>7% | |

**Role of Serious Complications of Severe Constipation**

In the pre-approval clinical trials of alosetron, constipation was found to be 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**. The majority of patients developing constipation did so within the **first 4 to 6 weeks of therapy** with alosetron. This constipation was severe enough to cause approximately 10% of patients taking alosetron to withdraw from clinical studies. It is worth noting that serious complications associated with severe constipation were not observed in the clinical studies.

Alosetron-induced constipation may become severe and result in fecal impaction. The longer stool is retained within the colon, the more water is reabsorbed by the colonic mucosa, and the firmer the stool becomes. Both constipation and fecal impaction promote increased intraluminal pressure. The combination of forces from impacted hard feces, increased intracolonic pressure, and physical compression of the smaller mucosal vessels can all impede mucosal circulation. The presence of an already weakened mucosa as seen in patients with diverticula and diverticulitis, or stercoral (hard feces induced pressure) ulceration, facilitates the development of perforation. Impedement of mucosal circulation can further promote colonic ischemia, gangrene and perforation.

The term "fecal impaction" is generally reserved for a large caliber collection of hard rock-like feces filling the rectal ampula and preventing normal expelling of stool by the patient. Usually it requires digital manipulation and/or strong cathartics to promote stool passage. Serious complications associated with fecal impaction have been reported to occur without patients being aware that they are constipated. It is known that liquid stool may seep around fecal impactions and prevent the patient from recognizing the presence of constipation or impending serious constipation-induced sequelae. In several of the cases of fecal impaction addressed in this document, the patients reported having bowel movements on the day they were later found to be impacted or obstructed.

Serious complications associated with severe constipation, as described in this review, were observed during the marketing of alosetron, but not pre-approval of the drug. These reports described patients taking alosetron who developed severe constipation associated with abdominal pain and occasionally rectal bleeding. Several known serious complications of constipation have been seen, most (86%) required hospitalization: fecal impaction, intestinal obstruction and ischemic (stercoral - hard feces induced) ulceration. Surgery was required in 30% (23/77) of these SAEs, in many patients for life-threatening emergencies like perforation and obstruction.

In the two deaths previously described among alosetron users, one occurred following severe symptomatic constipation and the other occurred following silent or "unreported" constipation and both subsequently developed colonic perforations and died. It remains the GI Team's belief that serious complications of constipation resulting in surgical emergencies and death, **should be preventable** or **greatly reduced** with proper prescribing, patient selection, adequate use of the Medication Guide, education, and supervision.

**Role of Unlabeled Usage and Serious Adverse Events**

Among these patients experiencing serious adverse events associated with the use of alosetron, is a group of patients prescribed this drug for a wide assortment of diarrheal conditions for which no evidence of clinical effectiveness exists. Alosetron was prescribed "off-label" and serious adverse events were experienced by patients treated for such medical conditions as:

Abdominal pain (unspecified)
Abdominal cramping pattern IBS
Alternating pattern IBS
Constipation (pre-existing)
Constipation pattern IBS
Bowel infection
Diarrhea associated with Crohn's disease
Post pancreatitis diarrhea
Post cholecystectomy diarrhea
Post rectal cancer surgery diarrhea
Post pelvic radiation diarrhea
Ulcerative colitis diarrhea
Bowel obstruction
Males with diarrhea predominant IBS

Whereas, this group of patients experienced SAEs, the risks associated with "off-label" usage should be **discouraged** until results of controlled clinical studies demonstrating safety and effectiveness are made available.

**Role of Concomitant Medications**

Many drugs potentially have anti-motility or a constipating effect upon the intestinal tract, and many patients took more than one of these drugs at the same time. Concomitant usage of drugs from the following groups with alosetron, may significantly enhance the likelihood of severe constipation and the risk of development of serious complications of constipation. However, neither clinical nor epidemiological studies are currently available to confirm their role in enhancing the constipating effects of alosetron.

| | | |
|---|---|---|
| antihypertensives | NSAIDs | antacids |
| H-2 blockers | proton pump inhibitors | antibiotics |

| | | |
|---|---|---|
| antidepressents | anti-emetics | anti-diarrheals |
| chemotherapeutic agents | narcotics | amphetamines |
| anti-convulsants | diuretics | nitrates |
| anti-cholinergics | 5-$HT_3$ receptor antagonists | antihistamines |
| iron preparations | 5-$HT_1$ receptor agonists | tranquilizers |
| hypoglycemics | muscle relaxants | hypnotics |
| anti-arrhythmics | HMG-CoA reductase inhibitors | SSRIs |
| bisphosphonates | | |

In Table 10 the concomitant medications taken by that group of 14 patients with alosetron-associated serious complications of constipation were presented. For those patients where concomitant medications were known, patients were taking between 2 and 10 additional medications. They included representatives of the preceeding groups of drugs known to have constipating effects:

| | | |
|---|---|---|
| SSRIs | HMG-CoA reductase inhibitors | NSAIDs |
| Antihypertensives | antidepressants | narcotics |
| proton pump inhibitors | muscle relaxants | SSRIs |

A number of drugs carry warnings about a low incidence of intestinal perforation as side effects associated with their use. Examples of these groups of drugs carrying this warning includes:

| | | |
|---|---|---|
| NSAIDs | β - interferon | antibiotics |
| corticosteroids | chemotherapeutic agents | antidepressants |

Of the 11 patients who experienced colonic perforations, several were taking antidepressants and/or NSAIDs. Furthermore, use of alosetron in the presence of diverticula and diverticulitis, with additional anti-motility drugs such as those in this list, may contribute to a higher risk for colonic perforation and obstruction.

**Pending Additional Safety Data and Recommendations from the Sponsor**

GlaxoSmith Kline (GSK), formerly Glaxo-Wellcome, will submit a sNDA containing data from study populations enrolled in randomized and open-label clinical trials not previously submitted to the Division. The emphasis of these reviews will be on safety evaluation. The data to be analyzed by early next year, are expected to provide a more accurate characterization of the safety of alosetron under controlled (as opposed to epidemiological) conditions. In addition, GSK will propose its recommendations for labeling revisions, restricted distribution and risk management to reduce the risk of similar SAEs for our review.

The Agency believes that relaunch of Lotronex must be under the restricted access of 21 CFR 314 Subpart H regulations or under an IND. Both programs allow the FDA to withdraw the drug from the marketplace if the risks are judged to be unsatisfactory or GSK does not ensure that all of the conditions of the Restricted Distribution Plan-Risk Management Program are being met.

**9. GI Team Summary Risk–Benefit Assessment to Prevent SAEs Associated With Alosetron Usage**

NDA 21-107 presented clinical efficacy studies supporting the treatment of IBS patients with predominantly mild diarrheal-type disease with alosetron 1 mg BID. Unblinded post hoc analysis, demonstrated a 12% to 15% therapeutic gain (symptoms relieved half the weeks) over placebo (26% to 29%). Constipation occurred in 25% to 30% of patients exposed to alosetron within clinical trials without a single case of serious complications. In ten percent (one-third of those who became constipated) it was severe enough to force discontinuation.

During the 9 months of marketing, labeling was depended on *to exclude patients with "presumed" risk factors to reduce the incidence of serious complications of severe constipation.* An attempt was made to reduce the occurrence of serious complications of constipation via labeling and Medication Guide warnings *to encourage stopping the drug at the earliest sign of constipation.* Early withdrawal of the drug by the Sponsor did not permit adequate time to evaluate the effectiveness of these preventive measures or to initiate the agreed upon studies to learn more about dose ranging and constipation management.

The cumulative post-marketing data collected by OPDRA ending July 31, 2001, revealed the occurrence of 5 deaths possibly/probably attributable to alosetron usage, over 130 SAEs (ischemic colitis [59], serious complications of constipation [74], and thrombosis of the mesenteric blood vessels [5]). With 84 hospitalizations, and 25 surgical procedures reported in association with usage of the drug for a medical condition for which these serious outcomes are seldom seen, the GI Division demanded reassessment of the relative Risk-Benefit Ratio associated with its usage by D-IBS patients.

Treatment of D-IBS patients with alosetron, like treatment with other drugs, requires that the physician weigh the potential benefits achievable against the potential harm associated with its use for each patient. D-IBS patients do not experience SAEs like hemorrhage requiring transfusion, complications requiring major life-threatening abdominal surgery, or death. For a medical condition like D-IBS, where there is a sizable placebo therapeutic effect and a rather modest therapeutic advantage with alosetron in mild to moderately severe patients , occurrence of SAEs of this severity does not seem acceptable. The benefit-risk assessment may be more favorable for the most incapacitated patients with severe D-IBS who have failed to respond to all other available treatments, if it can be shown that treatment provides significant improvement of these more incapacitated patients.

Thus it seems prudent to reassess the therapeutic merits of the drug in those patients who were severely incapacitated and/or experienced significant improvement without AEs during prior therapy with alosetron.

Since withdrawal, the GI Team has placed the following proposed studies on its priority list:

- Access to therapy for a population of severely symptomatic D-IBS alosetron responders with:
    1. Randomized withdrawal to placebo or continued therapy after a period of 8 to 12 weeks – the objective of this study is to obtain additional data on efficacy as well as safety
    2. Obtain Quality Of Life information as it relates to "functional improvement"
- Dose ranging studies (lower starting dose with step-up or step down)
- P.r.n.dosing
- Long-term safety in a population of patients with severely symptomatic D-IBS among known alosetron responders for 1 year
- Stricter management of constipation, i. e , discontinuation of alosetron therapy in D-IBS patients who based on their own definition - are experiencing constipation (defined as decreased or absent bowel movement each day; increased consistency; significant straining; or a combination of these manifestations)

The GI Team Medical Officers strongly support the need for additional efficacy and safety data ideally before considering re-introduction of alosetron into the marketplace, even under Subpart H. Whether the therapeutic gain is greater among more severely symptomatic patients has yet to be established. Until the data become available to demonstrate that the benefit of therapy outweighs the risk of serious outcome, only limited usage, under the restrictions of an IND or an equivalent restricted distribution program under Subpart H, should be permitted.

The major goal of the GI Team remains the assurance of safety for alosetron users, to decrease the frequency and severity of SAEs associated with alosetron usage. For now, treatment with alosetron requires a Restricted Distribution Plan, therapy managed by experienced, knowledgeable physicians and appropriately informed responsible patients and implementation of a Risk Management Program. The GI Team's recommendations for both RDP and RMP were initially outlined in the Lotronex Efficacy and Safety Summary document dated November 7, 2000.

## 10. Agency's Benefit-Risk Evaluation for Lotronex and Regulatory Actions

Because of additional reports of serious gastrointestinal adverse events in the post-marketing experience with alosetron, FDA began extensive interactions with the sponsor to initiate a RMP. Placement of a "Black Box Warning" and labeling changes requested by the Agency were met by strong objections from the sponsor and resulted in requesting of a formal dispute resolution on June 21, 2000. A second GI Advisory Committee Meeting was convened on June 27, 2000 to establish a Risk-Management Plan for these serious adverse events.

The GI Advisory Committee #2 of June 27, 2000 in conjunction with FDA and Glaxo Wellcome recommended an extensive, first of its kind, comprehensive Risk-Benefit Management Plan for Lotronex with the goal to reduce the incidence of LOTRONEX-associated serious adverse events.

The three major components were:

1. Risk identification
2. Risk communication (Dissemination of safety information)
3. Risk-benefit program monitoring-evaluation

The *Response to* Dispute Resolution Request of July 19, 2000 incorporated the above Risk Management Plan, initiated the subsequent approval of stricter labeling, distribution of a Medication Guide to be attached to *each medication container*, and Dear Doctor/Pharmacist letters on August 11, 2000. The Risk Management Plan underwent multiple revisions on May 17, June 14, July 25, and August 31, 2000. The plan was "finalized" on Sept. 26, 2000.

The Risk Management Plan proposed by the Agency in November 2000, included the following proposals to reduce the incidence and severity of alosetron–associated serious complications of constipation (and development of ischemic colitis, which may coexist at times with severe constipation):

1. Education programs targeted to physicians, pharmacists and patients
2. Initiation of a **Medication Guide** with mandatory distribution
3. Revised prescriber labeling (package insert)
    - Contraindication for the elderly and debilitated
    - Instruction to patients to stop Lotronex at the earliest sign of constipation
4. Planning proposed clinical studies to evaluate:
   (completion will require 1 to 2 years):
    - Constipation management options (S3B30034)
    - Additional dose ranging studies (S3B30040)
5. Planning proposed epidemiological studies to evaluate risk factors
   (completion will require 1 to 5 years):

6. Establishment of a patient registry mechanism to integrate with Restricted Distribution that will require comprehensive reporting of **all** AEs.

7. Although trial of therapy for first 2 weeks at 1 mg QD was acceptable, no suggestion was made that if patients tolerated this dosage without adverse events and improved adequately, then these patients may not need to advance to the recommended dosage of 1 mg BID.

8. Both physicians and patients need to be given clear, specific advise on:
   - what to do upon experiencing constipation
   - when patients were to call their doctor
   - if, when or how patients were to restart alosetron

9. Recommendation that patients with IBS be tried on conventional therapy, prior to initiating therapy with alosetron. (LOTRONEX as a second line therapy)

10. Put mechanisms in place to audit the process for implementation of the RMP and the education programs for patients, physicians, and pharmacists.

11. Whereas, there are suggestions of increased risk of serious adverse events under the following underlying or concurrent factors: (in addition to those specified in the current professional labeling), such individuals may manifest poor Risk-Benefit from use of this drug (more information is needed):
    - Individuals over age 65, especially those who may be prone to constipation
    - Patients who are bedridden, debilitated, or unable to understand or comply with the Medication Guide
    - Intestinal motility disorders or use of drugs that delay intestinal transit
    - Intestinal atherosclerosis
    - Hyperlipidemia
    - Surgical interventions altering mesenteric blood flow
    - Hypercoagulable states (most are occult)
    - Thrombophlebitis history
    - Thrombogenic drugs reported to induce ischemic colitis such as Birth control pills, estrogens, migraine medications, digitalis, cocaine, vasoconstrictors, neuroleptics , psychotropics, etc.
    - Diverticulae (very common in general population)
    - Long-term usage

**11. Expectations and Limitations of Possible Actions**
**(This is applicable to both, serious complications of severe constipation and ischemic colitis)**

At the time of withdrawal, no apparent effective methods were in place for reducing the frequency of serious adverse events occurring among patients on alosetron. It is quite disappointing that we still know very little about the risk factors responsible for ischemic colitis, and we have not successfully reduced the risk for serious complications of severe constipation. Based on the Agency's prior experience with other drugs with major safety issues, labeling changes cannot be depended upon to adequately resolve safety concerns. To implement a successful restrictive distribution program, achieve the goal of reducing the future incidence of serious adverse events associated with use of alosetron while at the same time improving the present Benefit-to-Risk balance, will require a major customized commitment by the sponsor. At this time the sponsor has expressed a desire to propose an additional restrictive distribution program which they expect will be acceptable to the Agency. Relaunching of Lotronex by GSK must depend upon a mutually acceptable RDP-RMP that must achieve a measurable reduction in the incidence and severity of serious adverse events including hospitalizations, hemorrhages, operations and deaths associated with the use of Lotronex.

**Scheldon Kress, M.D.**

**October 9, 2001**

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## APPENDIX 1

### GUIDELINES FOR CAUSALITY:
**Assessing the Relationship of Adverse Experiences to Test Drug**

The assessment of causality is reported according to the investigator's **best** clinical judgement. The confidence in a given **classification increases** as the number **and/or** intensity of its respective **criteria increase.**

| CRITERIA | CLASSIFICATION |
|---|---|
| The subject/patient **did not receive** the test drug.<br>**OR**<br>The temporal sequence of the AE onset **relative** to **administration** of the test drug is **not reasonable**.<br>**OR**<br>There is **another obvious** cause of the AE. | 1 = **Definitely not** related to test drug. |
| There is **evidence of exposure** to the test drug.<br>There is **another more likely** cause of the AE.<br>Dechallenge (if performed) is **negative or ambiguous.**<br>Rechallenge (if performed) is **negative or ambiguous.** | 2 = **Probably not** related to test drug. |
| There is **evidence of exposure** to the test drug.<br>The temporal sequence of the AE onset relative to administration of the test drug is reasonable.<br>The AE could have been due to **another equally likely cause.**<br>Dechallenge (if performed) is **positive.** | 3 = **Possibly** related to test drug. |
| There is **evidence of exposure** to the test drug.<br>The temporal sequence of the AE onset **relative** to **administration** of the test drug is **reasonable.**<br>The AE is **more likely explained** by the test drug than by another cause.<br>Dechallenge (if performed) is **positive.** | 4 = **Probably** related to test drug. |
| There is **evidence of exposure** to the test drug.<br>The temporal sequence of the AE onset **relative** to **administration** of the test drug is **reasonable.**<br>The AE is **more likely explained** by the test drug than by another cause.<br>Dechallenge (if performed) is **positive.**<br>Rechallenge (if feasible) is **positive.**<br>The AE shows a **pattern consistent** with **previous knowledge** of the test drug **or** test drug class. | 5 = **Definitely** related to test drug. |

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**NDA 21-107/S005**

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

**EXCLUSIVITY SUMMARY for NDA # 21-107/SE8-005**

**Trade Name** Lotronex **Generic Name** alosetron HCl
**Applicant Name** GlaxoSmithKline **HFD-180**

**Approval Date** June 7, 2002

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES /___/ NO /_X_/

   b) Is it an effectiveness supplement? YES /_X/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE8

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (*If it required review only of bioavailability or bioequivalence data, answer "NO."*)

      YES /___/ NO /_X_/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).**

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.**

**PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or

2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

Signature of Preparer — Date: 11/05/01

Title: _____

for RJ.

Signature of Office or Division Director — Date: 11/7/01

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

# MARKETING EXCLUSIVITY

## NDA 21-107

## LOTRONEX® (alosetron hydrochloride) Tablets

## Request for Marketing Exclusivity

Pursuant to Sections 505(c)(3)(D)(iv) and 505(j)(5)(D)(iv) of the Federal Food, Drug, and Cosmetic Act and Section 314.108(b)(5) of Title 21 of the Code of Federal Regulations, GlaxoSmithKline requests 3 years of exclusivity from the date of approval of this supplemental new drug application for LOTRONEX® (alosetron hydrochloride) Tablets, for women with diarrhea-predominant irritable bowel syndrome (IBS) who have failed to respond to conventional therapy.

GlaxoSmithKline is entitled to such exclusivity as this application contains reports from numerous "new clinical investigations" (other than bioavailability studies) that were "conducted or sponsored" by GlaxoSmithKline and that are "essential to approval." In total, this supplemental new drug application, seeking changes in approved conditions of use for LOTRONEX® (alosetron hydrochloride) Tablets, is supported by safety data from 40 "new" studies, i.e. investigations ongoing or initiated subsequent to the approval of NDA 21-107 on February 9, 2000. These 40 studies are described in the Table of Studies (Item 8, Section IV) of this application. In addition to hypertext linking to the report from the Table of Studies, each of the 40 new studies is identified by the designation "sNDA" under the column directing the reviewer to the location of the study reports.

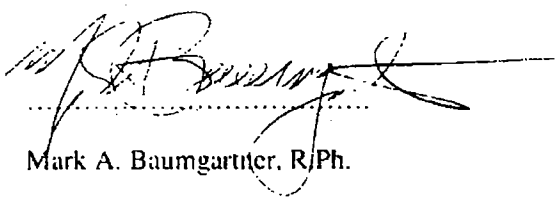
Pursuant to 21 CFR 314.50(j)(4)(i), we certify, to the best of GlaxoSmithKline's knowledge, that the clinical investigations referred to above are "new" in that the study results have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population of a previously approved drug product, nor do the study results duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product.

Pursuant to 21 CFR 314.50(j)(4)(ii), we certify that the clinical investigations referred to be above are "essential to approval" in that published studies and publicly available reports of investigations do not provide a sufficient basis for approval of this sNDA, which seeks changes in approved conditions of use of LOTRONEX® (alosetron hydrochloride) Tablets.

Pursuant to 21 CFR 314.50(j)(4)(iii), we confirm that we were the sponsor of each clinical investigation referred to above, in that a GlaxoSmithKline company (including any predecessor organization) was named as the sponsor in the Form FDA-1571 for the IND under which the clinical investigation was conducted, or if the clinical

investigation took place outside the framework of a U.S. IND, a GlaxoSmithKline company (including any predecessor organization) served as regulatory sponsor.

Signed



Mark A. Baumgartner, R.Ph.

Director, Regulatory Affairs

# Time Sensitive Patent Information

**Patent Information Pursuant to 21 C.F.R. § 314.53**
**for**

**LOTRONEX® (alosetron hydrochloride) Tablets**

**sNDA 21-107**

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The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

**Trade Name:** LOTRONEX®

**Active Ingredient:** alosetron hydrochloride

**Strength(s):** 1 mg

**Dosage Form:** oral tablet

---

| U.S. Patent | Expiration Date | Type of Patent | Patent Owner | U.S. Agent |
|---|---|---|---|---|
| 5,360,800 | 2 February 2010 | Drug<br>Drug Product<br>Composition/<br>Formulation<br>Method of Use | Glaxo Group Limited | SmithKline Beecham Corp. |
| 6,284,770 | 5 October 2018 | Method of Use | SmithKline Beecham Corp. | SmithKline Beecham Corp. |

The undersigned declares that U.S. Patent 5,360,800 covers the drug, formulation, composition and method of use of LOTRONEX® (alosetron hydrochloride) tablets, and that U.S. Patent 6,284,770 covers the method of use of LOTRONEX® (alosetron hydrochloride) tablets. This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

Please address all communications to:

David J. Levy, Ph.D.
Vice President and Patent Counsel
GlaxoSmithKline
Corporate Intellectual Property Department
Five Moore Drive
Research Triangle Park, NC 27709
(919) 483-2723

Respectfully submitted,

Date: 5 November, 2001

David J. Levy, Ph.D.
Attorney for Applicant
SmithKline Beecham Corp.

NDA 21-107
LOTRONEX® (alosetron hydrochloride) Tablets

Supplemental New Drug Application:
Changes in Labeling and Conditions of Use

DEBARMENT CERTIFICATION

Glaxo Wellcome hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

2 Nov 2001

Charles E. Mueller
Head, North American Clinical Compliance
World Wide Compliance

Date

## Item 20

# Pediatric Use Information

The following information is provided in accordance with the provisions of 21 CFR 314.50(d)(7) and 21CFR 314.55:

Description of GlaxoSmithKline Plans for Pediatric Studies

GlaxoSmithKline (GSK) previously provided FDA a description of its plans to conduct studies in pediatric patients older than 6 years of age as part of the original New Drug Application for LOTRONEX® Tablets (NDA 21-107: dated June 29, 1999; Volume 1.1, pages 20 through 25). A deferral for completion of studies and a request for a partial waiver for patients younger than 6 years was also included in the NDA. The Agency's response to the proposal was included in the approval letter for NDA 21-107 dated February 9, 2000.

Specific plans for clinical studies were also described by GSK in its proposed Pediatric Study Request (GSK letters of October 29, 1999 and November 5, 1999). The Agency responded to the GSK proposals in its letter dated April 7, 2000, at which time the FDA issued a formal Written Request, pursuant to Section 505A of FDAMA.

During early 2000, GlaxoSmithKline initiated several clinical trials in pediatric patients intended to obtain pharmacokinetic data as well as information on safety and effectiveness. Several of these studies had been initiated prior to receipt of FDA's Written Request for studies.

