

**GASTROINTESTINAL DRUGS ADVISORY COMMITTEE
and
DRUG SAFETY and RISK MANAGEMENT SUBCOMMITTEE
BACKGROUND PACKAGE
April 23, 2002**

INTRODUCTION

CONTENTS

- 1. Executive Summary** (V. Raczkowski)
- 2. Highlights of Regulatory History** (P. Levine)
- 3. FDA Perspectives on Safety** (H.Gallo-Torres)
 - Appendix 1: Randomized Clinical Trial Experience - H. Gallo-Torres (03/11/02)*
 - Appendix 2: Re-evaluation of the Risk of Ischemic Colitis - Z. Li (03/15/02)*
 - Appendix 3: Postmarketing Safety Review - A. Mackey and Z. Li (03/26/02)*
 - Appendix 4: Comments on Epidemiological Studies - A. Brinker (03/26/02)*
 - Appendix 5: Possible Mechanisms for Alosetron-Induced Ischemic Colitis - M.Barreiro (03/20/02)*
 - Appendix 6: Clinical Review of Serious Constipation - S. Kress (03/26/02)*
 - Appendix 7: Causality Assessment - Z. Li (03/26/02)*
- 4. Statistical Perspective** (D. Hoberman)
- 5. Goals of Risk Management** (T. Piazza-Hepp)

OVERVIEW

**OVERVIEW OF SELECTED ISSUES
LOTRONEX[®] TABLETS**

**Gastrointestinal Drugs Advisory Committee
Drug Safety and Risk Management Subcommittee
23 April 2002**

The Food and Drug Administration (FDA) is holding this meeting of the Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk Management Subcommittee to discuss the risk-benefit profile of Lotronex[®] (alosetron hydrochloride) Tablets. The Advisory Committee deliberations will assist FDA in determining whether Lotronex[®] should be returned to the market, and if so, under what conditions. A focus of the meeting will be on whether an appropriate risk-management program can be established for Lotronex[®], and if so, what the specific characteristics of such a program should be.

Lotronex[®] was marketed for eight or nine months before it was withdrawn from the market. The drug was approved by FDA on February 9, 2000 for the treatment of women with irritable bowel syndrome (IBS) whose predominant bowel symptom is diarrhea. But soon after Lotronex[®] was launched, FDA began receiving adverse event reports of serious outcomes associated with its use, including serious complications of constipation and 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 On November 28, 2000, Lotronex[®] was voluntarily withdrawn from the market by its sponsor at the time, Glaxo Wellcome, Inc.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[®]. This information includes data from clinical trials that were ongoing (and were terminated) when the drug was withdrawn from the market. The submission also includes data from adverse events reported when the drug was marketed. The scope of this information gives FDA a broader scientific foundation upon which to base any possible subsequent regulatory actions on Lotronex[®].

One goal of the Advisory Committee meeting will be to discuss the benefit-risk issues surrounding Lotronex[®] because very different perspectives have been voiced publicly. For example, when Lotronex[®] was still on the market, the Public Citizen Health Research Group petitioned FDA (September 8, 2000) to have it withdrawn. But after Lotronex[®] was withdrawn from the market, some patients with irritable bowel syndrome have expressed their need for the drug. Accordingly, on April 9, 2001 the Lotronex Action Group petitioned FDA to have the drug reintroduced. FDA would like to obtain the Advisory Committee's assessment of the risks associated with Lotronex[®] and whether the risk-benefit profile of Lotronex[®] has changed. FDA, therefore, has the following issues for your consideration:

- 1) What are the benefits of Lotronex[®] as defined by clinical trials and medical practice, and how do these compare to the drug's safety?

- 2) Does the safety of the drug differ in the setting of a clinical trial compared to practice?
- 3) Does benefit exceed risk? If so, under what circumstances? If not, do you have any recommendations on how to improve the benefit-risk profile?

A second goal of the meeting will be to obtain specific advice on whether an appropriate risk-management program can be established for Lotronex[®], and if so, what the specific characteristics of such a program should be. FDA would like the Committee to recommend details of appropriate risk management interventions. Although GSK has declined to make Lotronex[®] available under an investigational new drug application (IND), the company has been willing to pursue possible reintroduction to the marketplace under restricted conditions. FDA, therefore, has the following issues for your consideration:

- 1) Should this drug be available under restricted marketing conditions?
- 2) If so, what restrictions are needed to assure safe use? For example:
 - a) What is the patient population that should be indicated for Lotronex[®] (e.g., in which benefits would exceed risk)? Describe the population's characteristics.
 - b) What physicians should have access to prescribing Lotronex[®]? Describe the training and expertise needed.
 - c) What role should the pharmacist play in assuring safety and restricted use?
 - d) How should distribution of the drug be controlled? Should doctors be registered with GSK?
 - e) Should patients be registered with GSK? Should pharmacists check registration?
 - f) Should physicians be required to report adverse events?
- 3) How can success of the program be measured?
 - a) Should the program assess if patients are being informed of risks and benefits? Can you define an acceptable level of compliance?
 - b) Should the program audit what types of patients are receiving Lotronex[®] to ensure appropriate use?
 - c) Should the program evaluate (e.g., through an audit) whether physicians who are prescribing Lotronex[®] are the appropriate ones?
 - d) Should the program track adverse events to ensure low rates of prescribing to patients with contraindicated conditions? What rate would be acceptable?