During May of 2000, GSK communicated its intention to halt all pediatric clinical trials following discussions with FDA regarding post-marketing reports of ischemic colitis and complications of constipation associated with LOTRONEX Tablets. In its letter dated June 5, 2000, FDA raised ethical concerns about clinical research in pediatric patients pending resolution of safety issues in adults and formalized a clinical hold on the recently discontinued repeat-dose pediatric trials. FDA indicated that prior to reinitiating clinical trials in pediatric patients, additional information would need to be obtained in adults on ways to minimize possible risks of serious adverse events. Accordingly, GSK does not plan to conduct further studies in pediatric patients until such time that the concerns addressed in FDA's letter of June 6, 2000 have been addressed.

On November 28, 2000, GSK ceased further sale and distribution of LOTRONEX Tablets, halted all ongoing clinical studies, and initiated final data analyses activities for all completed or terminated trials.

Clinical Data Obtained in Pediatric Patients included in the Application

Included in this sNDA are the final study reports for the following 4, terminated studies, conducted in pediatric patients:

- S3B10903: An Open-Label, Non-Randomized, Single Dose Study of the Pharmacokinetics of Alosetron 1mg in Children 6-11Years of Age with Non-Constipated Irritable Bowel Syndrome (Report No. NN2001/00012/00).

- S3B10934: An Open-Label, Non-Randomized, Single Dose Study of the Pharmacokinetics of Alosetron 1mg in Adolescents 12-17 Years of Age with Non-Constipated Irritable Bowel Syndrome (Report No. NN2001/00017/00).

- S3B30015: An Eight-Week, Randomized, Double-Blind, Placebo-Controlled Study of Alosetron in Non-Constipated Adolescents with Irritable Bowel Syndrome (Report No. RM2001/00009/00).

- S3B30019: A Sixteen-Week, Open-Label, Safety Study of Alosetron in Non-Constipated Adolescents with Irritable Bowel Syndrome (Report No. RM2001/00007/00).

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 22, 2002

TO: Scheldon Kress, Medical Officer
HFD-180

FROM: Karen Lechter, J.D., Ph.D.
Social Science Analyst
Division of Surveillance, Research,
and Communication Support, HFD-410
Office of Drug Safety (ODS)

THROUGH: Anne Trontell, M.D., Director
Division of Surveillance, Research,
and Communication Support, HFD-410
Office of Drug Safety

SUBJECT: Patient Agreement Comments for Lotronex
NDA 21-107

The memorandum that follows contains suggested wording for part of the Patient/Physician agreement for Lotronex. The memorandum was sent to you on April 30.

*{See appended electronic signature page}*

**MEMORANDUM** **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: April 30, 2002

TO: Scheldon Kress, M.D.
HFD-180

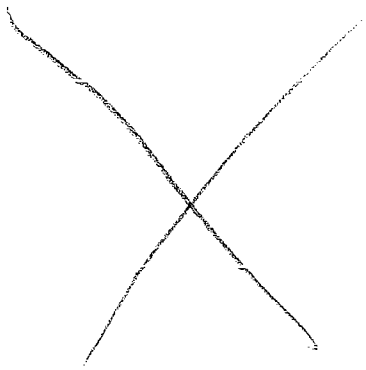
FROM: Karen Lechter, J.D., Ph.D.
Social Science Analyst
Division of Surveillance, Research,
and Communication Support, HFD-410
Office of Drug Safety (ODS)

SUBJECT: Wording for Lotronex Patient Agreement
NDA 21-107

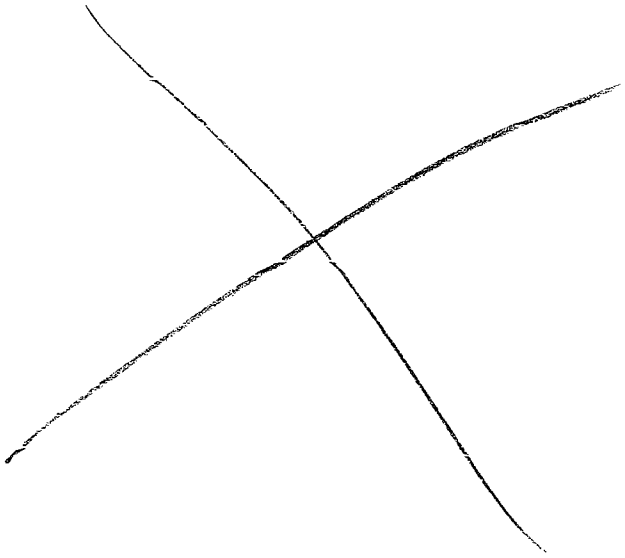
Below is your original proposed wording for additional language for the Lotronex Patient Agreement. Following that is our suggestion for simplifying the wording. As we do not have a current copy of the agreement readily available, we could not make suggestions about this ( / format. This new section should be consistent with or compatible with the format of the rest of the document in terms of using a ) / or not.

Please let us know if you have any questions. You can call me at x73241.

**GI Division Original**
To justify the risks associated with taking Lotronex,
I consider my IBS abdominal symptoms to be severe as they are:



**ODS/DSRCS Suggestion**



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

/s/

Karen Lechter
5/22/02 02:03:26 PM
UNKNOWN

Anne Trontell
5/23/02 07:56:26 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

# MEMORANDUM

DATE: May 21, 2002

FROM: Paul E. Levine, Jr., R.Ph.; Regulatory Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Request for Comment
NDA 21-107, Lotronex (alosetron HCl) Tablets

TO: Olivia Pinkett, Ph.D., Senior Director, GI/Inflammation, U.S. Regulatory Affairs

Please find attached the following items:

1. FDA *draft*-Product Information insert
2. FDA *draft*-Medication Guide
3. FDA *draft*-Patient-Physician Agreement
4. FDA *draft*-Physician Attestation Form
5. FDA preliminary requests for Phase-4 studies
6. FDA draft comments on GSK proposal for an Active Surveillance Program

These draft items are provided to facilitate future discussions about the drug product labeling and prospective Phase-4 commitments for Lotronex and are not intended to represent the Agency's final position on the matter.

If you have any questions, you may call me at 301-443-8347.

Attachments:

# MEMORANDUM OF MEETING MINUTES
## REGULATORY BRIEFING MEETING

**Meeting Date:** May 17, 2002
**Meeting Time:** 1:30– 3:00 PM
**Meeting Location:** Conference Room G, WOC II

**Application Number:** NDA 21-107; Lotronex™ (alosetron HCl) Tablets

**Meeting Chair:** John Jenkins, MD
**Meeting Facilitator:** Maureen Hess, MPH, RD
**Meeting Recorder:** Paul E. Levine, Jr., R.Ph.

**Meeting Purpose:** To discuss:

- the risk-benefit profile of Lotronex
- types of marketing restrictions needed to ensure safe use
- an appropriate risk management plan and program evaluation

**List of FDA Attendees:**

**Background:**
Lotronex was approved by FDA on February 9, 2000 for the treatment of women with irritable bowel syndrome (IBS) whose predominant bowel symptom is diarrhea. After introduction of Lotronex to the market, FDA began receiving adverse event reports of serious outcomes associated use of the drug, including serious complications of constipation and serious complications of ischemic colitis. In some cases, patients required surgery or died. On November 28, 2000, Lotronex was voluntarily withdrawn from the market by its sponsor at that time, GlaxoWellcome, Inc.

Since the withdrawal of Lotronex, however, substantial amounts of new information about the drug have become available. On December 7, 2001, GlaxoSmithKline (GSK) submitted new information to FDA about the safety and efficacy of Lotronex. The scope of this information gives FDA a broader scientific foundation upon which to base any possible subsequent regulatory actions on Lotronex.

SLIDE PRESENTATION

Victor Raczkowski (Acting Division Director, HFD-180) presented slides concerning the efficacy, clinical and post-marketing safety, risk management program, and proposed studies for Lotronex (see attachment).

Discussion on Drug Efficacy

Retrospective analyses of several studies in patients with severe urgency, performed by Dr. David Hoberman, provide some evidence that Lotronex is markedly effective in a fraction (about 13-21%) of women with severe diarrhea-predominant IBS (see slide #4). Also, a more stringent retrospective analysis showed that a greater percentage of patients with severe urgency who were treated with Lotronex had sustained relief of urgency for the full 12 weeks of treatment than did patients with severe urgency who were given placebo. If the drug is returned to the market, further data on patients with severe IBS symptoms might be needed. The randomized withdrawal study considered in the past would be less helpful now as few people are taking the drug. Rather, a new placebo-controlled trial in severely affected patients could be conducted. Also, post-marketing studies of new regimens that lower the dose or give the drug less frequently after initial response would likely be needed.

Discussion on Drug Safety

Comments:

- Adverse events of ischemic colitis and constipation associated with the use of Lotronex were observed before and after approval of the drug. The cases of ischemic colitis and constipation reported prior to approval were self-limiting with no sequelae. After approval, cases of these events were more serious, even fatal.

- The incidence of serious complications of constipation in clinical trials might not be representative of actual clinical practice because of "stopping rules" in the clinical trial that prevented patients with constipation from continuing treatment.

- The risks of ischemic colitis associated with use of Lotronex for more than 6 months is uncertain.

- With reference to the number of deaths indicated in slide #15: "Post-marketing: Small Bowel Ischemia Cases (n=6)", the Agency has recently received an additional report of death resulting from small bowel ischemia, bringing the total to 4 deaths.

Discussion on Risk Management

Questions: Has the sponsor agreed to Subpart H?

Response: The sponsor has agreed to the re-introduction of Lotronex to market under Subpart H.

Question: Does the sponsor's risk management plan include [redacted]

Response: No, there is no [redacted]

Question: Are there any plans to consult the various [redacted] The [redacted] have expressed an interest in working with the Agency on risk management activities.

Response: There is no indication that the sponsor has contacted [redacted] this might be necessary for the success of the proposed risk management plan.

Question: Who receives the spontaneous adverse event reports for Lotronex?

Response: The spontaneous adverse event reports for Lotronex will be submitted to both the Agency and the sponsor.

Question: Is there unit-of-use packaging that includes patient labeling?

Response: Yes, the sponsor proposes to dispense 30 tablets count bottles with attached medication guides as unit-of-use packaging. This is reflected in the proposed labeling.

Question: One of the major issues concerning the use of the claims database is that these databases are not created for the purpose of health outcomes research. Does the committee believe that claims data collected by the sponsor would provide adequate information to address the problems of risk management for Lotronex?

Committee's Response: There are major doubts that a claims database would provide enough detail to be useful. It is preferable to construct a registry with patients who could be asked questions about their experience with the drug. These patients could be asked, not required, to be part of a registry at the time they received the drug.

Discussion on Proposal for Additional Studies

Comments:

- The elimination of Lotronex may occur through three different metabolic pathways. The sponsor suggests, but has not demonstrated, that inhibition of one pathway might result in the shunting of metabolites of Lotronex through alternative pathways. Therefore, a pharmacokinetic (PK) study of Lotronex, especially in patients who are hepatically impaired, might be needed to understand the drug's metabolism. A drug-drug interaction study might also be needed.

- Some reviewers believe that long-term risks should be evaluated in a follow-up study.

QUESTIONS TO THE COMMITTEE

**1. Do the benefits of Lotronex exceed the risks under conditions of the RMP?**

Committee's Response: The benefit of Lotronex appear to exceed its risks for a specific subset of IBS patients who are severely affected and essentially disabled because of their IBS. More labeling and education is recommended to ensure that physicians understand that this subgroup is very small in number. Patients, too, need education that this drug is not for the average or most IBS patients.

Discussion

Question: [redacted] ymptoms for the s

Resp[redacted] experts on how to define severe [redacted]ptoms. Perhaps examples of patients with severe IBS could be listed in the labeling to help clinicians evaluate the severity of symptoms of their IBS patients.

Comment: Reference to the impact of the di[redacted]atients should be include[redacted]rovide adequ[redacted]proper eva[redacted]L STU[redacted]s of the labe[redacted]e drug is intended only [redacted]atients.

Question: Are fatal events included as part of the Indication?

Response: Fatal events are referred to in the Black Box Warning.

Comment: To provide appropriate emphasis on risk and the reason for limiting use, the indication could be revised to state clearly that, because of adverse events and deaths associated with the use of the drug, the indication is restricted to the most severely affected people.

Question: What percentage of patients would fit the narrowed definition for appropriate use of Lotronex?

Response:

Question: What is meant by the phrase "failed to respond to conventional therapy"?

Response: The phrase refers to patients who have not had adequate relief of their IBS symptoms by medications such as anti-spasmodics, sedatives, anti-depressants and benzodiazepianes, which are commonly prescribed for treatment of IBS.

Comment: There is debate on the effectiveness of these medications on the relief of IBS symptoms and whether these agents could be called "conventional therapy".

Question: Has efficacy of Lotronex been established in severe patients or are additional studies needed?

Response: The sponsor provided data in the clinical trials in which severe patients, as defined at baseline, experienced relief of their IBS symptoms similar to that of non-severe IBS patients. In addition, analyses of the severe patient population group by the review team statistician indicate that a subset of patients with severe IBS symptoms receive a significant, clinically meaningful, beneficial response from use of Lotronex.

Question: What is the benefit of the sponsor performing a randomized withdrawal study at this point?

Response: The randomized withdrawal design is useful when there are many (previously severely affected) people already on the drug, e.g., at the time of the drug withdrawal. Now, there are few such people. The trial that could be done now, probably post-approval, is a conventionally designed placebo-controlled trial in severely affected people.

Question: Is the benefit of Lotronex time-dependent?

Response: Some patients have a sustained drug effect while others do not. Some data suggest that patients who do not receive benefit after 1-2 weeks of therapy, most likely will not receive any benefit from Lotronex. The proposed labeling states that patients should stop taking Lotronex if their IBS symptoms are not adequately controlled after 4-weeks of use.

Question: How do you limit the use of Lotronex to severe patients when efficacy has also been demonstrated in less severe patients?

Response: The clinical trials included patients of various severity. The clinical trial section needs to be revised to refer only to severely affected patients.

**2. Is the RMP commensurate with the risks?**

Committee's Response: The risk management plan as proposed by the review division is sufficient for the risks in the severe IBS patient population.

Question: What happened to the idea for a registry?

Response: [redacted]

[redacted] attest have the option to receive additional education concerning the risks associated with prescribing Lotronex.

[redacted]

Question: Are there data available comparing the frequency of risks of Lotronex as compared to other drugs such as NSAIDS?

Response: Lotronex has been evaluated to have a risk of ischemic colitis of approximately 2-5/1000 patients at 3-months compared to drugs such as contraceptives which have a rate of VTE of 2-4/1000 patients/year and NSAID having a GI bleed risk of 2/100/year.

Question: Are any components of the risk management plan (sticker, agreement forms, etc.) directed at the education of patients?

Response: Since the patient generally relies on the doctor for information, most of the risk management components are directed toward educating the physician. The medication guide is intended to educate the patient about the risk associated with Lotronex. [redacted]

Comment: The sponsor should focus much more on educating the patient. In addition, salespersons and marketing forces could be used to support educating physicians and patients.

3. **Provide suggestions for the RMP, especially the program evaluation (e.g., is the claims database sufficient?)**

Committee's Response: Many of the suggestions have been included in the response to the preceding questions to the committee. The goals of a risk management program should be to get the drug to the right patient, inform the patient and physician about the problems associated with use of the drug, and assess how

the program is functioning. The proposed risk management for Lotronex could be revised to include patient education programs

Question: What is the sponsor's opinion about the proposed risk management plan?

Response: The sponsor supports most of the components of the risk management program, but there is resistance to the Agency's

4. **Provide suggestions for additional studies, including studies that should be required prior to approval.**

Committee's Response: There is no adequate reason not to approve the re-introduction of Lotronex The sponsor should commit to doing the studies post approval to evaluate lower doses and other dosing regimens.

ADDITIONAL DISCUSSION

Dr. Houn asked the committee to respond to the following questions.

1. What is the significance of a registry in the risk management program for Lotronex?

Response:

2. Should there be refills for Lotronex?

Response: There should be no refills for the short-term (1-3 months) use of the drug. Refills might be appropriate for patients receiving the drug for longer terms.

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/s/

Victor Raczkowski
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# Lotronex Tablets
# (alosetron hydrochloride)
# Regulatory Briefing

Victor F. C. Raczkowski, MD, MSc

May 17, 2002

# Overview of Presentation

- Efficacy
- Safety in Clinical Trials
- Safety Postmarketing
- Risk Management Program (RMP)
- Additional Studies
- Questions and Discussion

# Efficacy

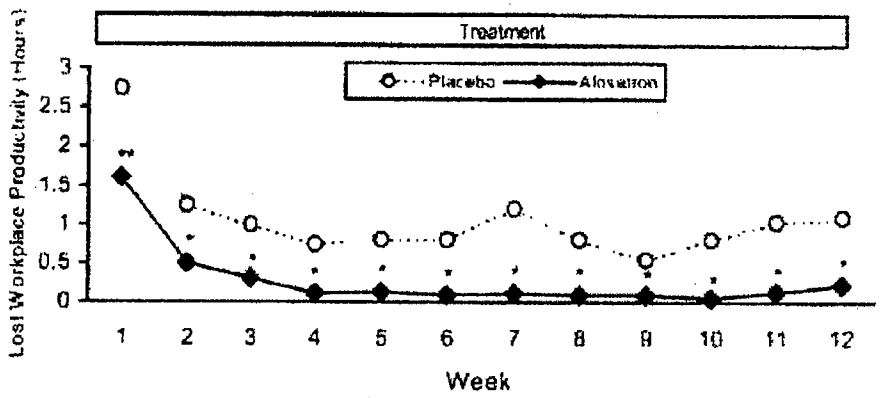
- Two multicenter R/DB/PC trials
- Women with non-constipated IBS
  - Alosetron: n= 633; Placebo: n=640
- 12 weeks: alosetron 1 mg p.o. b.i.d.
- Primary endpoint: adequate relief of abdominal pain and discomfort
- Results
  - Therapeutic gain: 10-15%
  - Secondary endpoints consistent

# Populations with Big Benefit? Urgency

- Responder:
  - Start above 5 days per week
  - End below 2 days per week (3 months)
- Studies 3001, 3002
  - alosetron 32%
  - placebo 19%
- Studies 30011, 30012 (more severe)
  - alosetron 50%
  - placebo 29%

# Population with Big Benefit? Productivity

**Median Hours of Lost Workplace Productivity Among Subjects Who Reported Working at Least 1 Week During the Treatment Phase Intent-to-Treat Population, S3B30011**




Imputed: * p<0.001; ** p<0.05

- Treatment difference 1 hour per week
- Less than spontaneous improvement in placebo

# Populations with Little Benefit?

- Stool consistency hard or lumpy
- Stool frequency <2 per day
- May also be at higher risk

# Safety Issues

- Ischemic Colitis (IC)
- Serious complications of constipation (SCC)
- Small bowel ischemia
- Death

# Safety in Clinical Trials

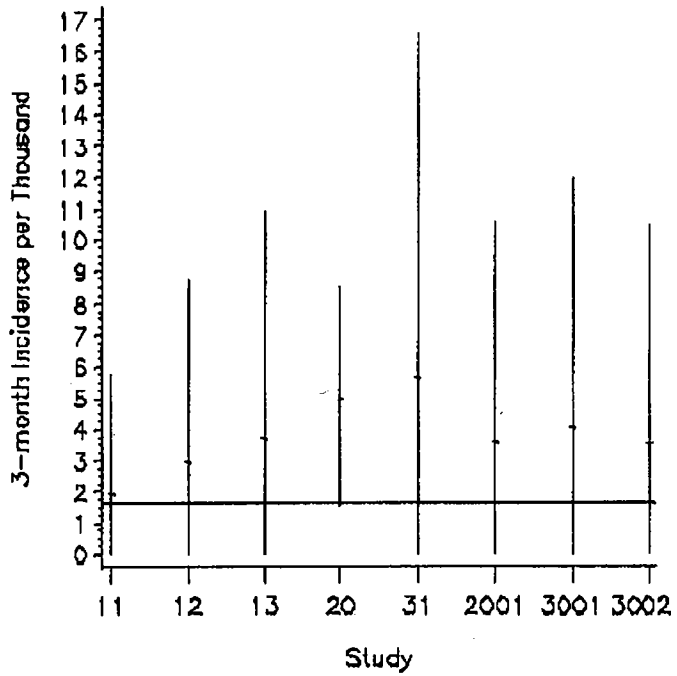
- What is the risk?
- How does it change over time?
- Are there risk factors?

# Constipation in Clinical Trials

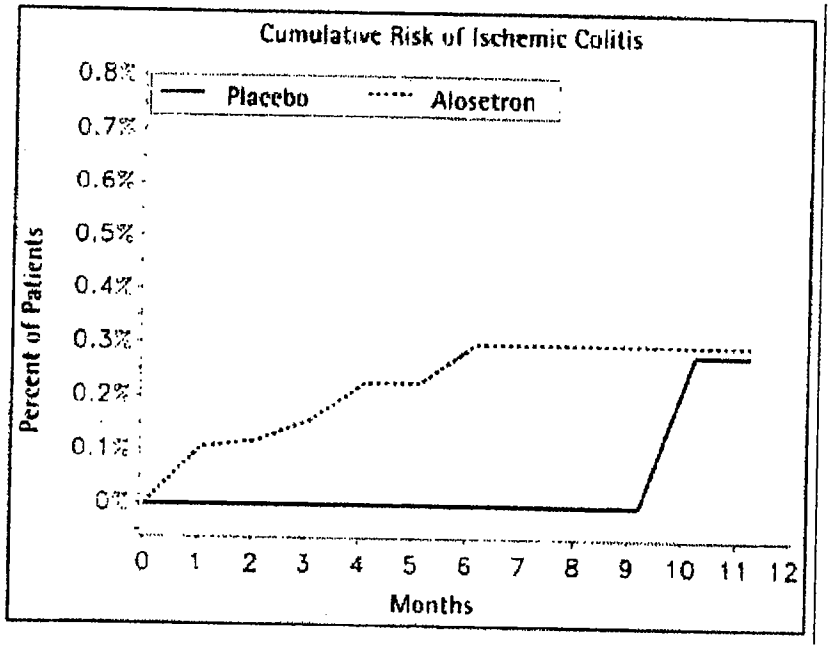
- Complications of constipation
  - 11/11,000 in controlled trials
  - 3/3,000 on placebo
  - Stopping rules
    - 10% dropout on alosetron
    - 1% on placebo

# Ischemic Colitis in Clinical Trials at 3 months

- 20 studies
  - >100 patients each
  - 11,000 patients on alosetron
  - 12 studies with no cases
- Overall rate 2/1000
- Study 20 has 10 of 18 cases
  - late study: better ascertainment?
  - rate 5/1000

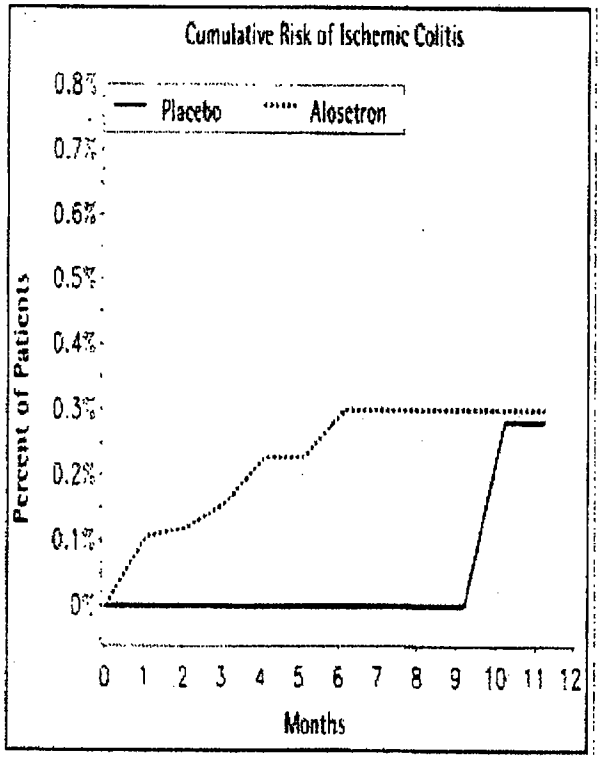


# Change over Time (12 months)




- Little information past 6 months
  - 700 alosetron patients at month 7
  - 12,000 at month 1
  - 1 case of ischemic colitis (placebo)

# Change over Time (6 months)




- Cumulative risk keeps rising
- Risk per unit time may decrease
- Cumulative risk is important
- Most cases in month 1, but 30% of exposure also in month 1

# Risk Factors for Ischemic Colitis

- Known in broad population
- None identified with alosetron
- Everyone is at risk

# Safety: Postmarketing

- Reports through March 8, 2002
- Ischemic colitis; n=84
- Small bowel ischemia; n=6
- Serious complications of constipation; n=113
- Death; n=7

# Postmarketing: Outcomes of IC Cases* (n=84)

- Required hospitalization: 54 (64%)
- Required surgery: 11 (13%)
  - Segmental resection: 10
  - Unknown: 1
- Required transfusions: 2 (2%)
- Death: 2 (2%)

*Not mutually exclusive

# Postmarketing:
# Small Bowel Ischemia Cases (n=6)

- Cases with ischemia, infarction, or necrosis of small bowel
- 5 Surgeries
- 3 Deaths

# Postmarketing: Outcomes of SCC Cases* (n=113)

- Required hospitalization: 83 (74%)
- Required surgery: 34 (30%)
  - Intestinal surgery: 25
  - Anorectal surgery: 9
- Transfusions: 2 (2%)
- Death: 2 (2%)

*Not mutually exclusive

# Deaths: Total AERS Experience

- Total of 14 deaths in patients receiving Lotronex
- Association with Lotronex cannot be reasonably excluded in 7 cases
  - 2 cases of IC
  - 3 cases of small bowel ischemia
  - 2 cases of SCC

# Clinical Trials (CT) vs. Postmarketing (PM) Experience

| Event | Population | Cases | Surgery | Death |
|---|---|---|---|---|
| IC | CT | 18 | 1 | 0 |
| | PM | 84 | 10 | 2 |
| SmB Isch | CT | 0 | 0 | 0 |
| | PM | 6 | 5 | 3 |
| SCC | CT | 11 | 1 | 0 |
| | PM | 113 | 34 | 2 |

# Conclusions: Ischemic Colitis and Mesenteric Ischemia

- Risk factors for ischemic colitis or mesenteric ischemia have not been identified
- Cumulative risk of ischemic colitis increases over time (~2-5/1000 at 3 months)
- Risk may decrease after 1 month, little information after 6 months

# Conclusions: Constipation

- Constipation is a frequent, dose-related side effect associated with Lotronex
- ~25-30% experience constipation with Lotronex at 1 mg twice daily
- ~10% withdrew from clinical trials because of constipation at 1 mg twice daily
- Some adverse outcomes of constipation are serious

# Risk Management Program

- Approved under 21 CFR Subpart H
- Narrowing of Indication
- Restriction to qualified physicians
- Educating Patients
- Reporting of serious adverse events
- Evaluation of risk-management program

# Narrowing of Indication

- Women with severe diarrhea-predominant IBS
- Severe:
  - frequent and severe abdominal pain/discomfort
  - frequent and extreme urgency or fecal incontinence
  - disability or restriction of daily activities
- Chronic IBS
- No GI anatomic or metabolic abnormalities
- Failed conventional therapy for 3 months

# Restriction to Qualified Physicians: Enrollment

- Understands use of Lotronex is restricted
- Understands risks/benefits of Lotronex, including package insert, medication guide, and Patient-Physician Agreement (PPA)
- Is able to diagnose and treat IBS
- Is able to diagnose and manage IC
- Is able to diagnose and manage SCC
- Will educate patients on risks/benefits

# Restriction to Qualified Physicians: Enrollment

- Will give Medication Guide to patient
- Will obtain patient's signature on PPA and will sign PPA
- Will place PPA in medical record and give a copy to the patient
- Will affix sticker to each prescription
- Will report serious adverse events

# Restricted to Qualified Physicians

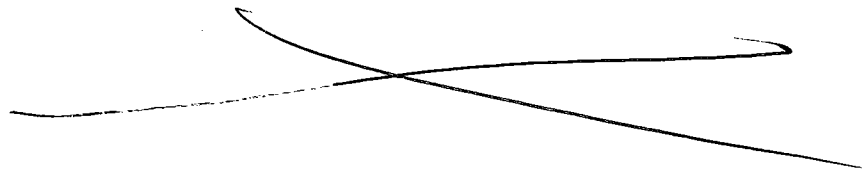
- Self-attest to qualifications
- Confirmation of self-attestation before distribution of prescribing materials
- Prescribing materials include stickers
-

# Educating Patients

- Patient-Physician Agreement form
  - Physician reviews benefits/risks of Lotronex with patient
  - Patient self-attests to severe IBS
  - Patient alerted to warning signs for SAEs
  - Patient signs PPA and physician co-signs
  - Physician gives copy to patient and files original in patient's medical record
- Medication Guide

# Evaluation of RMP

- GSK study: 15 million user claims database to obtain a sample of ~~x~~ users
  - Analyze use and prescribing information to target subsequent interventions
  - Survey patient knowledge
  - Monitor AEs
  - Collect patient demographic and medical data
  - Evaluate risk factors



# Additional Studies in Severe IBS

- R/DB/PC study of lower dosages in severely affected patients
- R/DB/PC study of "as needed" dosing
- Mechanistic studies to investigate etiology of alosetron-induced IC
- Pharmacokinetic studies

# Questions and Discussion

- Do the benefits of Lotronex exceed the risks under conditions of the RMP?
- Is the RMP commensurate with the risks?
- Provide suggestions for the RMP, especially the program evaluation (e.g., is the claims database sufficient?).
- Provide suggestions for additional studies.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-107

GlaxoSmithKline
Attention: Olivia Pinkett, Ph.D.
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101

Re: Request for Waiver

Dear Dr. Pinkett:

Thank you for your letter of April 15, 2002, regarding NDA 21-107 Lotronex (alosetron hydrochloride) Tablets, in which you requested a waiver as provided for under 21 CFR 314.90(a). This waiver would apply only to adverse event information received through attorneys representing persons who claim to have experienced an adverse event in association with Lotronex, or received as a result of actual or prospective litigation on behalf of such persons (hereafter, "information received in a legal context"). You have requested a waiver from the timeframes described in 21 CFR 314.80(1)(i) and (ii), to report each adverse drug experience that is both serious and unexpected, whether foreign or domestic, as soon as possible but in no case later than 15 calendar days of initial receipt of the information by the applicant, and to submit followup reports within 15 calendar days of receipt of new information. In lieu of 15 calendar days, you propose to submit initial and follow-up "Alert" reports of information received in a legal context not later than 30 calendar days after receipt of the information.

Your requested waiver is hereby granted. This waiver will remain in effect until further notice.

If you have any questions about this waiver, please do not hesitate to contact me at (301) 827-3219.

Sincerely,

*{See appended electronic signature page}*

Martin Himmel, M.D., M.P.H.
Deputy Director
Office of Drug Safety
Office of Pharmacoepidemiology and Statistical Science
Center for Drug Evaluation and Research

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/s/
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Martin Himmel
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# MEMORANDUM OF TELECON

DATE: May 8, 2002

APPLICATION NUMBER: NDA 21-170, Lotronex (alosetron HCl) Tablets

BETWEEN:

Name: Dr. David Wheaddon, Senior Vice President, US Regulatory Affairs
Phone: 919-483-2100
Representing: GlaxoSmithKline

AND

Name: Florence Houn, M.D., M.P.H.,
Director, Office of Drug Evaluation III (HFD-103)
Bronwyn Collier, B.S.N.
Associate Director for Regulatory Affairs, ODE III (HFD-103)

SUBJECT: Issues raised at the April 23, 2002, advisory committee meeting

Background: The Gastrointestinal Drugs and Risk Management Advisory Committees met jointly to discuss on April 23, 2002, to discuss risk management of Lotronex. The committee members concluded that there may be a sub-population of severely affected women with diarrhea-predominant IBS who may benefit from restricted market reintroduction of Lotronex.

Call: Dr. Houn summarized the review team's proposals for the risk management plan and postmarketing commitments:

1. Risk management plan
   a. Labeling revisions should include changes to the INDICATIONS section to specify the target population (bulleted items may be used to define the population and disease severity), BOXED WARNINGS (update to reflect the restricted use program and risks), HOW SUPPLIED (substantial revision to include information about the marketing restrictions), and updates to the PRECAUTIONS, WARNINGS, and ADVERSE EVENTS sections. Updates to the Medication Guide and Patient-Physician Agreement are also needed to make them consistent with the package insert.
   b. Physician qualifications for prescribing Lotronex
      i. Ability to diagnose and treat IBS.
      ii. Ability to diagnose and manage ischemic colitis.
      iii. Ability to diagnose and manage constipation and complications of constipation
      iv. Knowledge of the risks and benefits of Lotronex.
      v. Educating the patient on the risks and benefits of Lotronex.
      vi. Requirement to report adverse events related to the use of Lotronex.
   c. Physician qualification program: The program should be education-based with certification. Dr. Wheaddon said that they are contemplating a web-based mechanism for attestation to qualifications through a third party vendor. After attesting to having the

required qualifications, the physician would receive a prescribing kit that includes a qualification identification number, the Patient-Physician Agreement and prescription stickers. The qualification program will be augmented by hyperlinks to an appropriate organization offering educational material on the subject (CMEs may be awarded). Qualified physicians can reorder prescribing kits using their identification number.

d.

e. Prescription stickers: The prescription stickers should alert pharmacists that the prescription has been written by a Lotronex-qualified physician.

f. Sticker compliance study: A study should be conducted to determine whether prescriptions are being filled by unqualified physicians.

g. Education to pharmacists: The educational program should provide pharmacists and the risks of Lotronex, the restricted use program, prohibition against prescription refills, and the prescription stickers.

2. Postmarketing commitments

a. Active surveillance study: Observational study of patients taking Lotronex. Sample size- Data should be collected on adverse events, patient demographic and medical information, patient knowledge about the risks/benefits of Lotronex, and appropriateness of prescription and educational interventions. Blood samples could also be obtained for pharmacogenomic study. Dr. Wheaddon commented that a study of this size could slow introduction of the drug to the market.

The meeting scheduled for May 13, 2002 will be used to further discuss the proposed risk management plan and postmarketing commitments.

*See appended electronic signature page*

Bronwyn Collier
Associate Director for Regulatory Affairs

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/s/

Bronwyn Collier
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CSO

# Memorandum of Meeting Minutes

**Meeting Date:** February 26, 2002
**Meeting Time:** 9:00 – 10:30 am
**Meeting Location:** Conference Room C, Parklawn Building, 3rd floor,

**Application Number:** NDA 21-107; Lotronex™ (alosetron HCl) Tablets

**Type of Meeting:** Type C, Industry Meeting
**Meeting Chair:** Dr. Victor Raczkowski
**Meeting Recorder:** Mr. Paul E. Levine, Jr.

**List of FDA Attendees**

**Division of Gastrointestinal and Coagulation Drug Products (HFD-180)**
Victor Raczkowski, M.D., M.Sc., Acting Division Director
Joyce Korvick, M.D., Deputy Division Director
Hugo Gallo-Torres M.D., Ph.D., Team Leader (GI Drugs)
Marcello Barreiro, M.D., Medical Reviewer
Edward Kaminskas, M.D., Medical Reviewer
Paul E. Levine, Jr., R.Ph., Regulatory Project Manager

**Office of Drug Evaluation III (HFD–103)**
Florence Houn, M.D., Director

**Division of Drug Risk Evaluation (DDRE), ODS (HFD-430)**
Julie Beitz, M.D., Director, OPSS/DDRE
Toni Piazza-Hepp, Pharm.D., Associate Director
Zili Li, M.D., M.P.H., Medical Epidemiologist
Allen Brinker, M.D., M.S., Medical Epidemiologist
Ann Corken-Mackey, R.Ph., Safety Evaluator
Lanh Green, Team Leader

**Division of Biometrics II (HFD-715)**
Ed Nevius, Ph.D., Division Director
Tom Permutt, Ph.D., Statistical Team Leader
David Hoberman, Ph.D., Statistical Reviewer

NDA 21-107
Industry Meeting: 02/26/02

**List of External Constituents:**

**GlaxoSmithKline:**

David Wheadon, M.D., Senior Vice President, U.S. Regulatory Affairs.
Craig Metz, Ph.D., Vice President, Oncology/GI/Inflammation, U.S. Regulatory Affairs
Vanessa Ameen, Director, GI, Clinical Development Medical Affairs
Eric Mortensen, M.D., Ph.D., Director, GI, Clinical Development Medical Affairs
Eric Carter, M.D., Ph.D., Vice President, GI, Clinical Development Medical Affairs
June Almenoff, M.D., Ph.D., Director, Safety
David McSorley, Ph.D., Director, Statistics
Olivia Pinkett, Ph.D., Senior Director, GI/Inflammation, U.S. Regulatory Affairs
Mark Baumgartner, R.Ph., Director, GI/inflammation, U.S. Regulatory Affairs

## BACKGROUND

NDA 21-107 for Lotronex (alosetron hydrochloride) Tablets was approved on February 9, 2000, for the treatment of irritable bowel syndrome (IBS) in women whose predominant bowel symptom is diarrhea. On November 28, 2000, GlaxoSmithKline (GSK) voluntarily withdrew Lotronex from the market after considering the risk management options presented by the FDA in response to post-approval reports of ischemic colitis and complications of severe constipation, including death, associated with the use of Lotronex.

Since withdrawal of Lotronex from the market, substantial amounts of new safety information from clinical trials have become available. After discussions and meetings with the Agency about patient access and a possible Advisory Committee meeting, the sponsor agreed to submit new study data, a revised risk management plan, and revised product labeling as part of a supplement to the NDA for the possible re-introduction of Lotronex to the market. The complete supplement was submitted on December 07, 2001.

Following submission of the supplement, it was decided that a meeting with the Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management Subcommittee would be held to discuss the risk-benefit profile of Lotronex® (alosetron hydrochloride) Tablets. This meeting has been scheduled for April 23, 2002.

## MEETING PURPOSE

To Discuss issues related to the review of the NDA supplement and details of the Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management Subcommittee meeting on April 23, 2002.

**DISCUSSION POINTS**

Dr. Raczkowski welcomed the attendees and thanked the sponsor for continuing dialogue with the Agency concerning the process for the possible re-introduction of Lotronex to the market.

Dr. Raczkowski confirmed that a joint advisory committee meeting between the Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management Subcommittee would be held to discuss the risk-benefit profile of Lotronex® on April 23, 2002.

The sponsor was further informed of the following:

1. In order to minimize redundancy in the presentations on efficacy and safety, FDA anticipates that it will briefly acknowledge those areas where FDA and GSK have similar perspectives. FDA presentations instead will focus on new data/analyses/interpretations that differ from those of GSK.

2. The discussion of safety issues will focus on serious adverse events (e.g., ischemic colitis, serious complications of constipation, mesenteric infarction, death). Analyses of these data will include time-to-event analyses, cumulative risk, whether the hazard rates change over time, etc. In anticipation of this discussion, FDA requests that GSK calculate study –specific incidence rates of ischemic colitis (in person-years) among Lotronex users for 26 clinical trials in patients with IBS.

3. Discussions about risk factors that might indicate a predisposition for serious adverse events will likely arise and, therefore, should be addressed to the fullest possible extent. In anticipation of such a discussion, FDA requests that GSK perform an integrated evaluation of the safety data set to identify possible risk factors for serious adverse events, and to share the results with the Agency.

4. Efficacy questions that may arise include the following:

    a. Do patients with the most severe IBS symptoms respond to Lotronex similarly to patients with less severe IBS symptoms?
    b. Is there clinical trial evidence that Lotronex improves functional performance?
    c. Is there clinical trial evidence that other dosages or dosage regimens of Lotronex (e.g., lower doses or intermittent doses) are effective in some patients?
    d. Are there patient factors that can predict whether Lotronex treatment is likely to be effective?

Dr. Raczkowski referred to the draft agenda for the advisory committee meeting (see attachment) and asked if GSK had comments about the proposed discussion items or the allotted time for presentations.

The sponsor presented a general outline of the benefit-risk and risk management plan for Lotronex (see attachment). The sponsor indicated that a more detailed presentation of

approximately 90 minutes in length would be given at the Advisory Committee meeting. The presentation would be similar in content to the integrated summary of safety submitted as part of the supplemental NDA. In addition, the sponsor stated that although some efficacy information would be included in the background package, the advisory committee presentation would focus on safety.

The sponsor asked if the Agency had any comments about the proposed indication.

Dr. Raczkowski stated that the proposal to use Lotronex as a second-line therapy is acceptable, but limitation to severely affected IBS patients should be included as part of the indication.

The sponsor stated that there is no acceptable standard for the gradation of severity. The sponsor proposed that limiting the drug to second-line therapy would result in de facto limitation to severely affected IBS patients. The sponsor asked what changes in the proposed target population would the Agency suggest.

FDA suggested that the target population could be limited to patients with a history of disabling and chronic IBS who have not benefited from other medical interventions. In addition, Lotronex could be limited to patients for which IBS symptoms have markedly impaired daily functioning.

The sponsor agreed to consider the matter for later discussion.

The sponsor asked if the cut-off dates for adverse event reports could be extended to February 18, 2002, instead of the previously agreed date of January 31, 2002. The sponsor stated that approximately 29 bolus reports were recently received which included 9 new cases of medically serious events.

The sponsor was informed that the cut-off date could be extended to February 18, 2002. If necessary, the Agency would provide an update at the advisory committee meeting.

*Risk Management*

Slides on risk management were presented by Toni Piazza-Hepp (see attachment).

*Benefit/Risk – Epidemiology Data*

Slides on epidemiology data were presented by Allen Brinker (see attachment).

The sponsor stated that epidemiology data are not conclusive but provide context for thinking about Lotronex, ischemic colitis, and irritable bowel syndrome. GSK suggested that there could be a background incidence of adverse events such as ischemic colitis, including a possible "disease role" in events of ischemic colitis that arise in the IBS patient population.

FDA indicated that the significance of the epidemiology data has yet to be determined. The Agency's goal, at this point, is to inform GSK of possible issues that might be presented or arise at the advisory committee meeting.

The decision was made to have a future meeting to discuss additional details concerning the advisory committee presentations.

## CONCLUSION

1. A meeting will be scheduled between FDA and GSK to discuss additional details of the advisory committee presentation.

Attachments:

NDA 21-107
Industry Meeting: 02/26/02

# FDA PRESENTATION
# RISK MANAGEMENT PLAN

**Toni Piazza-Hepp, Pharm.D.**

## Lotronex Risk Management Plan: General Comments

**Toni Piazza-Hepp ODS/DDRE 2/25/02**
**Slide 1 of 2**

- Subpart H: [21 CFR 314.520] Restricted - Approval with restrictions to assure safe use
  - Applies to "serious or life-threatening disease"
    - discuss limiting to "disabling" IBS (definition/guidelines needed)
    - discuss need to rule out other GI pathology prior to starting Lotronex
  - FDA may withdraw approval if it is demonstrated that postmarketing restrictions are inadequate to assure safe use or if applicant fails to adhere to postmarketing restrictions
    - discuss adequacy or inadequacy of method(s) to measure adherence to restrictions: e.g. Eckerd Pharmacy / SEU plan expected to yield low sample size; probably inadequate to measure compliance to program/problems with representativeness
    - consider registration of patients or other means to more widely distribute survey

## Lotronex Risk Management Plan: General Comments

**Toni Piazza-Hepp ODS/DDRE 2/25/02**
**Slide 2 of 2**

- Monitoring of patients by physicians on a regular basis: completely missing from RMP
- Qualified MDs
  - Consider need to limit to gastroenterologists
  - Consider registration of MDs with GSK prior to receiving kit with stickers
- Discuss need for "no sticker-no drug" message: consider limited supply, no refills, no faxed or telephoned Rxs
- These are general comments; more detail and additional comments regarding specific points of plan will be included in the ODS Lotronex RMP evaluation consult

NDA 21-107
Industry Meeting: 02/26/02

# GLAXOSMITHKLINE
# SLIDE PRESENTATION

## February 26, 2002

NDA 21-107
Industry Meeting: 02/26/02

# LOTRONEX®(alosetron hydrochloride)

## General Outline of ADCOM Presentation and Briefing Document

## February 26, 2002 GSK/FDA Meeting

NDA 21-107
Industry Meeting: 02/26/02

# LOTRONEX®(alosetron hydrochloride)

- **I. Opening Remarks (Introduction and Background)**
  - Brief opening statement highlighting that the drug was approved, why it was withdrawn, why supplemental application was submitted.
  - Chronology of the key regulatory events
    - Approval - February 9, 2000
    - GI ADCOM - June 27, 2000
    - Withdrawal - November 28, 2000
    - sNDA submission - December 7, 2001
  - Agenda of the Presentation (Format of Briefing Document) to follow

# LOTRONEX®(alosetron hydrochloride)

- **II. Overview of Benefit-Risk**
  - Introduction
    - Purpose of the section
    - Information to be covered
  - Burden of illness/current management of IBS
    - What is IBS
    - Epidemiology information
    - How currently managed
  - Efficacy of LOTRONEX
    - Efficacy demonstrated in original application
    - Efficacy confirmed by data in sNDA
    - New efficacy data in sNDA
      - Efficacy in severe IBS patients
      - Impact on quality of life
      - Impact on productivity
      - Sustainability of effect

# LOTRONEX®(alosetron hydrochloride)

- **II. Overview of Benefit-Risk (continued)**
  - Safety of LOTRONEX
    - Introduction/extent of exposure
    - Adverse events of concern
      - Constipation
        - » Prevalence of constipation and risk
        - » Reports in clinical trials
        - » Spontaneous reports (through 31 Jan 02 cut-off)
      - Ischemic colitis
        - » Prevalence of ischemic colitis and risk
        - » Reports in clinical trials
        - » Spontaneous reports (through 31 Jan 02 cut-off)
      - Mesenteric ischemia
    - Reports involving surgery and death
    - Strategies to reduce the risk associated with CC and IC

# LOTRONEX®(alosetron hydrochloride)

- **III. Proposed Risk Management Plan (RMP)**
  - Proposed target population
    - Women with diarrhea-predominant IBS who have failed on conventional therapy
  - Elements of the proposed risk management plan
    - Population for whom benefit outweighs risk
    - Appropriate prescribers
    - Medication guide; patient-physician agreement
    - Communication of RMP
    - Monitoring and program evaluation
    - Modified labeling and packaging
- **IV. Clinician's Perspective**

# LOTRONEX®(alosetron hydrochloride)

## • V. Summary and Conclusions

- LOTRONEX should be re-introduced for use in the proposed target population for whom the benefit-risk profile is most favorable, namely, female patients with diarrhea-predominant IBS who have failed conventional therapy

- Since the original NDA approval, a significant body of new information has become available that allows for a more definitive assessment of the benefit-risk profile
  - Integrated clinical trials safety database includes 11,874 treated patients; a four-fold increase in exposures from time of approval
  - Evidence of significant benefit in patients with debilitating IBS symptoms
  - Evidence of quality of life and productivity improvement
  - Evidence of sustainability of benefit
  - Confirmation of the incidence of IC in controlled clinical trials

# LOTRONEX®(alosetron hydrochloride)

## • V. Summary and Conclusions (continued)

- Dominant risks reported in association with LOTRONEX
  - Complications of constipation
    - event is potentially avoidable
    - severe outcomes may be mitigated by careful monitoring of signs and symptoms and timely intervention
  - Ischemic colitis
    - *event is idiosyncratic*
    - severe outcomes may be mitigated by careful monitoring of signs and symptoms and timely intervention

- Based on the substantial body of data, GSK concludes that the benefits of LOTRONEX outweigh the possible risks when LOTRONEX is used with appropriate market controls

# LOTRONEX®(alosetron hydrochloride)

## • V. Summary and Conclusions (continued)

– Finally, a comprehensive Risk Management Plan has been proposed which is intended to

- Provide access to LOTRONEX by appropriately identified and informed patients without therapeutic alternatives
- Limit prescribing only by physicians with appropriate knowledge and experience
- Lower starting dose
- Appropriately balance the need to mitigate risks without creating extraordinary barriers to access by those patients most in need

NDA 21-107
Industry Meeting: 02/26/02

# FDA PRESENTATION
# EPIDEMIOLOGY

**Allen Brinker, M.D., M.S.**

# Lotronex Epi Studies

Allen Brinker, MD, MS
*Epidemiologist*
ODS - DDRE

## Limitations

- Results presented herein are based almost exclusively on [redacted] analysis of IBS patients in t[redacted] a subset of th[redacted] population.
  - Additional data from the GPRD from UK not confirmatory nor even supportive.
- Replication of th[redacted] findings in other US populations is needed for confirmation.

## Limitations (con't)

- I include some interim results from the RCTs.
  - 11 major trials of the 14 of IBS-D in females
- These results / analyses may be viewed as "smooth" as I collapse studies and assume constant risk.
- *Analyses are ongoing with focus on the* heterogeneity among the clinical trials.

## Outline

1 Lotronex prescribers
2 IBS diagnosis
3 IC in IBS patients
  - Believability (Is it real ?)
  - Implications for analysis of Lotronex trials
  - Absolute and Lotronex-specific incidence rates
    - RCT data

## 1. Lotronex prescribers

- Based on th[redacted] cohort, from marketing introduction to withdrawal:
  - ~1/3 gastroenterologists
  - ~1/4 internists
  - ~1/3 family or general practice
- Majority of prescribers not gastroenterologists.

## 2. IBS diagnosis

- [redacted] study cohort formed using ICD-9 code 564.1 "irritable colon"
  - 168,990 potential pts after an initial screen for 6 months of continuous enrollment.
  - 81,541 would be excluded for a disqualifying condition
    - "principally IBD"
    - 19% have a dx of IBD following a dx of IBS

## 2. IBS diagnosis

[redacted], study cohort

- from the study time period of 1995-1999
- n = 87,449
- 70.8% female, 29.2% male
- 1.44 yrs of observation on average

## 2. IBS diagnosis

- 900 (~1%) of patients in the IBS study cohort undergo bowel surgery following IBS diagnosis.
  - 5X "expected" rate
  - area for further study

## 2. IBS diagnosis

- 74 patients in IBS study cohort have a dx of ischemic colitis following dx of IBS.
- One estimate for the background rate or absolute risk of ischemic colitis in th [redacted] IBS study cohort.

## 2. IBS diagnosis

- Ischemic colitis in [redacted] IBS pts
  - Absolute incidence (based on 1.44 yrs on average)
    - 8.5 / 10,000
    - 8.9 / 10,000 (females only)
  - This hypothesis / estimate needs to be examined in another US dataset.

## 3. IC in IBS patients

- Believability
  - Limited by potential use of IBS in US medical practice as an "interim" diagnosis.
  - However, pending duplication, I believe the hypothesis that IC exists among IBS patients.
    - caused by inadequate work-up and/or misdiagnosis
    - horses verses zebras

## 3. IC in IBS patients

- Implications for analysis of Lotronex trials

  Given the hypothesis is correct, any study of ischemic colitis in association with Lotronex must be derived from placebo-controlled RCTs of Lotronex in IBS patients.

## 3. IC in IBS patients - RCT data

- [redacted] data limited to 11 of 14 trials of IBS-D (females)
- Absolute risk (incidence)
  - 1 case in 2,900 assigned placebo
    - 3.5 / 10,000
- Lotronex-specific risk (incidence)
  - 13 cases in 5,120 assigned Lotronex
    - 25.4 / 10,000

## 3. IC in IBS patients

- RR = 7.4 95% CI 0.96 - 56
  - Unknown if this is generalizable.
- If generalizable, "real world" rate of 8.5 / 10,000 reported in [redacted] tudy would increase to 63 / 10,000 with Lotronex exposure.

## 3. IC in IBS patients

- Differences in rates also useful in calculation of attributable risk.
  - (rate in exposed - rate in unexposed) / rate in exposed
  - attributable risk = 86%
  - We will "expect" ~86% of IC cases reported in association with Lotronex were due to Lotronex.

## Summary - Lotronex Epi Studies

- During initial marketing, the majority of Lotronex prescribers were not gastroenterologists.
- IBS diagnosis remains problematic: clinicians may
  - utilize "IBS" as an interim dx, or
  - misdiagnosis other conditions (IBD, IC) as IBS

## Summary - Lotronex Epi Studies

- These data support the hypothesis that misdiagnosed ischemic colitis exists among US IBS patients.
- Randomized trials in females with IBS-D suggest the rate of ischemic colitis among Lotronex-treated pts is higher (7-fold) then that of pts assigned placebo control.

# MEMORANDUM

DATE: February 21, 2002

FROM: Paul E. Levine, Jr., R.Ph.; Regulatory Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Information Request, NDA 21-107,
Lotronex (alosetron HCl) Tablets

TO: Olivia Pinkett, Ph.D., Senior Director, GI/Inflammation, U.S. Regulatory Affairs

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Please refer to your December 07, 2001, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lotronex™ (alosetron hydrochloride) Tablets, 1mg.

We are reviewing your submission and have the following information requests.

1. Calculate study-specific incidence rate of ischemic colitis (in person-year) among alosetron users for each of 24 clinical trials (Primary Safety population) that listed under page 23 of "Integrated Summary of Safety of Alosetron (GR68755) for the Treatment of Irritable Bowel Syndrome". The results should be presented in a format that is similar to Table 1 (see Attachment #1). If a study involved both male and female patients, the results should be presented separately.

2. Assess the role of concurrent medications, especially estrogen and beta-blockers, in the development of ischemic colitis among alosetron users in the trial conducted under protocol # S3B30020.

3. Perform an integrated analyses of your placebo-controlled efficacy data set to evaluate whether patients starting Lotronex with more severe symptoms have similar responses to therapy compared patients with less severe symptoms. For example, patients receiving Lotronex in clinical trials could be divided into subsets (e.g., quartiles, tertiles) based on the severity of presenting symptoms (e.g., abdominal pain, urgency, diarrhea) and then evaluated as to whether the most severely affected subset had a response of "adequate relief of abdominal pain and discomfort" that is similar to the less severely affected subsets (collectively).

4. Perform an integrated analyses of your placebo-controlled efficacy data set to evaluate whether patients treated with Lotronex have greater improvement in functional performance (e.g., days going to work or school, ability to go on social outings) than patients on placebo.

5. Perform an integrated evaluation of your safety data set for risk factors that may predispose patients receiving Lotronex to have one of the following outcomes: (a) ischemic colitis, (b) severe constipation (e.g., constipation leading to serious outcomes or to withdrawal from a clinical trial), or (d) death. Factors that should be assessed include sex, age, race/ethnicity, dose, duration of treatment, cumulative dosage, treatment with Lotronex for a diagnosis other than for diarrhea-predominant IBS, use of concurrent medications (e.g., hormone-replacement therapy)

6. Identify predisposing factors, including baseline stool consistency, which predict lack of efficacy, and which may also be associated with severe constipation or any other severe adverse event. One of the goals of the risk management program is to lessen the chance that a patient will develop severe constipation. With that in mind, FDA has found evidence in the 2 NDA trials that patients on Lotronex who entered with an average stool consistency of 3 or less, had a chance of adequate response in the first month which was no greater than placebo's. Patients on Lotronex with more formed stools also appear to have had a better chance of developing severe constipation leading to withdrawal than those with higher stool consistency scores at baseline. Consequently, we are interested in identifying predisposing factors that would predict a lack of an efficacious response in order to minimize exposure of those patients who stand to gain little or no benefit from the drug.

Attachment:

# Attachment #1

**Table 1. Study-Specific Incidence Rates of Ischemic Colitis among Primary Safety Population from 24 Clinical Trials, Stratified by Sex (if a study involved both male and female patients)**

| | Trial Sites (US, Non-US or Both) | Number of Patients in Alosetron Treatment Group | Intended Duration of Drug Treatment (Weeks) | Age Range in years (Mean) | Number of Ischemic Colitis Cases | Person Years of Drug Exposure (Cumulative) | Incidence Rate (per 1,000 person-years) |
|---|---|---|---|---|---|---|---|
| S3B20023<br>Male | | | | | | | |
| S3B30004 | | | | | | | |
| S3B30006 | | | | | | | |
| S3B30011 | | | | | | | |
| S3B30012 | | | | | | | |
| S3B30013 | | | | | | | |
| S3B30015<br>Male<br>Female | | | | | | | |
| S3B30017 | | | | | | | |
| S3B30019<br>Male<br>Female | | | | | | | |
| S3B30020 | | | | | | | |
| S3B30025 | | | | | | | |
| S3B30026 | | | | | | | |
| S3B30028 | | | | | | | |
| S3B30031 | | | | | | | |
| S3B30033 | | | | | | | |
| S3B40031 | | | | | | | |
| S3B40032 | | | | | | | |
| S3BA2001<br>Male<br>Female | | | | | | | |
| S3BA3001 | | | | | | | |
| S3BA3002 | | | | | | | |
| S3BA3003<br>Male<br>Female | | | | | | | |
| S3BB3001 | | | | | | | |
| S3BB3002 | | | | | | | |
| S3B-P12<br>Male<br>Female | | | | | | | |

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/s/
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Paul Levine
2/21/02 11:06:12 AM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

# MEMORANDUM

DATE: February 13, 2002

FROM: Paul E. Levine, Jr., R.Ph.; Regulatory Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Information Request, NDA 21-107,
Lotronex (alosetron HCl) Tablets

TO: Olivia Pinkett, Ph.D., Senior Director, GI/Inflammation, U.S. Regulatory Affairs

Please refer to your December 07, 2001, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lotronex™ (alosetron hydrochloride) Tablets, 1mg.

We are reviewing your submission and have the following information requests.

A. We refer to your questionnaire "About How You Feel" containing the following scale for possible responses:
   1. not at all
   2. slightly
   3. moderately
   4. quite a bit
   5. extremely (or "a great deal")

   Please provide an evaluation of responses from baseline to week 12 that includes only patients that have experienced improvement from ***severe*** to ***no or mild*** symptoms.

   The group representing ***severe symptoms*** will include all responders under "4. quite a bit" and "5. extremely (or a great deal)" listed in the above scale.

   The group representing ***no or mild symptoms*** will include all responders under "1. not at all" and "2. Slightly" listed in the above scale.

B. We refer to your questionnaire "Arranged According to Subscales", and to the following scale for possible responses:
   1. not at all
   2. slightly
   3. moderately
   4. quite a bit
   5. extremely (or "a great deal")

   Please provide an evaluation of responses based only upon improvement from baseline to week 12 for the categories "Interference of Activities", especially ability to work and "Sexual", that includes only patients that have experienced improvement from ***severe*** to ***no or mild*** symptoms.

   The group representing ***severe symptoms*** will include all responders under "4. quite a bit" and "5. extremely (or a great deal)" listed in the above scale.

   The group representing ***no or mild symptoms*** will include all responders for "1. not at all" and for "2. Slightly" listed in the above scale.

If you have any questions, call me at 301-443-8347.

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/s/
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Paul Levine
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CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

# MEMORANDUM

DATE: February 6, 2002

FROM: Paul E. Levine, Jr., R.Ph.; Regulatory Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Information Request, NDA 21-107,
Lotronex (alosetron HCl) Tablets

TO: Dr. Olivia Pinkett

**Question from Dr. Brinker:**

The first —— study, entitled "Lotronex Safety Studies: The occurrence of colonic ischemia, complications of constipation, and non-specific colitis in relation to IBS - phase 1" and dated May 11, 2001 reports a 65,063 individuals with ICD9 564.1 out of a baseline study population of 5.4 million.

The second —— study, entitled "The occurrence of colonic ischemia, complications of constipation, and bowel surgery in relation to IBS - phase 2" and dated Oct 31, 2001 reports 168,998 (81,541 excluded + 87,449 included) individuals with ICD9 564.1 from the same population.

**Why do these counts differ ?**

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/s/
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Paul Levine
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DIVISION OF GASTROI TESTINAL AND COAGULATION DRUG PRODUCTS

CLINICAL PHARM. COLOGY AND BIOPHARMACEUTICS REVIEW

| | |
|---|---|
| NDA: | 21-107/S-005 |
| Date Submitted: | December 7, 2001 |
| Sponsor: | GlaxoSmithKline<br>Research Triangle Park, NC |
| Drug: | LOTRONEX® (Alostron hydrochloride)<br>Tablets for oral administration |
| Pharmacological Catego : | 5-$HT_3$ receptor antagonist |
| Material Reviewed: | LOTRONEX®: Adverse events reported in the Clinical pharmacology and Biopharmaceutics studies (NDA 21-201/S-005) |
| Reviewers: | Suliman Al-Fayoumi, Ph.D.<br>&<br>Hugo Gallo-Torres, M.D., Ph.D. |

**The following Table summarizing safety data from 18 PK/PD studies with Lotronex has been formulated in conjunction with Dr. Hugo Gallo-Torres, Team Leader, GI drugs. The Table includes a summary of the major adverse events by study, which were reported in the Clinical Pharmacology and Biopharmaceutics section of Lotronex (Alosetron) supplement (NDA 21-107/SE8). Only adverse events in Alosetron treatment arms have been reported in the Table.**

**Overall, no serious adverse events were reported in the PK/PD studies (18 studies). There were no cases of Ischemic Colitis, Serious Complications of Severe Constipation or Bloody Diarrhea reported. Results from safety evaluation of these PK/PD studies will be integrated into the overall safety summary appraisal being prepared by Dr. Sheldon Kress.**

**Summary of the adverse events in the Clinical Pharmacology and Biopharmaceutics Studies (N 21-207)**

| Study # | n | IC | SCSC | Bloody Diarrhea | Constipation | Abd. Discomfort | Abd. Dist. | N/V | H/D |
|---|---|---|---|---|---|---|---|---|---|
| S3B10942 (SD PK, healthy Koreans) | 24 | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 9 |
| S3B10903 (SD PK in IBS Peds 6-11 yrs) | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | |
| S3B10934 (SD PK in IBS Peds 12-17 yrs) | 21 | 0 | 0 | 0 | 1M | 4 (3F, 1M) | 0 | 0 | 2 |
| S3B10947 (Mass Balance Study) | 7 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| S3B10935 (DDI w Fluoxetine) | 11 | 0 | 0 | 0 | 1 (1F) | 3 | 0 | 1 | 1 |
| S3B10936 (DDI w Amitriptyline) | 12 | 0 | 0 | 0 | 1 | 2 | 0 | 1 | |
| S3B10937 (DDI w *hydrocodone/Paracetamol*) | 12 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| S3B10938 (DDI w alprazolam) | 12 | 0 | 0 | 0 | 1 | 2 | 0 | 0 | 0 |
| S3B10939 (DDI w Ibuprofen) | 12 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| S3B10948 (DDI w OCs) | 17 | 0 | 0 | 0 | 11 | 10 | 0 | 0 | 7 |
| S3B10906 (Effect on Colonic Transit Time) | 30 | 0 | 0 | 0 | 4 | 3 | 0 | 2 | 5 |
| S3BA1000 (Effect on Cholecystokinin-induced Colonic Motility in IBS pts | 22 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| S3BB1002 (Effect of MD on 24-hr small bowel motility in IBS pts) | 8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| S3B10926 (Effect on Visceral hypersensitivity) | 24 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| S3BA10 (Effect on Colonic Transit Time w Mebeverine+Alosetron vs. Alosteron in healthy females) | 13 | 0 | 0 | 0 | 18 | 5 | 6 | 0 | 4 |
| S3B1093 (Effect on [illegible] in healthy fen | 20 | 0 | 0 | 0 | 4 (3 @ 1 mg, 1 @ 2 mg) | 3 (1 @ 1, 2 & 4 mg each) | 0 | 3 | 8 |
| S3B10[illegible] (Effect on Serotonin Synthesis Rates) | 23 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| S3BA2002 (PET study of regional brain activity | 47 | 0 | 0 | 0 | 11 | 0 | 0 | 0 | 0 |

IC = Ischemic Co[illegible], SCSC = Serious Com[illegible]tions of Severe Constipation, Abd. Dist. = Abdominal Distention, N/V = Nausea/Vo[illegible], H/D = Headache/I[illegible]ness.

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/s/

Sulimar Ifayoumi
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Hugo Ga. Torres
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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Attachment A

PID NUMBER: #D000674

DATE: November 16, 2000 (Redacted Version)

TO: Lilia Talarico, M.D., Director
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

FROM: Kathleen Uhl, M.D., Acting Division Director
Zili Li, M.D., M.P.H., Medical Epidemiologist
Ann Corken Mackey, R.Ph., M.P.H., Safety Evaluator
Division of Drug Risk Evaluation II (DDRE II), OPDRA, HFD-440

Paul Stolley, M.D., M.P.H., Epidemiology Consultant
OPDRA, HFD-400

SUBJECT: NDA 21-107: Lotronex (alosetron) Safety & Risk Management Summary

## 1. EXECUTIVE SUMMARY

DDRE2 in OPDRA has prepared two separate presentations regarding the data on the risk of Lotronex (alosetron), indicated for the treatment of women with diarrhea-predominant irritable bowel syndrome (IBS). On November 7, 2000, OPDRA made a presentation to Dr. Janet Woodcock, CDER Center Director, on the adverse event reports received since the approval of Lotronex, on February 8, 2000, and on the risk of Lotronex. OPDRA prepared for a presentation to be given during the face-to-face meeting with the sponsor, GlaxoWellcome, on November 13, 2000. However, due to time constraints at this meeting, no OPDRA presentation was made. The modified data prepared for this November 13, 2000 meeting are attached to this document (Attachment 1). The data have been modified to include all reports received up to November 10, 2000, including several new reports, and reconciling duplicate reports that were received as both direct and sponsor reports.

The salient details of the data from both presentations will be discussed in this memo. In addition, we will state why we do not accept the sponsor's conclusions that all the severe adverse events for Lotronex are directly related to constipation and that a risk management strategy targeting constipation will prevent the serious outcomes seen with the use of Lotronex. It may be that preventing Lotronex-induced constipation will reduce the serious complications of prolonged or severe constipation, and that would be desirable. It has not been proved, however, that preventing constipation will also prevent ischemic colitis, occlusive or non-occlusive, "primary" or "secondary".

It is our interpretation of the cases in AERS that Lotronex is associated with colonic mucosal ischemia and sometimes transmural infarction as well as severe complications of constipation. Some of these cases of colon ischemia may be the result of severe constipation leading to subsequent pressure-related colon ischemia, necrosis, or perforation resulting in colon resection and/or death. Other cases of colon ischemia are not clearly linked to constipation but occur in relatively young women (age < 65 years) with or without bloody diarrhea. Any risk management program aimed at controlling the risk of Lotronex therapy via identification and management of constipation **only** will not be successful. Constipation has **not** been identified in all cases that resulted in hospitalization, blood transfusion, surgery, and death. Also, the sponsor has not identified a subset of women who will respond to Lotronex therapy safely. Therefore, a risk management plan cannot be successful that will eliminate deaths, colectomies, ischemic colitis, and complications of treatment that were never seen previously in the management of IBS.

## 2. BACKGROUND

Lotronex as a therapy for IBS, represents a drug with a new mechanism of action, with modest efficacy for only women with the diarrhea-predominant form of IBS. Therapeutic gain in comparison to placebo was modest.

Ischemic colitis was seen in 3 patients of the 921 treated with Lotronex in the Phase 3 studies for Lotronex. One more patient in an ongoing study was reported just before the November 16, 1999 Advisory Committee meeting. Constipation was the major reason for discontinuation and drop outs in the Phase 3 studies. Constipation was dose-related and the most frequent reason for withdrawal. About one-third of women taking the recommended dose of 1mg twice daily will develop symptomatic constipation and about 10% will have to discontinue the drug permanently.

In the Medical Team Leader Secondary Review by Dr. Hugo Gallo-Torres, November 17, 1999, Table 15 compares the key findings in the Lotronex-treated patients developing colitis in the randomized clinical trials (NDA dataset). Four cases were identified. Interestingly, all 4 patients were under age 65 (ages: 33, 48, 41, 61). One of these 4 had constipation symptoms and the remaining 3 had diarrhea symptoms, and all 4 had rectal bleeding. These 4 cases represent the clearest association between Lotronex use and the development of ischemic colitis. There was no argument that these cases were confounded or represented some distinct classification of "primary" vs. "secondary" ischemia.

## 3. METHODS

OPDRA reviewed all adverse event reports received for Lotronex as of November 10, 2000, after 36 weeks of marketing. Those with any mention of death, mesenteric vasculopathy, ischemic colitis, or severe constipation were entered into an ACCESS database to capture key details and allow for a surveillance strategy. Data sources included cases provided via the Adverse Event Reporting System (AERS) at FDA and drug utilization data provided under contract by IMS Health. Cases were excluded if the key event could not be verified by FDA.

Case definitions for two of the serious outcomes used in this review are:

(1) Ischemic Colitis: A diagnosis of ischemic colitis, ischemic changes or necrosis of colon based on any or a combination of the following: (1) clinical judgement, (2) endoscopic examination or (3) pathology report;

(2) Severe Constipation: constipation or suspected constipation that led to ER visit, hospitalization, or complications, including but not limited to, fecal impaction, bowel obstruction, necrosis or rupture.

(3) In OPDRA's analysis, those surgical cases classified as ischemic colitis had to have clinical diagnosis or histologic evidence of ischemic colitis to meet that classification.

Data and cases were compared between those presented at the GI Advisory Committee meeting on June 27, 2000 (through June 1, 2000) and those known as of November 10, 2000.

4. RESULTS

As of November 10, 2000, there were 49 cases of ischemic colitis, 21 cases of severe constipation, 3 cases of mesenteric vasculopathy, and 5 cases of death, of which 3 are "probable". This is a sharp increase from the number of cases presented at the June 27, 2000 GI AC meeting. As of that date there were 5 cases of ischemic colitis, 5 cases of severe constipation, no cases of mesenteric vasculopathy, and no cases of death. The cumulative number of prescriptions for Lotronex dispensed between March and October 2000 was 435,000 (data presented by GlaxoWellcome to HFD-180 on October 25, 2000), leading to a reporting rate of 113 cases of reported ischemic colitis per million prescriptions and 48 cases of reported severe constipation per million prescriptions.

The severity of the Lotronex-associated adverse events requires specific comment. Of the 49 cases of ischemic colitis, 2 had visits to the ER without hospitalization, however, 30 (65%) required hospitalization, 5 (11%) required surgery for an obstructed, necrotic, or ruptured bowel, and 2 died. Of the 21 cases of severe constipation, 2 had visits to the ER without hospitalization, however, 14 (67%) required hospitalization, 5 (24%) required surgery for an obstructed, necrotic, or ruptured bowel, 6 (29%) had a bowel obstruction that did not require surgery, and 1 died. A full representation of all cases is depicted in the Attachments (Tables 1-1, 1-2, and 5).

Of the 49 cases of ischemic colitis, 38 (78%) had either histological, endoscopic, or radiologic evidence of ischemic colitis, ischemic change, or necrosis (Table 1-3). Fourteen cases (29%) had both histological and endoscopic evidence. Eight (16%) had only endoscopic evidence; 13 (27%) had only histological evidence; 3 (6%) had only radiological evidence.

The severity of the cases as of the June 27, 2000 GI AC meeting, demonstrate that no cases required transfusion, no cases of ischemic colitis required surgery, but 2 cases of severe constipation required surgery (Table 2-1). As of November 10, 2000, 2 cases required red blood cell transfusion (one each for ischemic colitis and severe constipation), 5 cases of ischemic colitis required surgery, and 5 cases of severe constipation required surgery. Additionally, there were 2 deaths in the ischemic colitis and 1 death in the severe constipation groups. We have received a total of 5 reports of deaths in Lotronex users: we have enough data on 3 to rate them as "probable"; 1 is tied up in litigation and we cannot get any more information; and 1 is "unlikely". Much has changed since the June 27, 2000 AC meeting.

Three complicated cases of mesenteric vasculopathy were reported in conjunction with Lotronex use. These cases are "confounded" but represent true use of a drug product once approved. One patient (Case #68) had a history of a DVT and had a Factor V Leiden hypercoagulable state. Case #66 had a pre-existing history of ischemic bowel, had discontinued Lotronex for an uncertain amount of time prior to developing a superior mesenteric artery thrombosis and died. Case #67 had a presumptive diagnosis of mesenteric ischemia/thrombosis with a normal CT scan and colonoscopy 3 days later.

5. GlaxoWellcome's arguments concerning the cases

In the meeting with GlaxoWellcome on November 13, 2000, the sponsor presented a rebuttal of all cases reported on Lotronex associated with mesenteric vasculopathy, death, and surgery. An argument that GlaxoWellcome advanced was to differentiate between "primary" and "secondary" ischemic colitis or colon ischemia. Their consultant, Dr. Lawrence Brandt of Montefiore Medical Center, indicated that 70% of cases are usually transient, reversible, spontaneous, do not recur and are classified as primary ischemic colitis. Dr. Brandt indicated that 30% of cases of colon ischemia are due to secondary ischemia that is irreversible and the result of mechanical issues like stricture, toxic dilation of the colon, and distention. Their contention was that all the cases of "ischemia" identified by FDA were of the secondary ischemia variety and could therefore be eliminated via proper identification and management of constipation. Their contention was that none of the cases the FDA classified as ischemic colitis were of the primary ischemic colitis variety. They do not agree that primary ischemic colitis has led to death or sequelae.

It is irrelevant whether the ischemia is classified as "primary" or "secondary" and this distinction is arbitrary. It is more likely that ischemic colitis represents a spectrum of severity rather than two separate disorders. If secondary ischemia occurs only in the situation where there is mechanical obstruction, if the obstruction is severe enough and of long enough duration, the bowel will dilate, the wall will thin, necrosis, and perforation will result. Colon ischemia, as defined by their consultant, occurs most commonly in the elderly who are otherwise healthy, is not painful, is accompanied by rectal bleeding and bloody diarrhea. It is not true that all the cases of ischemic colitis identified by FDA were "secondary" (using Dr. Brandt's terminology). The first three cases seen in the NDA studies were all of the relatively mild, reversible, "primary" type.

In the surgical bowel resection cases, 7 involved resection of the sigmoid colon only, 1 involved the sigmoid and left colon, 1 involved the right colon, and 1 involved the right and transverse colon.

Of the 3 cases (Cases #64, 21, & 43) that resulted in death (Table 5), 2 had presenting symptoms of abdominal pain, only one had constipation, and none had bloody diarrhea. Therefore, constipation cannot accurately predict risk in those patients who died. Case #64 had "colonic obstruction leading to dilatation and death" per GlaxoWellcome. Ogilvie's syndrome is characterized by massive dilation of the colon in the absence of a mechanical obstruction. This patient had Alzheimer's disease, no report of constipation or bloody diarrhea and was admitted due to change in her mental status. Her pathology report indicated ischemic colitis with necrosis. She underwent surgery within 10 hours of presentation to the ER and died within 4 days of surgery.

Case #21 was a 70 y.o. female with a history of IBS and diverticulosis who took Lotronex for 18 days, stopped it, was given Lomotil (ER report indicates that only one dose was taken), and presented to the ER 3 days after stopping Lotronex. A CT scan performed at admission to the hospital indicated a colonic perforation with abscess, diverticular disease and free air in the abdomen. She underwent a sigmoid colon resection that revealed a transmural perforation with ischemic colitis and she had stool in her pelvis. Her pathologic report indicated a recent thrombus in the mesenteric artery and vein, with no emboli or vasculitis. She had surgery within 12 hours after presentation and died less than 24 hrs following surgery. The sponsor argued that she had a hypotensive episode in the ER and that the colon ischemia was secondary and the colon perforation was due to diverticular disease.

Case #43 had an upper GI bleed possibly due to alendronate therapy. She did not have surgery, but repeat CT scan indicated gas in the portal vein and she was given supportive care.

One additional death case (Case #69) had indicated that the reporter was not sure if the patient was taking the drug around the time of illness. This patient had constipation and abdominal pain. She underwent colectomy for a ruptured colon and at surgery the entire colon was packed with solid stool.

Of the 10 surgery cases (including deaths, Table 5), 9 had presenting symptoms of abdominal pain, only 2 had presenting symptoms of constipation, and possibly 1 had bloody diarrhea. Therefore, once again, prospective complaints of constipation do not accurately predict risk in those patients who required surgery, and were found to be constipated at surgery.

Several illustrative surgical cases follow. Case #25 was treated with Lotronex, then stoppped, and was restarted following colonoscopy. Two weeks later she presented with abdominal pain and constipation. She underwent a colectomy and had evidence of ischemic colitis, bowel wall less than 0.1cm, and a colon full of stool. Case #61 had alternating type IBS, treated with 2 1/2 weeks of Lotronex. She presented with abdominal pain, no constipation, and underwent a colectomy for a perforated sigmoid colon and had fecal material in the abdomen. Case #65 had 1 month of Lotronex therapy and presented with abdominal pain and no constipation. She underwent a colectomy for a stercoral ulcer with perforation and ischemic necrosis and was noted at surgery to have copious amounts of hard stool in the colon. Case #74 had 6 weeks of Lotronex therapy; she presented with abdominal pain and no constipation. She had a colectomy and mural perforation of the colon with associated acute serositis was found on resection.

Of the 49 cases of ischemic colitis, only 9 (18%) had complaints of constipation at the time of event. Of the 21 cases of severe complications of constipation, 16 (76%) had complaints of constipation at the time of event. Constipation in the remaining cases was supported by radiologic, surgical, or pathologic evidence of constipation, i.e., colon full of hard stool. Obviously some patients that had severe complications of constipation were not able to recognize the signs or symptoms of constipation.

From a post-marketing risk management or a post-marketing safety assessment, it is irrelevant whether the ischemia is primary or secondary. The sponsor makes much of this distinction but we fail to see its importance.

6. GlaxoWellcome's argument that age is a risk factor

During the November 13, 2000 meeting, GlaxoWellcome acknowledged that the majority of the cases occurred in the "elderly" and that PRECAUTIONS for use in women over 65 would control the risk.

Two of the cases of ischemic colitis requiring surgery (Cases 25 & 74) were under 65 years of age and two of the cases of severe constipation requiring surgery (Cases 65 & 78) were under 65 years of age also (Table 2-2 & Table 5). Of the 49 cases of ischemic colitis, 36 (73%) were under 65 years of age. Of the 21 cases of severe complications of constipation, 12 (57%) were under 65 years of age.

The majority of cases as seen to date occurred in women less than 65 years of age. Therefore, a risk management program limiting use of Lotronex in women over 65 years of age will not prevent further occurrences of ischemic colitis or complications of constipation.

7. GlaxoWellcome's argument that controlling constipation will manage the risk

During the November 13, 2000 meeting with GlaxoWellcome, they did acknowledge that severe constipation results in significant morbidity and mortality. They claimed that controlling constipation will manage the risk of Lotronex therapy.

As summarized in Section 4 above, of the 3 cases that resulted in death, 2 had presenting symptoms of abdominal pain, only one had constipation, and none had bloody diarrhea (Table 5).

Of the 10 surgery cases (including deaths Table 5), 9 had presenting symptoms of abdominal pain (patient not reporting pain had Alzheimer's disease), only 2 had constipation complaints in the ER, and possibly 1 had bloody diarrhea. Of those cases that were classified as severe constipation, only 1 had constipation as a presenting symptom. In 3 cases the surgeon indicated that the colon was packed with stool at the time of surgery (i.e., constipated), and 1 case had radiologic evidence of impaction. These cases also clearly indicate that some of the patients with severe complications of constipation were unable to recognize constipation. Therefore, constipation would not have accurately predicted serious risk in those patients who died or required surgery.

Case #78, is a 39 year old female who was found at surgery to have extremely hard stool within the colon and sigmoid as well as formed stool in her abdominal cavity that had eroded into the abdomen. She underwent a second surgery 7 days later and pathology indicated ischemic necrosis of the bowel wall. In the case report, she did not have constipation nor did she verbalize complaints of constipation.

Case #65, is a 57 year old female who had a perforated sigmoid colon from a stercoral ulcer. Preoperative X-ray revealed copious amounts of stool throughout the colon. She underwent a colectomy and had large amounts of hard stool noted at surgery. On admission she was able to pass very small amounts of soft stool and no complaint of constipation was recorded.

Cases #78 & #65 above illustrate two cases that required surgery in which prospective constipation was absent as a presenting symptom. Once again, any risk management

program targeted to identify and manage constipation will be unsuccessful in managing the risk of serious adverse outcomes associated with Lotronex use.

8. Adverse and serious adverse events with other drugs, specifically those used to treat IBS

GlaxoWellcome argued at the November 13, 2000 meeting that there are serious adverse events associated with other drugs used to treat IBS. They cited the drug label Contraindications, Warnings, and Precautions sections of the labels for Bentyl (dicyclomine), Imodium (loperamide), Levsin (hyoscyamine), and Lomotil (diphenoxylate). In addition, they indicated that FDA AERS reports included complications of constipation, such as ileus, impaction, obstruction, and colitis for amitriptyline, diphenoxylate, and loperamide. They also included a table of "Deaths" from AERS 1969 - June 30, 2000 (a 31 year period) for Dicyclomine (30), hyoscyamine (32), loperamide (25), diphenoxylate (63), bismuth subsalicylate (19), and amitriptyline (382). The sponsor did not present any evaluation of the relevance of these reports, for example, the cause of death, concomitant medications, or disease being treated.

OPDRA evaluated the raw number of reports received in AERS from 1969 to present for 21 selected serious gastrointestinal events for several agents (loperamide, amitriptyline, diphenoxylate, hyoscyamine, and diclyclomine) used in IBS (Table 6).* There is extensive market experience with 3 of these 5 products: loperamide (approved 1976), amitriptyline (approved 1961) and dicyclomine (approved 1950). With loperamide there are 204 total reports of constipation, including 1 report of death, and 7 reports of hospitalization. With amitriptyline there are 78 total reports of constipation, including 4 reports of death, and 13 reports of hospitalization. With dicyclomine there are 10 total reports of constipation, including no reports of death, and 2 reports of hospitalization. In the 4 different intestinal perforation event categories, there are 8 total reports for loperamide, including 1 report of death, and 8 reports of hospitalization; there are 2 total reports for amitriptyline, including no reports of death, and 2 reports of hospitalization. In contrast there are no reports of intestinal perforation for dicyclomine or hyoscyamine. In the 3 different hemorrhagic colitis event categories, there was 1 report for loperamide, including 1 report of death and 1 report of hospitalization; there are 3 total reports for amitriptyline, including 2 reports of death and 2 reports of hospitalization. Again, there are no reports with this event for dicyclomine or hyoscyamine. With loperamide, there are 5 total reports of rectal bleeding, including no reports of death, and 1 report of hospitalization. With amitripyline, there are 2 total reports of rectal bleeding, including no reports of death, and 2 reports of hospitalization. With diphenoxylate, there is 1 total report of rectal bleeding, including no reports of death, and 1 report of hospitalization. Again, there are no reports of rectal bleeding for dicyclomine and hyoscyamine.

OPDRA evaluated the distribution of cases of ischemic colitis in AERS from November 1997 through October 2000 (Figure 3-1). Ischemic colitis as a search term in AERS did not exist before November 1997. A raw total of 180 cases of ischemic colitis was identified.* Forty-eight cases (27%) were associated with Lotronex, 7% with Imitrex, 4% with Premarin, and the remaining 62% with 78 different drugs. NO cases of ischemic colitis were identified for any other drugs used "off-label" to treat IBS, including Imodium, Lomotil, Valium, Librium, Levsin, and Levsinex. NO cases of ischemic colitis were identified with other 5-HT3 receptor antagonists, including Zofran (ondansetron),

* This data was generated using computer printouts, and some of the numbers may reflect duplicate reporting.
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Kytril (granisetron), and Anzemet (dolasetron). It should be recognized that these 5-HT3 receptor antagonists are currently approved for the prevention/treatment of emesis induced by cancer chemotherapy or preoperatively, and therefore are not used chronically like Lotronex, but only as single-dose or short-term treatment.

The argument that publicity has increased the number of reports can be refuted in that Rezulin has only one case of drug-associated ischemic colitis despite over 213 articles in major newspapers that discussed the drug and associated risk (Table 3-2). Two drugs already known to cause ischemic colitis, Imitrex and Premarin, have 12 and 8 reports respectively**.

9. Restricted Access Program for Lotronex

At the November 13, 2000 meeting, GlaxoWellcome mentioned a certification/education program similar to Accutane, although the details were not available. The Division of Gastrointestinal and Coagulation Drug Products presented a succinct summary of the limitations of such a program at the November 7, 2000 briefing to Dr. Woodcock. A restricted distribution plan will not manage the risk, but will only decrease the number of patients exposed and hence decrease the number of patients with a serious adverse outcome due to Lotronex. The risk is not managed, because the risk factors for serious adverse outcome have not been identified or categorized.

10. IBS is being minimized

One of GlaxoWellcome's consultants, Dr. Emeran Mayer of the UCLA Division of Digestive Diseases, indicated that some people may look at IBS as "not a real disease" or a "trivial disease". IBS is truly a disease that has significant morbidity and compromises the quality of life of some patients. The natural history of IBS however is not comprised of bleeding that requires transfusion (Case #15 & #73) or surgery for constipation, either with (Cases #9, #21, #25, #64, #74) or without (Cases #58, #61, #65, #69, #78) resultant bowel ischemia. IBS is not associated with ischemic colitis if untreated. IBS does not lead to surgery, does not shorten the life span and does not cause death. Differentiating the symptoms of IBS from the symptoms due to the serious adverse consequences of Lotronex therapy is impossible. Early warning of the dire side effects of this drug is clearly not feasible.

11. CONCLUSIONS

The warning signs and symptoms of ischemic colitis or colonic ischemia are not always clear, not always typcial, and do not always occur. The reversibility or moderation of ischemic colitis or colonic ischemia has not been established. The signs and symptoms of an adverse effect are too similar to those of the disease being treated and/or the desired pharmacologic effect (i.e., "constipation" to relieve diarrhea). Constipation is **not** necessarily the major risk factor for ischemic colitis or colonic ischemia or colon resection. Any risk management program entirely centered on predicting and preventing constipation will not manage the risk from Lotronex therapy. The basic premise of the entire risk management program is as follows: if you can predict constipation, you can manage constipation, and if NOT, you undermine the whole risk management program.

** This information is from IMS HEALTH National Prescription Audit Plus (NPA) ™ and National Disease and Therapeutic Index (NDTI) ™ and is not to be used outside of the FDA without prior clearance from IMS HEALTH.

The only acceptable risk management program would have to show promptly and persuasively a cessation of deaths, colectomies, severe and serious complications of treatment that were unknown in the long history of IBS in patients taking other therapy, whether or not those therapies were effective.

From our analysis there are no known risk factors to predict either ischemic colitis or severe constipation, so any risk management strategy that focuses on the patient's age or the management of constipation will fail to manage the risk in the majority of patients exposed to Lotronex.

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ATTACHMENT 1

# WHAT IS KNOWN ABOUT THE RISK OF ALOSETRON

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***OPDRA Alosetron Risk Assessment Group***

***November 13, 2000***

1. *Four Key Questions:*
   - ***(a) What is known about the risk of alosetron now?***
   - ***(b) What has changed regarding patterns of alosetron-associated ischemic colitis or severe constipation since the GI Advisory Committee meeting on June 27, 2000?***
   - ***(c) What is the evidence that those adverse events and associated serious outcome, such as bowel surgery and death are drug related?***
   - ***(d) Is a risk management strategy feasible?***

2. *Methodology:*
   - *(a) Data Source:*
     - ***(1) Data provided by Adverse Event Reporting System (AERS) at FDA***
     - ***(2) Drug utilization data provided by IMS Health***
   - *(b) Case Definition:*
     - *(4) Ischemic Colitis:* ***A diagnosis of ischemic colitis, ischemic changes or necrosis of colon based on any or a combination of the following: (1) clinical judgement, (2) endoscopic examination or (3) pathology report;***
     - *(5) Severe Constipation:* ***constipation or suspected constipation that led to ER visit, hospitalization, or complications, including but not limited to, fecal impaction, bowel obstruction, necrosis or rupture.***
   - *(c) Inclusion Criteria:*
     ***All ischemic colitis and/or severe constipation cases reported to FDA through MedWatch or by Glaxo Wellcome before November 10, 2000.***
   - *(d) Exclusion criteria:*
     ***The key event cannot be independently verified by FDA.***

3. *Findings:*
   - ***(a) Risk of alosetron: two dimensions - incidence and severity. This assessment focuses on severity. Refer to question A (page 2).***
   - ***(b) Changes since AC meeting on June 27, 2000: Increased severity. Refer to Question B (page 3).***
   - ***(c) Evidence supporting a causal relationship: Epidemiological and Individual Assessment; Refer to question C (page 4-6).***
   - ***(d) Current risk management strategies: Refer to Question D (page 7).***

4. *Conclusions:*
   - ***(a) The pattern of reported cases of ischemic colitis cannot be reasonably explained by anything but a true effect between the drug and the event;***
   - ***(b) Death is no longer a speculation or a remote possibility, but a reality. The cases of ischemic colitis that led to necrotic or ruptured bowel requiring surgery are also a reality;***
   - ***(c) No pattern has emerged with regard to factor or factors that can provide a meaningful prediction for those patients who developed ischemic colitis or constipation that required surgery.***

*Question A: What is known about the risk of alosetron now?*

**Table 1-1.** Number of alosetron-associated cases of ischemic colitis and severe constipation, United States, cumulative, week ending November 10, 2000 (36th week of the marketing)

| **Key Adverse Events** | Ischemic colitis | Severe constipation | Total |
|---|---|---|---|
| Number of reported cases | 49 | 21 | 70 |
| Cumulative number of prescriptions* | 435,000 | | |
| Report rate per million prescriptions | 113 | 48 | 161 |

* Estimated number of prescriptions dispensed between March and October 2000. Data was provided by Glaxo Wellcome at a Safety Presentation to FDA's GI division on October 25, 2000

**Table 1-2.** Severity of alosetron-associated cases of ischemic colitis and severe constipation, United States, cumulative, week ending November 10, 2000 (36th week of marketing)

| **Selected Outcomes**[1] | **Key Adverse Events**[1] | | | |
|---|---|---|---|---|
| | Ischemic Colitis (n=49) | | Severe Constipation (n=21) | |
| | Number | Percentage | Number | Percentage |
| ER visit without hospitalization | 2 | 4% | 2 | 10% |
| Hospitalization | 30 | 65% | 14 | 67% |
| Blood transfusion without surgery | 1 | 2% | 1 | 5% |
| Bowel obstruction without surgery | 0 | 0 | 6 | 29% |
| Disimpaction performed | 0 | 0 | 3 | 14% |
| Surgery due to obstructed, necrotic, or ruptured bowel | 5 | 11% | 5 | 24% |
| Death[2] | 2 | 4% | 1 | 5% |

1. Selected outcomes are not mutually exclusive; the key adverse events are mutually exclusive.
2. There were two additional death cases that did not meet the criteria; therefore, the total number of death cases as of November 10, 2000 is five.

**Table 1-3.** Diagnostic certainty of alosetron-associated cases of ischemic colitis, United States, cumulative, week ending October 28, 2000 (34th week of marketing)

| **Diagnostic Certainty of Ischemic Colitis** | **Number** | **Column Distribution** | **Cumulative Distribution** |
|---|---|---|---|
| Both histological and endoscopical evidence of ischemic colitis or ischemic change or necrosis | 14 | 29% | 29% |
| Endoscopical evidence of ischemic colitis or ischemic change or necrosis | 8 | 16% | 45% |
| Histological evidence of ischemic colitis or ischemic change or necrosis | 13 | 27% | 72% |
| Radiological evidence of ischemic colitis or ischemic change or necrosis | 3 | 6% | 78% |
| Ischemic colitis without above evidence* | 11 | 22% | 100% |
| Total number of cases | 49 | 100% | |

* Among those 11 cases, one was a surgical case that will be discussed later. Five cases had both abdominal pain and bloody diarrhea. Only one of those cases was a direct report from consumer.

*Question B: What has changed since the GI Advisory Committee meeting on June 27, 2000?*

**Table 2-1.** Changes in severity of alosetron-associated provisional cases of ischemic colitis and severe constipation, United States, before and after Advisory Committee Meeting on June 27, 2000 (includes post-marketing, non-study cases only).

| Selected Outcomes | Ischemic Colitis | | Severe Constipation | |
|---|---|---|---|---|
| | Pre-AC Meeting (n=5) | Post-AC Meeting (n=44) | Pre-AC Meeting (n=4)* | Post-AC Meeting (n=17) |
| Blood transfusion without surgery | 0 | 1 | 0 | 1 |
| Surgery due to obstructed, necrotic, or ruptured bowel | 0 | 5 | 2 | 3 |
| Death | 0 | 2 | 0 | 1 |

**** The original number was five cases; one of the constipation cases did not meet the case definition.***

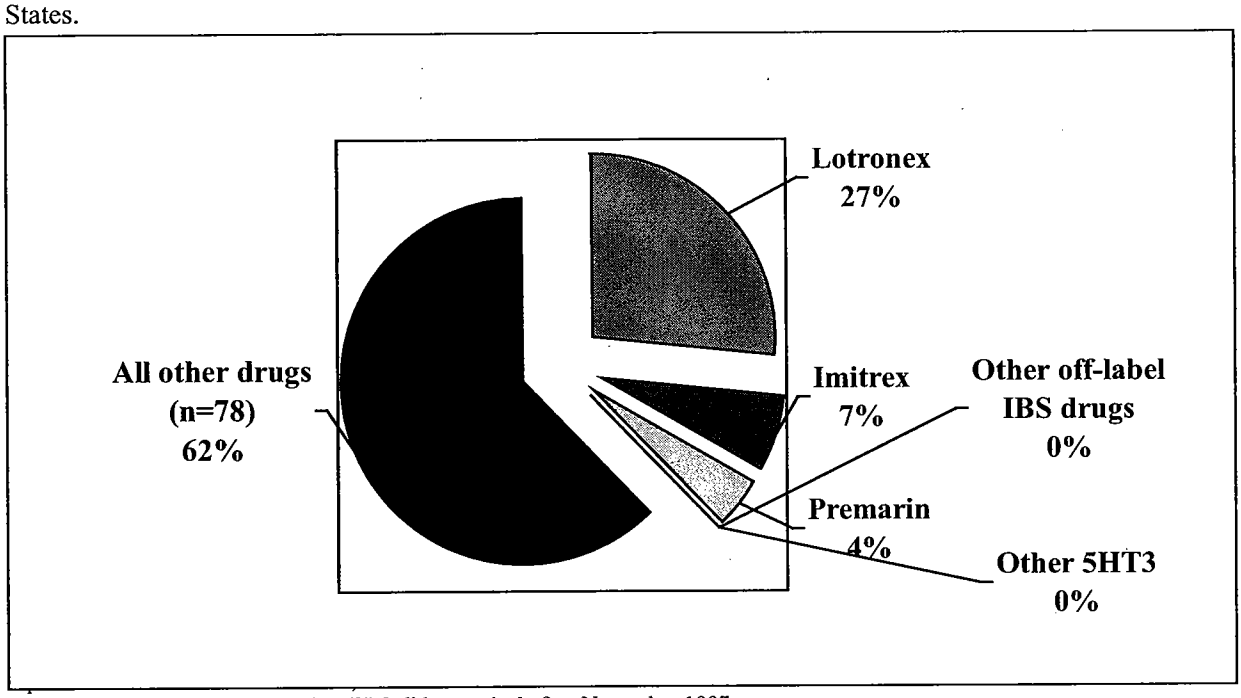
**Table 2-2.** Changes in severity of alosetron-associated surgical cases of ischemic colitis and severe constipation, United States, before and after Advisory Committee Meeting on June 27, 2000 (includes post-marketing, non-study cases only).

| Items | Number of Reported Cases | |
|---|---|---|
| | Before Advisory Committee Meeting (n=2) | After Advisory Committee Meeting (n=8) |
| Age: % < 65 years old | 0/2 | 4/8 |
| Colectomy | 1/2 | 8/8 |
| Sigmoid colon only | 2/2 | 5/8 |
| Death | 0/2 | 3/8 |

*Question C: What is the evidence that those adverse events and associated serious outcome, such as bowel surgery and death, are drug related?*

## 1. Epidemiological Assessment:

**Figure 3-1.** Distribution of reported cases of ischemic colitis* by the suspected drug, according to FDA's Adverse Event Reporting System (AERS) data** between November 1997 and October 2000, United States.




Ischemic colitis as a search term in AERS did not exist before November 1997.

* * Note that no reports of ischemic colitis were found in AERS between November 1997 and October 2000 for other drugs used "off-label" to treat IBS (e.g. Imodium, Lomotil, Valium, Librium, Levsin, and Levsinex) or other 5-$HT_3$ drugs, including Zofran, Kytril, and Anzemet.

*Table 3-1.* ***Reported cases of drug-associated ischemic colitis per million prescriptions for selected drugs, AERS and IMS data, United States, November 1997 and October 2000***

| | Lotronex | Imitrex | Premarin |
|---|---|---|---|
| Date of Approval | 2/9/00 | 12/28/92<br>6/1/95 | Prior 82 |
| Reported Cases | 49 | 12 | 8 |
| Surgical cases | 5 | 1 | 0 |
| Estimated number of prescriptions (X 1,000)* | | | |
| Reported rate of ischemic colitis per million prescriptions | | | |

**** Estimated number of prescriptions dispensed between November 1997 and October 2000. Data cannot be released from FDA without prior approval from IMS Health.***

*Table 3-2.* ***Reported cases of drug-associated ischemic colitis per million prescriptions for selected drugs, AERS and IMS data, United States, November 1997 and October 2000.***

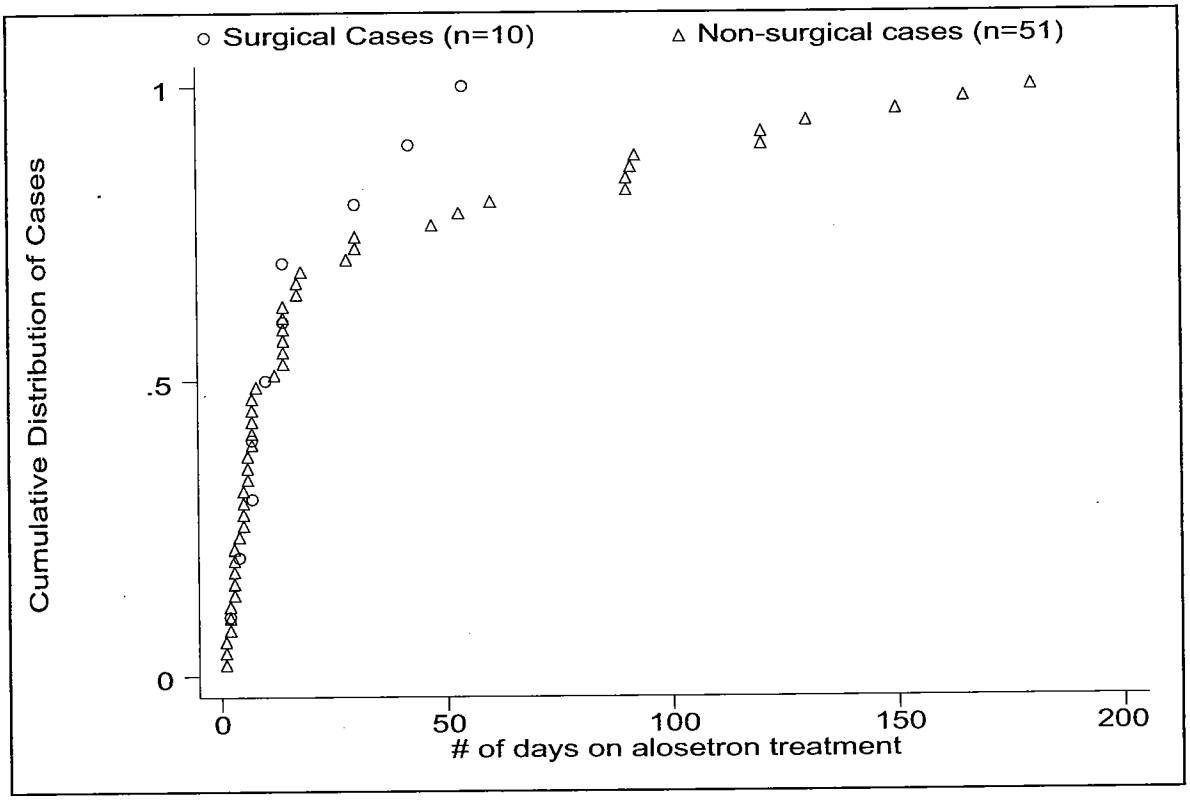
| | Lotronex | Vioxx | Rezulin | Lotronex* |
|---|---|---|---|---|
| Date of Approval | 2/9/00 | 5/20/99 | 1/29/97 | 2/9/00 |
| Media Effect† | 17 articles | -- | 213 articles | 1 article |
| Reported Cases | 49 | 5 | 1 | 23 |
| Surgical cases | 5 | | | 1 |
| Estimated number of prescriptions (X 1,000)$ | | | | |
| Reported rate of ischemic colitis per million prescriptions | | | | |

* Lotronex-associated ischemic cases reported before August 31, 2000.

† Articles that appeared in major newspapers that discussed the drug and associated risk.

***$ Estimated number of prescriptions dispensed between November 1997 and October 2000. Data cannot released from FDA without prior approval from IMS Health.***

**Figure 3-2.** Cumulative distribution of alosetron-associated surgical and non-surgical cases by reaction onset (days), United States, week ending October 28, 2000.



## 2. Individual Assessment:

### (a). FDA CASE #9 (Manufacturer control number A0121632A)

A 69-year-old female, one week after the treatment with Lotronex, developed an epidsode of ischemic colitis at transverse colon that was supported by both colonscopy and pathology report. The drug was reported to be discontinued. Approximately 6 weeks later, she was hospitalized with abdominal pain. Patient underwent a right hemicolectomy associated with large bowel obstruction secondary to ischemic stricture at mid transverse colon. Pathology report confirmed a broad area of acute ulceration that is compatible with ischemic colitis of right colon. Occasional small vessels with a thrombus are seen at the base of the ulcer. Patient had a normal colonscopy examination on December 15th,1999. On March 17, she was diagnosed by her GI specialist as having IBS and started Lotronex 1 mg b.i.d. One month after the first episode of ischemic colitis, her GI specialist raised a possibility of ulcerative colitis or Crohn's colitis due to unclers on her right hip and abdomen. One week later, GI specialist also raised a possibility a vasculitis with immune complex disease. Only diagnostic test received at FDA was a pathology report on 5/9/00 that showed epidermal ulceration with eschar formation on a specimen from right midtrunk. There is no evidence to suggest vasculitis.

**Chain of Events: Drug-induced ischemic colitis - stricture at prior ischemic site - bowel obstruction - colectomy**

### (b). Ischemic colitis case: (FDA case #21, manufacturer number A0126868A)

A 70-year-old female, a week after beginning treatment with Lotronex, presented to ER with a sudden onset of abdominal pain, nausea and vomiting, but no bloody diarrhea. An X-ray showed normal bowel gas pattern and stool within the large bowel. CT showed evidence of large pelvic and lower abdominal abscess most likely related to diverticulitis. The patient became hypoxic, hypotensive, and acidotic; she was intubated in the ER and brought for an emergency surgery where a perforated sigmoid colon was found with solid stool in the pelvis. A sigmoid colon resection with colostomy was performed and the pathology report showed ischemic colitis and transmural perforation with associated diverticulosis. Diverticulitis was not mentioned in the pathology report. Mesenteric vein and arteries showed recent thrombus; but were negative for emboli and tumor. The patient became septic and died on the second hospital day. She was in good health over all and had no history of diabetes and heart disease. She was taking estrogen but had been on it as long as her primary care physician could remember. The manufacturer's follow-up report stated that the physician suspected that the events could have been due to impaction and were possibly related to the use of alosetron.

**Chain of Events: Drug-induced ischemic colitis - secondary infection - rupture - colectomy**

*Question D: Is a risk management strategy feasible?*

**Table 4-1.** Indications, contraindications and presenting symptoms for patients who required surgery and/or died.

| Items | Ischemic colitis | Severe Constipation |
|---|---|---|
| Indications | | |
| Female | 5/5 | 5/5 |
| Diarrhea-predominant IBS | 4/5 | 4/5 |
| Contraindications | | |
| Current constipation | 0/5 | 0/5 |
| History of chronic, severe constipation; obstruction; toxic megacolon; GI perforation; adhesions; ischemic colitis or active diverticulitis | 0/5 | 0/5 |
| Presenting symptoms at ER | | |
| Abdominal pain | 4/5 | 5/5 |
| Bloody diarrhea | 0/5 | 1/5 |
| Constipation | 1/5 | 1/5 |

## 2. Illustrative cases of constipation:

**Case #78:** A 39-year-old female presented to the ER because of sudden onset of severe abdominal pain. While in the ER, she became hypotensive and was intubated. It was reported that the ***patient did not have constipation nor did she verbalize complaints of constipation.*** However, during exploratory laparotomy she was found to have an extremely hard stool within the colon. It appeared that the stool had eroded into the abdomen, as formed stool was discovered. The area at the perforation was noted to have complete ischemic necrosis. A sigmoid colectomy was performed.

**Case #65:** A 57-year-old female, 4 weeks after beginning treatment with Lotronex, presented to the ER due to crampy abdominal pain that had started five days earlier. ***She was able to pass very small amounts of soft stool at admission and no complaint of constipation was recorded.*** However, X-ray revealed copious amounts of stool throughout the colon. One day later, she was taken to surgery and perforated stercoral ulcer of the sigmoid colon was found. The patient's colon was found to have copious amounts of hard stool.

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Table 5. Characteristics of the Ten Surgical Cases

| **Characteristics of Surgical Cases** | **Case #9** | **Case #21** | **Case #25** | **Case #64** | **Case#74** | **Case #58** | **Case #61** | **Case #65** | **Case #69[3]** | **Case #78** |
|---|---|---|---|---|---|---|---|---|---|---|
| FDA Classification | Ischemic colitis | Ischemic colitis | Ischemic colitis | Ischemic Colitis | Ischemic Colitis | Constipation | Constipation | Constipation | Constipation | Constipation |
| **Presenting symptom (ER)** | | | | | | | | | | |
| Abdominal pain | Yes | Yes | Yes | No[1] | Yes | Yes | Yes | Yes | Yes | Yes |
| Bloody diarrhea | -- | -- | -- | -- | -- | -- | -- | -- | -- | Yes[6] |
| Constipation | -- | -- | Yes | -- | -- | Yes | --[5] | -- | -- | -- |
| **Clinical impression (before surgery)** | Ischemic colitis | Diverticulitis | Not Available | Acute abdomen, bowel obstruction | Probable ischemic colitis or a colitis with perforation | Sigmoid diverticulitis | Not available | Colonic atony secondary to Lotronex | Acute abdomen, r/o diverticulitis; r/o ischemic bowel | Not available |
| **Radiologic examination** | Not available | CT revealed a perforated colon | x-ray showed no free air, no dilation; colon full of stool | x-ray showed distended loops of small bowel | CT: thickened colon at descending colon | x-ray showed that colon was full of stool | CT showed air fluid levels and a mass outside the bowel | Copious amounts of stool in colon; no diverticulitis | CT showed some bowel wall thickening | Not available |
| **Endoscopic examination** | Ischemic colitis | Not done | Not done | Not done | Not done | Not done | Not done | Not done | Not done | Not done |
| **Report of Operation** | (on 6/5/00, 6 weeks after this episode); bowel obstruction due to ischemic stricture at transverse colon | Perforated colon at the rectosigmoid partially contained within the mesentery, however, evidence of frank feculent peritonitis | Not available | Ogilvie's syndrome[2] with necrotic sigmoid | Sigmoid colitis with air in the mesentery and mesenteric infection | Not available | Perforated sigmoid colon and fecal material in the peritoneum | No sign of ischemic change of diviticulitis; Stercoral ulcer of colon | Ruptured colon; entire colon packed with solid stool, feeling like a rock | Extremely hard stool within colon and sigmoid; it appeared that stool had eroded into the abdomen |
| **Pathology report** | Not available for this episode; however surgical specimen on 6/5/00 showed right colon - consistent with ischemic colitis | Ischemic colitis including transmural perforation; associated diverticulos-is; Mesenteric veins and arteries showed recent thrombus | Change consistent with ischemic colitis; Bowel wall thinned in many areas to the point of near translucency | Mucosal erosion with gland atrophy and acute inflammation suggestive of an ischemic colitis | Mural perforation of colon with associated acute serositis; acute fat necrosis and pericolic microabscess formation | Not done at time of surgery | Not available | Ulcer with perforation and necrosis (sigmoid colon); acute ulcer and necrosis with ischemic changes (left colon) | Diverticu-losis and diverticulitis with perforation | Two segments of colon showing focal area of perforation and peritonitis associated with epithelial invagination |

**Table 5.** (Continued)

| Characteristics of Surgical Cases | Case #9 | Case #21 | Case #25 | Case #64 | Case#74 | Case #58 | Case #61 | Case #65 | Case #69[3] | Case #78 |
|---|---|---|---|---|---|---|---|---|---|---|
| Demographics | | | | | | | | | | |
| **Age** | 69 | 70 | 54 | 67 | 48 | 68 | 72 | 57 | 82 | 39 |
| Gender | F | F | F | F | F | F | F | F | F | F |
| Indication[7] | Yes | Yes | No | Yes | Yes | Yes | No | Yes | Yes | Yes |
| Date of Event | 3/22/00 | 7/31/00 | 8/15/00 | 9/9/00 | 8/18/00 | 4/7/00 | 4/6/00 | 8/29/00 | 8/24/00 | 6/17/00 |
| Date of Initial Report | 6/12/00 | 9/6/00 | 9/11/00 | 10/8/00 | 9/7/00 | 5/3/00 | 5/23/00 | 10/3/00 | 10/10/00 | 7/7/00 |
| **Drug Exposure Data** | | | | | | | | | | |
| Days on Rx before the key GI event | 7 | 7 | 14 | 54 | 42 | 2 | 4 | 30 | 10 | 14 |
| Dose | 2 mg/day | 2 mg/day | Unknown | 1 mg/day | 2 mg/day | 2 mg/day | 2 mg/day | 2 mg/day | 2 mg/day | 2 mg/day |
| **Surgical Information** | | | | | | | | | | |
| Location of necrotic or ruptured colon | Right and transverse | Sigmoid | Right | Sigmoid | Sigmoid | Sigmoid | Sigmoid | Sigmoid and left | Sigmoid | Sigmoid |
| Type of surgery | Colectomy | Colectomy | Colectomy | Colectomy | Colectomy | Colostomy | Colectomy | Colectomy | Colectomy | Colectomy |
| Mesenteric artery/vein Thrombus | Yes | Yes | -- | No | No | -- | -- | No | No | No |
| **Potential Confounding** | | | | | | | | | | |
| Estrogen | Yes | Yes | -- | Yes | -- | -- | -- | -- | -- | -- |
| Diverticulitis | No | No | No | No | No | No | -- | No | Yes | No |
| Diverticulosis | No | Yes | No | No | No | Yes | -- | No | Yes | No |
| Others | Vasculitis ? | No | Raynaud's syndrome ? | Ogilvie's syndrome[2] | No | Polyps | No | No | No | No |
| Physician assessment re. association of event with alosetron | -- | Possible | -- | -- | Possible[4] | -- | Possible | Possible[4] | Not related | Possible |
| Prior colonscopy before treatment | Negative | Diverticu-losis, polyps | -- | -- | Negative | -- | -- | -- | Diveticulosis | -- |
| **Death** | No | Yes | No | Yes | No | No | No | No | Yes | Yes |

1. Patient had Alzheimer's disease and was not be able to provide this information.
2. Ogilvie's syndrome (acute pseudo-obstruction of the colon) is a massive colonic distention in the absence of a mechanically obstructing lesion.
3. Case #69 is a legal case.
4. As stated in the medical records.
5. Patient did complain of constipation in the Dr.'s office.
6. Small amount of fresh blood in stool.
7. Labeling followed when alosetron was prescribed (e.g., females with diarrhea-predominant IBS).

**Table 6. SELECTED GASTROINTESTINAL EVENTS FOR SELECTED AGENTS USED IN IRRITABLE BOWEL SYNDROME (IBS) FROM THE ADVERSE EVENT REPORTING SYSTEM (AERS)[1]**

| | Total # / # Deaths / # Hospitalized | | | | |
|---|---|---|---|---|---|
| **EVENT (MEDRRA PREFERRED TERM)** | **LOPERAMIDE IMODIUM® AND OTHERS Approved 1976** | **AMITRIPYLINE ELAVIL® AND OTHERS Approved 1961** | **DIPHENOXYLATE / ATROPINE LOMOTIL®[2] AND OTHERS** | **HYOSCYAMINE LEVSIN®[3] AND OTHERS** | **DICYCLOMINE BENTYL® AND OTHERS Approved 1950** |
| SOC GASTROINTESTINAL DISORDERS: TOTAL | 1635/49/159 | 771/58/173 | 82/9/22 | 77/1/22 | 137/1/10 |
| COLITIS HAEMORRHAGIC | 1/1/0 | 2/2/1 | 1/1/0 | 0 | 0 |
| COLITIS NOS | 14/0/12 | 5/1/3 | 3/0/1 | 0 | 1/0/0 |
| COLONIC HAEMORRHAGE | 1/0/1 | 0 | 0 | 0 | 0 |
| COLITIS ISCHAEMIC[4] | 0 | 1/0/1 | 1/1/1[5] | 0 | 0 |
| COLONIC PERFORATION | 2/0/2 | 0 | 1/1/1 | 0 | 0 |
| CONSTIPATION | 204/1/7 | 78/4/13 | 5/0/0 | 2/0/0 | 10/0/2 |
| FECAL IMPACTION | 5/0/3 | 3/0/3 | 1/1/1 | 1/0/1 | 0 |
| GASTROINTESTINAL NECROSIS | 2/0/1 | 2/0/2 | 0 | 0 | 0 |
| GASTROINTESTINAL OBSTRUCTION | 1/0/1 | 3/1/3 | 0 | 0 | 0 |
| ILEUS | 53/11/25 | 15/2/9 | 10/0/3 | 2/0/2 | 3/0/2 |
| ILEUS PARALYTIC | 4/2/1 | 3/1/2 | 0 | 0 | 0 |
| INTESTINAL OBSTRUCTION NOS | 27/1/21 | 10/2/8 | 3/0/2 | 1/0/1 | 0 |
| GASTROINTESTINAL PERFORATION | 0 | 0 | 1/0/1 | 0 | 0 |
| INTESTINAL PERFORATION NOS | 6/1/6 | 1/0/1 | 2/1/0 | 0 | 0 |

[1] Some of the numbers presented may reflect duplicate reports. One report may contain more than one event, so these numbers are not mutually exclusive. AERS contains data from 1969 to present. Data are reflective of information in AERS from approval date of drug (or from 1969 for drugs approved before that date) to 11/14/2000.

[2] Drug approved prior to 1969

[3] Hyoscyamine is a prescription drug available pre-1938 (no NDA; "Grandfather Drug")

[4] MedDRA Preferred Term (PT) Colitis Ischaemic available as term for coding adverse events November 1997

[5] This patient was a 70 yo female who also received Lotronex®.

| Total # / # Deaths / # Hospitalized | | | | | |
|---|---|---|---|---|---|
| **EVENT (MEDRRA PREFERRED TERM)** | **LOPERAMIDE IMODIUM® AND OTHERS Approved 1976** | **AMITRIPYLINE ELAVIL® AND OTHERS Approved 1961** | **DIPHENOXYLATE / ATROPINE** LOMOTIL®[2] AND OTHERS | **HYOSCYAMINE LEVSIN®[3] AND OTHERS** | **DICYCLOMINE BENTYL® AND OTHERS Approved 1950** |
| INTESTINAL ULCER PERFORATION | 1/0/1 | 0 | 0 | 0 | 0 |
| LARGE INTESTINAL PERFORATION NOS | 1/0/1 | 1/0/1 | 0 | 0 | 0 |
| RECTAL BLEEDING | 5/0/1 | 2/0/2 | 1/0/1 | 0 | 0 |
| SMALL INTESTINAL OBSTRUCTION NOS | 1/0/1 | 0 | 0 | 0 | 0 |
| SMALL INTESTINAL PERFORATION NOS | 0 | 0 | 0 | 0 | 0 |
| TOXIC DILATATION OF COLON | 1/0/1 | 0 | 0 | 0 | 0 |

Table 1. Summary of Six Cases of Small Bowel Ischemia Attachment B

| Characteristics of Small Bowel Ischemic Cases | ODS Case #43 Mfr# A0127461A | ODS Case #66 Mfr# A0123214A | ODS Case #68 Mfr# A0125536A | ODS Case # 149 Mfr# A0141438A | ODS Case # 152 Mfr# A0153528A | ODS Case #157 Mfr# A0133921A |
|---|---|---|---|---|---|---|
| **FDA Classification** | Small Bowel Ischemia | Small Bowel Ischemia | Small Bowel Ischemia | Small Bowel Ischemia | Small Bowel Ischemia | Small Bowel Ischemia |
| **Presenting symptoms (ER)** | | | | | | |
| Abdominal pain | Yes | Not mentioned | Yes | Yes | Yes | Yes |
| N/V | Yes | Not mentioned | Not mentioned | Yes | Not mentioned | Not mentioned |
| Bloody diarrhea | Not mentioned | Not mentioned | Not mentioned | Yes | No | Yes |
| Constipation | No | Not mentioned | Not mentioned | No | Not mentioned | Not mentioned |
| **Radiologic examination** | CT showed extensive air in relation to the wall of the stomach and the upper small bowel; appearance in keeping with necrotic changes in the stomach and upper small bowel | Not available | Not available | Arteriogram showed complete occlusion of the celiac and SMA arteries with stenotic but patent IMA | Not available | Unknown |
| **Endoscopic examination** | Pan upper endoscopic changes suggestive of severe diffuse ischemic process | Not mentioned | Not mentioned | Colonscopy: Question of ischemic and necrotic small bowel (4/24/00) | Unknown | Terminal ileum showing acute ulcerations, likely infectious enteritis (5/11/00) |
| **Report of Operation** | Not Done | Severe ischemia of the entire gastrointestinal tract with early necrosis of the small bowel and colon | A two-foot section of jejunum was resected | SMV bypass | SMV thrombosis, entire small bowel was infarcted requiring small bowel resection from proximal jejunum to distal ileum | A necrotic small bowel, presumably from superior mesenteric vein occlusion (5/14/00) |
| **Pathology report** | Not available | Not available | Small bowel resection-hemorrhagic gangrenous necrosis, secondary to mesenteric venous thrombosis | Small bowel biopsies: Necrotizing inflammatory changes consistent with ischemic injury (4/25/00) | Not available | Acute enderitits (5/12/00), small bowel and proximal colon with extensive henmorrhagic necrosis (5/14/00) |

| Characteristics of Small Bowel Ischemic Cases | Case #43 Mfr# A0127461A | Case #66 Mfr# A0123214A | Case #68 Mfr# A0125536A | Case # 149 Mfr# A0141438A | Case # 152 Mfr# A0153528A | Case #157 Mfr# A0133921A |
|---|---|---|---|---|---|---|
| Demographics | | | | | | |
| **Age** | 81 | 50-60 | 33 | 63 | 46 | 46 |
| Gender | F | F | F | F | F | F |
| Indication | IBS | IBS | IBS | D-IBS | IBS | IBS |
| Date of Event | 8/11/00 | 4/24/00 | 7/00 | 4/21/00 | 10/2/00 | 5/10/00 |
| Date of Initial Report | 9/8/00 | 7/5/00 | 8/14/00 | 4/14/01 | 1/12/01 | 12/19/00 |
| **Drug Exposure Data** | | | | | | |
| Days on Rx before the key GI event | 120 | Unknown, happened after the drug was discontinued | 2 | 10 | 4 hours after first dose | 4 |
| Dose | 2 mg/day | Unknown | 2 mg/day | 2 mg/day | 1 mg | 2 mg/day |
| **Surgical Information** | | | | | | |
| Location | Small bowel only | Small bowel and colon | Small bowel only | SMV bypass | Small bowel only | Small bowel and colon |
| Mesenteric artery/vein Thrombus | Unknown | Unknown | Yes | Yes | Yes | No |
| **Potential Confounding** | | | | | | |
| Estrogen | Report mentions oestradiol, therapy dates unknown | Report mentions conjugated estrogen, therapy dates unknown | Unknown | No | No | Yes |
| Hypercoaguable Disorder | Unknown | Unknown | Yes ? | Unknown | No | Unknown |
| Others | Fosamax, hx of Raynaud's Syndrome | Unknown | Hx of DVT Overweight | SMA stenosis 6 years ago; s/p angioplasty | No | Hx of narcotic drug abuse, Coumadin use |
| Physician assessment re. association of event with alosetron | Could not be determined | Not possible | Possible | Possible | Very likely | Possible |
| **Surgery** | No | Yes | Yes | Yes | Yes | Yes |
| **Death** | Yes | Yes | No | No | No | Yes |

# APPENDIX 4

November 27, 2001

GlaxoSmithKline

Mellon Client Services Center RM 670
Food and Drug Administration
Food and Drug Administration (360909)
500 Ross Street
Pittsburgh, PA 15262-0001

GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709
Tel. 919 483 2100
www.gsk.com

**Re: NDA 21-107; LOTRONEX® (alosetron hydrochloride) Tablets**
**User Fee ID Number — Supplemental New Drug Application with Clinical Data**

Please find enclosed GlaxoSmithKline check number 00854111 in the amount of $154,823.00. This payment represents 100% of the application fee for the Supplemental New Drug Application that is being filed with the Center for Drug Evaluation and Research, FDA.

Please find below, requested information regarding this application.

| | | |
|---|---|---|
| **Type of Application:** | New Drug Application with Clinical Data | |
| | New Drug Application without Clinical Data. | |
| | Supplemental New Drug Application with Clinical Data | X |

Should you have any questions, please contact me at (919) 483-3073. Thank you.

Sincerely,

Mark A. Baumgartner, R.Ph.
Director
Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

# USER FEE COVER SHEET

***See Instructions on Reverse Side Before Completing This Form***

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

SmithKline Beecham Corporation d/b/a GlaxoSmithKline
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101

2. TELEPHONE NUMBER *(Include Area Code)*

( 919 ) 483-2100

3. PRODUCT NAME

Lotronex® (alosetron hydrochloride) Tablets

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

N021107

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____ (APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
*(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
*(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
*(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
*(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
*(Self Explanatory)*

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO
*(See item 8, reverse side if answered YES)*

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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| SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE | TITLE | DATE |
|---|---|---|
| [signature] | Mark Baumgartner, R.Ph.<br>Director, US Regulatory Affairs | November 27, 2001 |

FORM FDA 3397 (4/01)

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GLAXOSMITHKLINE
FP0825
P.O. BOX 13681
PHILADELPHIA PA 19101-3681

GlaxoSmithKline

FOOD AND DRUG ADMINISTRATION
P.O. BOX 360909
PITTSBURGH PA 15259-0001

PAYMENT DATE 11/09/01


## STATEMENT OF REMITTANCE

| VOUCHER NO. | INVOICE NUMBER/REMARKS | INVOICE DATE | GROSS | DISCOUNT | NET |
|---|---|---|---|---|---|
| 02074487 | CR USER FEE<br>NDA 21-107 | 10/23/01 | 154,823.00 | | 154,823.00 |
| VENDOR NO.<br>00401882 | | | | | $154,823.00 |

DETACH AND RETAIN THIS STUB FOR YOUR RECORDS.

CHECK # 00854111 ATTACHED BELOW

THE AREA OF THE DOCUMENT CHANGES COLOR GRADUALLY AND EVENLY FROM LIGHT TO DARK WITH DARKER EDGES

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FP0825
P.O. BOX 13681
PHILADELPHIA PA 19101-3681

GlaxoSmithKline

VENDOR NO.

No. 00854111

11/09/01

PAY TO THE ORDER OF FOOD AND DRUG ADMINISTRATION
P.O. BOX 360909
PITTSBURGH PA 15259-0001

**********$154,823.00

VOID AFTER 180 DAYS

*One hundred fifty four thousand eight hundred twenty three and 00/100 Dollars*

CITIBANK DELAWARE, A SUBSIDIARY OF CITICORP
ONE PENN'S WAY, NEW CASTLE, DE 19720

Charles J. Kelly Jr.

⑈00854111⑈ ⑆031100209⑆ 3910465 9⑈

THE BACK OF THIS DOCUMENT CONTAINS AN ARTIFICIAL WATERMARK - HOLD AT AN ANGLE TO VIEW

| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINSTRATION | **ODS POSTMARKETING SAFETY REVIEW** | |
|---|---|---|
| **TO:** Florence Houn, MD, Director<br>Office of Drug Evaluation III<br>HFD-103 | **FROM:**<br>Ann Corken Mackey, RPh, MPH<br>Safety Evaluator<br>Division of Drug Risk Evaluation<br>(DDRE) HFD-430 | **ODS PID #** D020215<br>May 22, 2002 |

| | | |
|---|---|---|
| **DATE REQUESTED:** | **REQUESTOR/Phone #:** | |
| **DATE RECEIVED:** | | |
| **DRUG (Est):** Alosetron | **NDA/IND #** 21-107 | **SPONSOR:** GlaxoSmithKline |
| **DRUG NAME (Trade):** Lotronex | **THERAPEUTIC CLASSIFICATION:** | |
| **EVENT:** Hepatic events | | |

**Executive Summary**: This memorandum communicates an update of hepatic events associated with alosetron up to March 8, 2002 at the request of Dr. Florence Houn. Note that a previous consult on gallbladder complications associated with Lotronex was sent to HFD-180 on January 24, 2002 (see Attachment A). Four additional reports of cholecystectomy have been received since the date of that consult up to March 8, 2002; all four reports were submitted by lawyers or consumers and provided very little information.

The purpose of this consult is to summarize postmarketing reports of hepatic events associated with alosetron use, due to a concern at the time of the June 2000 Lotronex Advisory Committee meeting (three cases of hepatotoxicity had been reported [one case pre-approval and two cases post-approval]). This consult describes 28 cases of liver events possibly associated with alosetron. A total of 23 out of 28 cases described elevated liver function tests. Other events reported included hepatitis (3 reports), jaundice (2 reports), hepatomegaly (2 reports), fatty liver (4 reports), hepatotoxicity (1 report), hepatic cyst (1 report), and "liver damage" (1). The ALT values for the three hepatitis cases ranged from 67 to 891; bilirubin levels were not reported for the two patients who experienced jaundice. There were no cases of liver failure reported in this case series. There was one fatality; however, the information was submitted by an attorney who provided little information other than a death resulting from intestinal obstruction and liver damage (no lab values provided). Of the ten hospitalizations, five patients were hospitalized for reasons other than their liver events and found to have elevated liver function tests (an additional consumer was hospitalized for reasons not clearly stated and was found to have a fatty liver). One patient reported disability, but her elevated liver function tests were not the reason for her disability. There was one report of hepatotoxicity/acute hepatitis; however, causality was difficult to establish (note that the patient received only two doses of alosetron). Several patients were taking concomitant medications known to cause hepatic events (e.g., lansoprazole, lisinopril, diazepam) and/or had underlying conditions (i.e., excision of liver mass in the patient reporting a hepatic cyst) which could have caused their hepatic events. Nine of the reports in this case series were submitted by consumers or attorneys, therefore, the quality and completeness of the data are not as good as reports received from health care professionals. The alosetron labeling states that elevations of ALT, abnormal bilirubin levels, and a single case of hepatitis have been reported. There were 3,867 total adverse events in AERS for alosetron from the time of marketing (March 13, 2000) through March 8, 2002 (note that this number may represent duplicates), including 28 cases of liver events; liver events represent less than 1% of all events reported. There were no cases of acute liver failure seen in this case series. There was one fatality; however, because little information was provided, cause of death from the liver event is difficult to determine. There was one case of a hospitalized patient with hepatitis, however, the patient recovered and did not develop liver failure. Our case series did not identify any new hepatic events other than what had been seen in clinical trials.

**Reason for Request/Review:** This review is a result of a concern for hepatotoxicity associated with alosetron. At the time of the June 2000 Advisory Committee meeting, there were three cases of hepatotoxicity (one case pre-approval and two cases post-approval).

**Relevant Product Labeling:** The labeling for alosetron states that elevations of ALT were seen in patients receiving alosetron versus placebo (0.5% versus 0.4%, respectively) in studies of 12 weeks and 12 months duration. A single case of hepatitis (elevated ALT, AST, alkaline phosphatase, and bilirubin) without jaundice was reported in a 12-week study. Abnormal bilirubin levels are listed as occurring infrequently.

| | |
|---|---|
| **Search Date:** May 2, 2002 | **Search Type(s):** AERS |

**Search Criteria:** Drug Names: Alosetron (Lotronex)

MEDDRA Terms: Hepatic events were identified from a printout of *Hepatobiliary Disorders* (SOC) search.

**Search Results:**

**DEMOGRAPHIC DATA (n = 28)**

AGE (YEARS): MEAN= 56, MEDIAN= 52, (RANGE 18 TO 80) (n = 23)
SEX: F (26), UNK (2)
YEAR: 2000 (21), 2001 (6), 2002 (1)
SOURCE: DOMESTIC (28)
DECHALLENGE: 13
RECHALLENCE: 1
DOSE PER DAY: 2 MG (19), 1 MG (3), 2 MG DECREASED TO 1 MG (1), 1 MG VARIABLE (1), UNK (4)
ONSET TIME: MEAN = 75 DAYS (RANGE 1 TO 270 DAYS) (n = 19)
OUTCOME: DE (1), HO (10). DISABILITY (1), UNK (16)
EVENTS*§: ELEVATED LIVER FUNCTION TESTS (23), CHOLESTATIC HEPATITIS (1), HEPATITIS (2), JAUNDICE (2), HEPATOMEGALY (2). FATTY LIVER (4), HEPATOTOXICITY (1), HEPATIC CYST (1) "LIVER DAMAGE" (1)

* Events not mutually exclusive.
§ ALT values for the three hepatitis cases ranged from 67 to 891; bilirubin levels were not reported for the two patients who experienced jaundice.

Case of hepatotoxicity after two doses of alosetron:

Case# 3472866 (Mfr# A0119607A) (2000) A 75-year-old female experienced elevated liver function tests, hepatotoxicity, and acute hepatitis among other events after taking two doses of alosetron to treat abdominal pain "presumably" associated with irritable bowel syndrome. Her liver function tests were reported as follows: ALT 891, AST 260, and alkaline phosphatase 59; no baselines provid ed. Before taking alosetron, the patient had had a three to four week history of fluid retention edema felt to be due to mirtazapin e. She had started ciprofloxacin two days earlier to treat COPD. The patient presented with bloody stools, systolic blood pressure between 70 and 80, and pitting edema up to her waist and presacral region. She was hospitalized with dehydration, hypotension, anasarca, and evidence of GI bleeding; hyperkalemia and thrombocytopenia were noted. She improved after treatment with intravenous fluids, dopamine, and kayexalate enema. While hospitalized, she developed acute renal failure with oliguria. Chest x-ray showed questionable congestive heart failure with small dependent effusion, superimposed upon long standing pleural thickening at both bases. Ultrasound of the liver showed "hyperechoic" liver and some ascites; this was felt to be either fatty changes or cirrhos is. She was hospitalized for seven days. Discharge diagnosis was acute hepatitis with severe hepatotoxic reaction, possibly due to medi cation. The patient had an extensive medical history including intractable nausea and vomiting, COPD, anorexia, malnutrition, partial lobectomy, appendectomy, small bowel obstruction, and hysterectomy; she had never had episodes of hepatotoxicity, renal failure , or GI bleeding. Concomitant medications included mirtazapine, torasemide, ciprofloxacin, and guaifenesin.

Representative case:

Case# 3477084 (Mfr# A0120634A) An 80-year-old woman was hospitalized with a diagnosis of hepatitis after receiving 2 mg of alosetron a day for 35 days to treat IBS. Her liver enzymes were reported as follows: AST 299 (baseline 31), ALT 210 (baseline 10), and alkaline phosphatase 155 (no baseline reported). Her CT scan was normal except for possible mild dilation of intrahepatic d ucts and seriologies were negative for hepatitis B and C; no liver biopsy was performed. Alosetron was discontinued and her liver en zymes returned to normal within three days. Her medical history included hypertension; concomitant medications included lansoprazole, spironolactone, nadolol, furosemide, amlodipine, hyoscyamine, and rofecoxib.

**Discussion/Conclusion:** There were no cases of liver failure reported in this case series. There was one fatality; however, the information was submitted by an attorney who provided little information other than a death resulting from intestinal obstructi on and ver damage (no lab values provided). Of the ten hospitalizations, five patients were hospitalized for reasons other than thei r liver ents and found to have elevated liver function tests (an additional consumer was hospitalized for reasons not clearly stated and was found to have a fatty liver). One patient reported disability, but her elevated liver function tests were not the reason for he r disability. There was one report of hepatotoxicity/acute hepatitis; however, causality was difficult to establish (note that the patient re ceived only two doses of alosetron). Several patients were taking concomitant medications known to cause hepatic events (e.g., lansoprazol e, lisinopril, diazepam) and/or had underlying conditions (i.e., excision of liver mass in the patient reporting a hepatic cyst) w hich could have caused their hepatic events. Nine of the reports in this case series were submitted by consumers or attorneys, therefore, the quality and completeness of the data are not as good as reports received from health care professionals. The alosetron labeling states that elevations of ALT, abnormal bilirubin levels, and a single case of hepatitis have been reported . There were 3,867 total adverse events in AERS for alosetron from the time of marketing (March 13, 2000) thro ugh March 8, 2002 (note that this number may represent duplicates), including 28 cases of liver events; liver events represent less than 1% of all events reported. There we re no cases of acute liver failure seen in this case series. There was one fatality; however, because little information was provided, caus e of death from the liver event is difficult to determine. There was one case of a hospitalized patient with hepatitis, however, the patie nt recovered and did not develop liver failure. Our case series did not identify any new hepatic events other than what had been s een in clinical trials.

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| **Reviewer's Signature / Date:** Ann Corken Mackey 5/21/02 | **Team Leader's Signature / Date:** Lanh Green 5/21/02 |
| **Division Director Signature / Date:** Julie Beitz 5/22/02 | |

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| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINSTRATION | **ODS POSTMARKETING SAFETY REVIEW** | |
|---|---|---|
| **TO:** Victor Raczkowski, M.D., Acting Director<br>Division of Gastrointestinal & Coagulation Drug Products, HFD-180 | **FROM:**<br>Ann Corken Mackey, R.Ph., M.P.H., Safety Evaluator<br>Zili Li, M.D., M.P.H., Medical Epidemiologist<br>Division of Drug Risk Evaluation (DDRE) HFD-430 | **ODS PID #** D020028<br>February 1, 2002 |
| **DATE REQUESTED:** | **REQUESTOR/Phone #:** ODS generated. | |
| **DATE RECEIVED:** | | |
| **DRUG (Est):** Alosetron | **NDA/IND #** 21-107 | **SPONSOR**: GlaxoSmithKline |
| **DRUG NAME (Trade):** Lotronex | **THERAPEUTIC CLASSIFICATION:** | |
| **EVENT:** Ischemic colitis and complications of serious constipation events as of December 31, 2001. | | |

**Executive Summary:** Alosetron was approved on February 8, 2000 for the treatment of women with diarrhea-predominant irritable bowel syndrome (IBS). As of December 31, 2001, there were 85 cases of ischemic colitis and 107 cases of complications of seriou s constipation in the Adverse Event Reporting System (AERS) database. It should be noted that the reports received in AERS since marketing suspension of alosetron (November 28, 2000) have come primarily from consumers, therefore, the quality and completeness of the data are not as good as the reports received before November 28, 2000. In addition, since the alosetron upd ate of July 31, 2001, ODS has been receiving reports from class action lawsuits; the quality and completeness of the data also are not as good. There has been no follow up on the consumer or class action lawsuit reports.

| Search Date: December 31, 2001 | Search Type(s): AERS |
|---|---|

**Search Results:** As of December 31, 2001, there were 85 cases of ischemic colitis and 107 cases of serious constipation in the Adverse Event Reporting System (AERS) database. These counts represent unduplicated patient cases, not individual reports. The case definition for ischemic colitis for epidemiological risk assessment was based on any or a combination of the following: (1) the term "ischemic colitis" is explicitly used in the AERS report as a possible diagnosis, (2) any endoscopic or histologic evidence of ischemic change or necrosis, or (3) any radiological evidence of ischemic colitis. The case definition for complications of serious constipation was constipation or suspected constipation that led to ER visit, hospitalization, or complications, including but not limited to, fecal impaction, bowel obstruction, necrosis, or rupture. Deaths were counted as an outcome only when there was evidence of a possible association with alosetron therapy.

It should be noted that ODS has been receiving reports from class action lawsuits since the update of July 31, 2001. Although most of these reports provide minimal information (e.g., patient demographics, description of the event), they have been included in the data analysis. No attempt will be made to acquire follow up on these class action lawsuit reports.

Of the 85 cases of ischemic colitis, 52 (61%) required hospitalization; 9 (11%) required surgery for an obstructed, necrotic, ruptured bowel, or rectal problems; and 2 died. Of the 107 cases of serious constipation, 78 (73%) required hospitalization; 30 (28%) required surgery for an obstructed, necrotic, ruptured bowel, or rectal problems; and 2 died. Of the 192 total cases, 11 patients were male (2 cases of ischemic colitis, 2 cases of serious constipation, 3 cases of ruptured colon, 1 case of partial bowel removal, and 1 case of bowel obstruction); the gender was not known for 2 of the ischemic colitis cases and 1 of the serious constipation cases. The mean age for the ischemic colitis cases was 55 years (n = 68); the mean age for the serious constipation cases was 55 years (n = 81).

The following tables show the changes in the number of cases of ischemic colitis and serious constipation, selected outcomes for those cases. and diagnostic certainty of ischemic colitis cases before and after the market suspension (withdrawal) of alosetron. It should be noted that the reports received in AERS since market suspension of alosetron (November 28, 2000) have come primarily from consumers, therefore, the quality and completeness of the data are not as good as the reports received before November 28, 2000. In addition, ODS has been receiving reports from class action lawsuits; the quality and completeness of these data also are not as good. Before market suspension of alosetron, there was 1 case (2%) and no cases of ischemic colitis reported by consumers or as part of a lawsuit, respectively, compared to 9 cases (28%) and 14 cases (44%), respectively, after market suspension. There were 9 cases (38%) and no cases of serious constipation reported by consumers or as part of a lawsuit, respectively, before market suspension compared to 46 cases (55%) and 19 cases (23%), respectively, after market suspension. There has been no follow up on these consumer or lawsuit reports.

Table 1-1. Number of alosetron-associated cases of ischemic colitis and severe constipation before and after marketing suspension*, United States, cumulative, ending December 31, 2001.

| Key Adverse Events | Pre-suspension (n=77) | Post-suspension (n=115) | Total (n=192) |
|---|---|---|---|
| Ischemic colitis** | 53 (69%) | 32 (28%) | 85 (44%) |
| Serious constipation complications | 24 (31%) | 83 (72%) | 107 (56%) |

* Date of marketing suspension was November 28, 2000.

Table 1-2. Selected outcomes of alosetron-associated cases of ischemic colitis and serious constipation before and after marketing suspension, United States, cumulative, ending December 31, 2001.

| Selected Outcomes (not mutually exclusive) | Pre-suspension | | Post-suspension | | Total | |
|---|---|---|---|---|---|---|
| | Ischemic colitis (n=53) | Serious Constipation (n=24) | Ischemic colitis (n=32) | Serious Constipation (n=83) | Ischemic colitis (n=85) | Serious Constipation (n=107) |
| Hospitalization | 35 (66%) | 17 (71%) | 17 (53%) | 61 (73%) | 52 (61%) | 78 (73%) |
| Total colectomy | 0 | 0 | 0 | 0 | 0 | 0 |
| Segmental resection | 4 | 6 | 5 | 10 | 9 | 16 |
| Oversew perforation | 0 | 1 | 0 | 1 | 0 | 2 |
| Anal/rectal surgery† | 0 | 0 | 0 | 6 | 0 | 6 |
| Miscellaneous$ | 0 | 0 | 0 | 6 | 0 | 6 |
| Total surgery due to obstructed, necrotic, ruptured bowel, or other | 4 (13%) | 7 (29%) | 5 (16%) | 23 (28%) | 9 (11%) | 30 (28%) |
| Death | 2 (4%) | 1 (4%) | 0 | 1 (1%) | 2 (2%) | 2 (2%) |

† Two cases involved surgery due to rectal tearing and rectocele; four cases involved hemorrhoid surgery (status of constipation unknown for one case).

$ One patient was to have surgery to repair a perforated bowel, but died in OR; second patient had unspecified "surgery to remove blockage"; four cases (status of constipation unknown at this time) were reported as ruptured colon, colon surgery, colon surgery with colostomy, and ruptured bowel

Table 1-3. Diagnostic certainty of alosetron-associated cases of ischemic colitis before and after the drug marketing suspension, United States, cumulative, ending December 31, 2001.

| Diagnostic Certainty of Ischemic Colitis (mutually exclusive)** | Pre-suspension (n=53) | Post-suspension (n=32) | Total (n=85) |
|---|---|---|---|
| **PROBABLE CASES OF ISCHEMIC COLITIS** | | | |
| Both histologic and endoscopic evidence of ischemic colitis | 19 (36%) | 5 (16%) | 24 (28%) |
| Endoscopic evidence of ischemic colitis only | 9 (17%) | 5 (16%) | 14 (16%) |
| Histologic evidence of ischemic colitis only | 12 (23%) | 3 (9%) | 15 (18%) |
| Radiologic evidence of ischemic colitis only | 5 (9%) | 0 | 5 (6%) |

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| **Reviewer's Signature / Date: Ann Corken Mackey 30/02** | **Reviewer's Signature / Date: Zili Li 1/30/02** |
| **Division Director Signature / Date: Julie Beitz 2/1/01** | **Team Leader's Signature / Date: Lanh Green 1/30/02** |

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/s/

Ann Corken
2/7/02 01:48:51 PM
PHARMACIST

Julie Beitz
2/8/02 02:20:06 PM
DIRECTOR

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Ann Corken
2/7/02 01:48:51 PM
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Julie Beitz
2/8/02 02:20:06 PM
DIRECTOR

Julie Beitz
2/8/02 04:58:35 PM
DIRECTOR

| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINSTRATION | **ODS POSTMARKETING SAFETY REVIEW** | |
|---|---|---|
| **TO:** Victor Raczkowski, M.D., Acting Director<br>Division of Gastrointestinal & Coagulation Drug Products<br>HFD-180 | **FROM:**<br>Ann Corken Mackey, R.Ph., M.P.H.<br>Safety Evaluator<br>Zili Li, M.D., M.P.H.<br>Medical Epidemiologist<br>Division of Drug Risk Evaluation<br>(DDRE) HFD-430 | **ODS PID #** D020006<br>January 24, 2002 |

| | | |
|---|---|---|
| **DATE REQUESTED:** | **REQUESTOR/Phone #:** ODS generated. | |
| **DATE RECEIVED:** | | |
| **DRUG (Est):** Alosetron | **NDA/IND #** 21-107 | **SPONSOR:** |
| **DRUG NAME (Trade):** Lotronex | **THERAPEUTIC CLASSIFICATION:** | |
| **EVENT:** Gallbladder complications | | |

**Executive Summary**: The purpose of this consult is to summarize postmarketing reports of gallbladder complications associated with the use of alosetron, due to ongoing concerns about gallbladder complications associated with a drug in the same class, tegaserod (Zelnorm®). (Note that tegaserod has not yet been approved; it is currently under review within the agency.) This consult describes 9 cases of gallstones, 3 cases of cholecystitis, and 8 cases of miscellaneous symptoms (e.g., gallbladder dysfunction, abdominal pain) leading to 13 cases of cholecystectomy, 3 cases of unspecified gallbladder surgery, and 4 unknown outcomes (see attachment for description of cases). Risk factors for gallbladder complications include female gender, increased age, and obesity (1). Of the 20 cases described in the consult, 19 patients were female, 9 patients were greater than 65 years of age, and 3 patients were obese. In addition, 5 patients were taking concomitant drugs known to cause gallbladder complications and 2 patients had a history of gallbladder problems. Of the 20 cases, 9 cases (45%) were submitted by consumers, therefore, the quality and completeness of the data are not as good as reports received from health care professionals. Five reports were submitted after marketing suspension of alosetron (November 28, 2000). A total of 514,000 alosetron prescriptions were dispensed by retail pharmacies from March 1, 2000 through December 31, 2000; marketing of alosetron has been temporarily suspended. The Office of Drug Safety (ODS) does not have sufficient evidence to establish a relationship between alosetron and gallbladder disorders; however, because of concerns of gallbladder complications associated with tegaserod, we wanted to bring this issue to the attention of the review division. We will continue to monitor alosetron for reports of gallbladder complications.

**Reason for Review:** This review is a result of a concern for gallbladder surgeries associated with use of tegaserod (Zelnorm), which is in the same drug class as alosetron (Lotronex).

**Relevant Product Labeling:** There are no gallbladder-related adverse events in the alosetron labeling.

| | |
|---|---|
| **Search Date:** January 4, 2001 | **Search Type(s):** AERS IMS |

**Search Criteria:** Drug name: Alosetron (Lotronex)

MEDDRA Terms: *Gallbladder disorders* (HLGT) and *Biliary tract and gallbladder therapeutic procedures* (HLT). The search produced 21 cases; one case was not included in the analysis because the report stated only that the patient had a gall bladder problem.

1. Extrahepatic biliary disorders. In. Beers MH, Berkow R, eds. The Merck Manual of Diagnosis and Therapy. Whitehouse Station, NJ: Merck Research Laboratories, 1999; p. 400.

**Search Results:**
DEMOGRAPHIC DATA (N = 20)

| | |
|---|---|
| **AGE (YEARS):** | **55 MEAN, 64 MEDIAN, (RANGE 19 TO 85) (N = 19)** |
| **SEX:** | **M (1), F (19)** |
| **SOURCE:** | **DOMESTIC (20)** |
| **YEAR:** | **2000 (15), 2001 (5)** |
| **DOSE PER DAY:** | **2 MG (16), 1 MG (1), 1 MG PRN (1), UNK (2)** |
| **ONSET (DAYS)&:** | **54 MEAN, 38 MEDIAN (RANGE 3 TO 174) (N = 11)** |
| **PTS TAKING CONCOMITANT MEDS KNOWN TO CAUSE GB PROBLEMS*:** | **5** |
| **PT WITH RISK FACTORS FOR GB PROBLEMS§:** | **4** |
| **OUTCOME:** | **CHOLECYSTECTOMY (13), UNSPEC GALLBLADDER (GB) SURGERY (3), UNK (4)** |
| CLINICAL: | GB STONES (9), CHOLECYSTITIS (3), "SWOLLEN GB" (1), GB DYSFUNCTION (1), GB INFLAMED/INFECTED (1), OTHER# (5) |

& Some patients took alosetron on and off; in such cases, onset was calculated from the first day they started taking the drug.
* Concomitant medications include estrogen, lansoprazole, and paroxetine.
§ Risk factors include obesity, history of gallbladder stones, gallbladder polyps; female gender and age greater than 65 years also are risk factors (out of 20 patients, 19 were female and 9 were greater than 65 years of age).
# Symptoms reported by patients include abdominal pain, nausea.

Representative case:

Case# 3576653 (Mfr# A0133817A) (U.S., 2000) A 40-year-old woman developed gallbladder stones and underwent a cholecystectomy after taking 2 mg of alosetron a day off and on for 38 days to treat alternating irritable bowel syndrome. Init ially she took alosetron for 10 days and discontinued its use because of constipation. Two weeks later her symptoms recurred and she rest arted alosetron. Approximately two weeks after restarting alosetron, she experienced severe abdominal pain; she was diagnosed with gallbladder stones by endoscopic retrograde cholangiopancreatography and had a cholecystectomy. Her medical history included [redacted]lon polyps, gastroesophageal reflux disease (GERD), and degenerative joint disease; concomitant medications included [redacted]nsoprazole, conjugated estrogens, and naproxen.

**Drug Use**

There were a total of [redacted] alosetron prescriptions dispensed by retail pharmacies (chain, independent, food stores, and mail order) in the U.S from March 1, 2000 thro ugh December 31, 2000. (Note that alosetron sales were suspended November 28, 2000.) **This information is from IMS Health National Prescription Audit Plus (on-line) and is not to be used outside of the FDA without prior clearance by IMS Health.**

**Discussion:** The purpose of this consult is to summarize postmarketing reports of gallbladder complications associated with the use of alosetron, due to ongoing concerns about gallbladder complications associated with a drug in the same class, tegaserod (Zelnorm ®). (Note that tegaserod has not yet been approved; it is currently under review within the agency.) This consult describes 9 cases of gallstones, 3 cases of cholecystitis, and 8 cases of miscellaneous symptoms (e.g., gallbladder dysfunction, abdominal pain) lea ding to 13 cases of cholecystectomy, 3 cases of unspecified gallbladder surgery, and 4 unknown outcomes (see attachment for description of cases). Risk factors for gallbladder complications include female gender, increased age, and obesity (1). Of the 20 cases descr ibed in the consult, 19 patients were female, 9 patients were greater than 65 years of age, and 3 patients were obese. In addition, 5 p atients were taking concomitant drugs known to cause gallbladder complications and 2 patients had a history of gallbladder problems. Of the 20 cases, 9 cases (45%) were submitted by consumers, therefore, the quality and completeness of the data are not as good as rep orts received from health care professionals. Five reports were submitted after marketing suspension of alosetron (November 28, 2000 ). A total of 514,000 alosetron prescriptions were dispensed by retail pharmacies from March 1, 2000 thro ugh December 31, 2000; marketing of alosetron has been temporarily suspended. The Office of Drug Safety (ODS) does not have sufficient evidence to establish a relationship between alosetron and gallbladder disorders; however, because of concerns of gallbladder complications associated with tegaserod, we wanted to bring this issue to the attention of the review division. We will continue to monitor a losetron for reports of gallbladder complications.

1. Extrahepatic biliary disorders. In. Beers MH, Berkow R, eds. The Merck Manual of Diagnosis and Therapy. Whitehouse Station, NJ: Merck Research Laboratories, 1999; p. 400.

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| **[redacted]eviewer's Signature / Date: Ann Corken Mackey 1/23/02** | **Team Leader's Signature / Date: Lanh Green 1/23/02** |
| **Reviewer's Signature / Date: Zili Li 1/23/02** | **Division Director Signature / Date: Julie Beitz 1/24/02** |

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| | Case# | Mfr# | Age | Year | Sex | Daily Dose | Onset | De+ | Re+ | Event | Outcome | Med history | C |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1* | 374387 | A0158271A | 32 | 2001 | F | Unk | Unk | Unk | Unk | Weight gain | Unspec gallbladder (GB) Surgery | Weight loss, diarrhea, insomnia, panic attacks | |
| 2* | 357665 | A0158883A | Unk | 2001 | F | Unk | Unk | Unk | Unk | Constip, bloody stool, diarrhea, abd pain | Cholecyst-ectomy | Unk | |
| 3* | 357665 | A0133817A | 40 | 2000 | F | 2 mg | 38 days | Yes | N/A | Abd pain, GB stones | Laparoscopy cholecyst-ectomy, HO | IBS-A, colon polyps, GERD, degener joint dis | Estro |
| 4* | 357400 | A0133092A | 69 | 2000 | F | 2 mg | 4 days | Yes | Unk | GB stones | Cholecystec-tomy, HO | IBS-D, GB polyps, HTN | |
| 5* | 362734 | A0136454A | 85 | 2000 | F | 2 mg | Unk | Yes | Unk | Abd pain, diarrhea, diverticulosis, fecal impact, GB stones | Unk | Hepatitis, rectocele, mitral valve prolapse, IBS-D | |
| 6* | 362874 | A0134714A | 67 | 2000 | F | 2 mg | Unk | No | N/A | Constip, abd pain, GB stones | "GB surgery" for gall stones scheduled next month | Stomach, esophageal surgery; IBS-C; depression, anxiety | |
| 7 | 362874 | A0136661A | 75 | 2001 | F | 1 mg prn | 60 days | Unk | Unk | Severe constip, nausea, stomach pain | GB surgery | Unk | |
| 8 | 359070 | A0136357A | 31 | 2000 | F | 1 mg | 56 days | Yes | Yes | Bowel obstruct then diarrhea, abd pain, nausea, cholecystitis | Cholecyst-ectomy, HO | IBS-D, HTN, allergies | |
| 9 | 357530 | A0133461A | 71 | 2000 | F | 2 mg | Unk | No | N/A | Abd pain, constip, GB stones | Cholecyst-ectomy, HO | IBS-A, diverticulitis, hypothyroid, polio, colectomy ruptured diverticulum | T |
| 10 | 348970 | Direct | 25 | 2000 | F | 2 mg | 3 days | Yes | N/A | N/V, Cholelithiasis | Unk | UC-D; hepatic, renal dysfunc, cholelithiasis, weight=185 lbs | |
| 11 | 358235 | A0134855A | 66 | 2000 | F | 2 mg | 174 days | N/A | N/A | Constip then abd pain; N/V; pancreatitis; inc lipase, amylase | Cholecyst-ectomy, HO | IBS, HTN, hypothyroid osteoarthritis, weight=200 lbs | Hyza |
| 12 | 358235 | A0134963A | 35 | 2000 | F | 2 mg | Unk | Yes | Yes | Cholecystitis, chest pain, SOB, tachy-cardia, nausea | cholecyst-ectomy | Unk | |
| 13* | 358100 | A0134395A | 59 | 2000 | F | 2 mg | 14 days | Yes | N/A | Fecal impact; abd pain; GB enlarg, stones; jaundice | Cholecyst-ectomy, HO | IBS-D | |
| 14* | | A0138132A | 63 | 2001 | F | 2 mg | Unk | Yes | N/A | Constip | Cholecyst-ectomy | IBS | |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 15* | 357529 | A0133210A | 42 | 2000 | F | 2 mg | 70 days | Yes | N/A | Abd pain, twisted colon, swollen GB, "GB stuck to intestine", pancreatitis, resp arrest | GB "drained" cholecystectomy removal of part of intestine | Diarrhea, abd pain, part colectomy, extensive med hist | c m |
| 16 | 357529 | A0133273A | 19 | 2000 | F | 2 mg | 135 days | Yes | Yes | Abd pain, bloody diarrhea, nausea, GB dys-function, dehydration | Cholecystect-omy, HO | Diarrhea, total colectomy, Gardner's syndrome, weight=190 lbs | |
| 17 | 358687 | A0133423A | 66 | 2001 | M | 2 mg | 21 days | Yes | N/A | Diarrhea; insomnia; abd cramps; vomiting; GB inflammed and infected | Cholecystect-omy, HO | Diarrhea, Diabetes | |
| 18 | 365911 | A0142306A | 69 | 2000 | F | 2 mg | Unk | N/A | N/A | Mes thrombosis, splenomegaly, diarrhea, colitis, bowel resect, GB stones, extensive list adverse events | HO | IBS, diverticulosis, hemorrholds, depression, pt had extensive med hist | |
| 19 | 346733 | A0115430A | 64 | 2000 | F | 2 mg | 21 days | Unk | N/A | Abd pain, hematuria, pelvic pain, constip, hematemesis, GB stone, possible diverticulitis | HO | IBS, diverticulosis, diverticulitis | |
| 20 | 348005 | A0120835A | 68 | 2000 | F | 2 mg | Unk | N/A | N/A | Chronic cholecystitis | Cholecystect-omy, HO | IBS | |

* Reports submitted by consumers or as part of class-action lawsuit

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

/s/

Ann Corken
1/25/02 03:13:52 PM
PHARMACIST

Julie Beitz
1/30/02 02:06:50 PM
DIRECTOR

| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINSTRATION | **OPDRA POSTMARKETING SAFETY REVIEW** | |
|---|---|---|
| **TO:** Victor Raczkowski, M.D., Acting Director<br>Division of Gastrointestinal & Coagulation Drug Products, HFD-180 | **FROM:**<br>Ann Corken Mackey, R.Ph., M.P.H., Safety Evaluator<br>Zili Li, M.D., M.P.H., Medical Epidemiologist<br>Division of Drug Risk Evaluation I I (DDREII) HFD-440 | **OPDRA PID #** D010508<br><br>**November 6, 2001** |

| | | |
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| **DATE REQUESTED:** | **REQUESTOR/Phone #:** OPDRA generated. | |
| **DATE RECEIVED:** | | |
| **DRUG (Est):** Alosetron | **NDA/IND #** 21-107 | **SPONSOR:** GlaxoSmithKline |
| **DRUG NAME (Trade):** Lotronex | **THERAPEUTIC CLASSIFICATION:** | |

**EVENT:** Ischemic colitis and complications of serious constipation events as of September 30, 2001.

**Executive Summary:** Alosetron was approved on February 8, 2000 for the treatment of women with diarrhea-predominant irritable bowel syndrome (IBS). As of September 30, 2001, there were 84 cases of ischemic colitis and 95 cases of complications of serious constipation in the Adverse Event Reporting System (AERS) database. It should be noted that the reports received in AERS since marketing suspension of alosetron (November 28, 2000) have come primarily from consumers, therefore, the quality and completeness of the data are not as good as the reports received before November 28, 2000. In addition, since the last alosetron update (July 31, 2001), OPDRA has been receiving reports from class action lawsuits; the quality and completeness of the data also are not as good. There has been no follow up on the consumer or class action lawsuit reports.

**Search Date:** September 30, 2001 **Search Type(s):** AERS

**Search Results:** As of September 30, 2001, there were 84 cases of ischemic colitis and 95 cases of serious constipation in the Adverse Event Reporting System (AERS) database. These counts represent unduplicated patient cases, not individual reports. The case definition for ischemic colitis for epidemiological risk assessment was based on any or a combination of the following: (1) the term "ischemic colitis" is explicitly used in the AERS report as a possible diagnosis, (2) any endoscopic or histologic evidence of ishemic change or necrosis, or (3) any radiological evidence of ischemic colitis. The case definition for complications of serious constipation was constipation or suspected constipation that led to ER visit, hospitalization, or complications, including but not limited to, fecal impaction, bowel obstruction, necrosis, or rupture. Deaths were counted as an outcome only when there was evidence of a possible association with alosetron therapy.

It should be noted that OPDRA has been receiving reports from class action lawsuits since the last update of July 31, 2001. Although most of these reports provide minimal information (e.g., patient demographics, description of the event), they have been included in the data analysis. No attempt will be made to acquire follow up on these class action lawsuit reports.

Of the 84 cases of ischemic colitis, 45 (54%) required hospitalization, 9 (11%) required surgery for an obstructed, necrotic, or ruptured bowel, and 2 died. Of the 95 cases of serious constipation, 52 (55%) required hospitalization, 22 (23%) required surgery for an obstructed, necrotic, or ruptured bowel, and 2 died. Of the 179 total cases, 9 patients were male (2 cases of ischemic colitis, 2 cases of serious constipation, 2 cases of ruptured colon, and 1 case of bowel obstruction); the gender was not known for 2 of the ischemic colitis cases. The mean age for the ischemic colitis cases was 55 years (n = 68); the mean age for the severe constipation cases was 54 years (n = 74).

The following tables show the changes in the number of cases of ischemic colitis and serious constipation, selected outcomes for those cases, and diagnostic certainty of ischemic colitis cases before and after the market suspension (withdrawal) of alosetron. It should be noted that the reports received in AERS since market suspension of alosetron (November 28, 2000) have come primarily from consumers, therefore, the quality and completeness of the data are not as good as the reports received before November 28, 2000. In addition, OPDRA has been receiving reports from class action lawsuits; the quality and completeness of these data also are not as good. Before market suspension of alosetron, there was 1 case (2%) and no cases of ischemic colitis reported by consumers or as part of a lawsuit, respectively, compared to 9 cases (29%) and 13 cases (42%), respectively, after market suspension. There were 9 cases (39%) and no cases of serious constipation reported by consumers or as part of a lawsuit, respectively, before market suspension compared to 38 cases (54%) and 15 cases (21%), respectively, after market suspension. There has been no follow up on these consumer or lawsuit reports.

Table 1-1. Number of alosetron-associated cases of ischemic colitis and severe constipation before and after marketing suspension*, United States, cumulative, ending September 30, 2001.

| Key Adverse Events | Pre-suspension (n=77) | Post-suspension (n=102) | Total (n=179) |
|---|---|---|---|
| Ischemic colitis** | 53 (69%) | 31 (30%) | 84 (47%) |
| Serious constipation complications | 24 (31%) | 71 (70%) | 95 (53%) |

* Date of marketing suspension was November 28, 2000.
** Two cases were excluded from analysis because ischemic colitis was eventually ruled out; one case was excluded from analysis due to evidence of self diagnosis by a patient.

Table 1-2. Selected outcomes of alosetron-associated cases of ischemic colitis and serious constipation before and after marketing suspension, United States, cumulative, ending September 30, 2001.

| Selected Outcomes (not mutually exclusive) | Pre-suspension | | Post-suspension | | Total | |
|---|---|---|---|---|---|---|
| | Ischemic colitis (n=53) | Serious Constipation (n=24) | Ischemic colitis (n=31) | Serious Constipation (n=71) | Ischemic colitis (n=84) | Serious Constipation (n=95) |
| Hospitalization | 31 (58%) | 10 (42%) | 14 (45%) | 42 (59%) | 45 (54%) | 52 (55%) |
| Total colectomy | 0 | 0 | 0 | 0 | 0 | 0 |
| Segmental resection | 4 | 6 | 5 | 7 | 9 | 13 |
| Oversew perforation | 0 | 1 | 0 | 1 | 0 | 2 |
| Anal/rectal surgery† | 0 | 0 | 0 | 2 | 0 | 2 |
| Miscellaneous$ | 0 | 0 | 0 | 5 | 0 | 5 |
| Total surgery due to obstructed, necrotic, ruptured bowel, or other | 4 (13%) | 7 (29%) | 5 (16%) | 15 (21%) | 9 (11%) | 22 (23%) |
| Death | 2 (4%) | 1 (4%) | 0 | 1 (1%) | 2 (2%) | 2 (2%) |

† Two cases involved surgery due to rectal tearing and rectocele.
$ One patient was to have surgery to repair a perforated bowel, but died in OR; second patient had unspecified "surgery to remove blockage"; three cases (status of constipation unknown at this time) were reported as ruptured colon, colon surgery with colostomy, and ruptured bowel.

Table 1-3. Diagnostic certainty of alosetron-associated cases of ischemic colitis before and after the drug marketing suspension, United States, cumulative, ending September 30, 2001.

| Diagnostic Certainty of Ischemic Colitis (mutually exclusive)** | Pre-suspension (n=53) | Post-suspension (n=31) | Total (n=84) |
|---|---|---|---|
| **PROBABLE CASES OF ISCHEMIC COLITIS** | | | |
| Both histologic and endoscopic evidence of ischemic colitis | 19 (36%) | 5 (16%) | 24 (29%) |
| Endoscopic evidence of ischemic colitis only | 9 (17%) | 5 (16%) | 14 (17%) |
| Histologic evidence of ischemic colitis only | 12 (23%) | 3 (10%) | 15 (18%) |
| Radiologic evidence of ischemic colitis only | 5 (9%) | 0 | 5 (6%) |
| **POSSIBLE CASES OF ISCHEMIC COLITIS** | | | |
| Ischemic colitis without above evidence‡ | 8 (15%) | 18 (58%) | 26 (30%) |

‡ At the time of analysis, we were unable to obtain supporting documentation.

| | |
|---|---|
| **Reviewer's Signature / Date:**<br>**Ann Corken Mackey / 11-01/01** | **Reviewer's Signature / Date:**<br>**Zili Li / 11-06-01** |
| **Acting Division Director Signature / Date:**<br>**Julie Beitz / 11-06-01** | **Team Leader's Signature / Date:**<br>**Lanh Green/ 11-05-01** |

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HFD-103 Houn
HFD-180 Division File/Div Dir/Kress/Korvick/Gallo-Torres/Barreiro/Project Manager
HFD-430/440 Beitz/Mackey/Green/Piazza-Hepp/Dempsey/Li/Chron/Drug
HFD-240 Kremzner
HFI-20 Brodsky

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/s/
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Zili Li
11/6/01 03:33:26 PM
MEDICAL OFFICER

Julie Beitz
11/7/01 08:37:38 AM
DIRECTOR

# April 23, 2002
# Advisory Committee Meeting

# Background Material and Transcripts

# See

**http://www.fda.gov/ohrms/dockets/ac/cder02.htm#GastrointestinalDrugs**