We understand the issues are very complex and appreciate your assistance in providing FDA with your best possible advice. The package enclosed is to provide background data on the above. We look forward to hearing from you on April 23rd.

EXECUTIVE SUMMARY

Executive Summary
LOTRONEX[®] TABLETS

Gastrointestinal Drugs Advisory Committee
Drug Safety and Risk Management Subcommittee
23 April 2002

Goals of the meeting

The Food and Drug Administration (FDA) is holding this meeting of the Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk Management Subcommittee to discuss the risk-benefit profile of Lotronex[®] (alosetron hydrochloride) Tablets. The Advisory Committee deliberations will assist FDA in determining whether Lotronex[®] should be returned to the market, and if so, under what conditions. A focus of the meeting will be on whether an appropriate risk-management program can be established for Lotronex[®], and if so, what the specific characteristics of such a program should be. FDA is seeking advice from the Advisory Committee on issues summarized in the cover document titled *Overview of Selected Issues: Lotronex Tablets*.

Regulatory History of Lotronex[®]

Major events in the regulatory history of Lotronex[®] are summarized in tab 2 of this package (*Highlights of Regulatory History*). Briefly, Lotronex[®] was marketed for eight or nine months before it was withdrawn from the market. The drug was approved by FDA on February 9, 2000 for the treatment of women with irritable bowel syndrome (IBS) whose predominant bowel symptom is diarrhea. But soon after Lotronex[®] was launched, FDA began receiving adverse event reports of serious outcomes associated with its use, including serious complications of constipation and 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, Glaxo Wellcome, 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[®]. This information includes data from clinical trials that were ongoing (and were terminated) when the drug was withdrawn from the market. The submission also includes data from adverse events reported when the drug was marketed. The scope of this information gives FDA a broader scientific foundation upon which to base any possible subsequent regulatory actions on Lotronex[®].

FDA Perspectives on the Efficacy of Lotronex[®]

The primary focus of this Advisory Committee meeting is on the safety of Lotronex[®] and on risk-management issues. However, any discussion of the risk-benefit of Lotronex should also consider how the benefits might be optimized.

Randomized, placebo-controlled clinical trials have demonstrated that Lotronex[®] is effective in women with IBS whose predominant bowel symptom is diarrhea. Outcome measures that have typically been evaluated in these trials include adequate relief of abdominal pain and discomfort, changes in stool consistency or frequency, and relief of urgency.

However, the benefit-risk profile of Lotronex[®] might be further enhanced by either quantitatively or qualitatively improving the drug's benefits. Options include, but are not limited to, the following:

- a) Use of the drug in patients with the most severe symptoms. Given the possibility of greater benefit, patients with the most debilitating symptoms may have a more-favorable risk-benefit profile than patients with lesser symptoms.
- b) Use of the drug in subsets of patients most likely to benefit from its use.
- c) Demonstrating in clinical trials that the drug not only improves symptoms but that it also improves functional performance (e.g., decreases days lost from work or school because of IBS symptoms).

To address some of these issues, FDA has performed additional efficacy analyses from the randomized clinical trials. The results are summarized in the medical review in tab 3, appendix 1 (*Randomized Clinical Trial Experience*), and in the statistical review in tab 4 (*Statistical Perspective*).

FDA Perspectives on the Safety of Lotronex[®]

In the evaluation of the safety of Lotronex[®], FDA performed an assessment of the risk and an analysis of the sponsor's proposed risk-management plan.

A. RISK ASSESSMENT

FDA performed a multidisciplinary review of the safety of Lotronex[®], a summary of which may be found in tab 3 of this package (*FDA Perspectives on Safety*). FDA centered its reviews on analyses of selected serious (or potentially serious) adverse events including ischemic colitis, mesenteric ischemia/infarction, serious complications of constipation, and death. Data from the clinical trials as well as from the marketed use of Lotronex[®] were evaluated.

From a statistical perspective, FDA focused on three main areas concerning the risk of serious adverse events (particularly the risk of ischemic colitis): risk quantification, whether the risk changes over time, and whether subsets of patients at greater or lesser risk can be identified.¹

1. Risk quantification for ischemic colitis

GlaxoSmithKline indicates that 17 cases of ischemic colitis were reported by 17 out of 11,874 subjects receiving Lotronex[®] (crude rate of 1 in 698 subjects) compared to 1 out of 3500 subjects receiving placebo (crude rate of 1 in 3500 subjects). Although FDA medical

¹ Written with the assistance of Dr. Thomas Permutt.

reviewers identified one additional case of ischemic colitis among subjects receiving Lotronex[®], this additional case does not make FDA's estimate of the crude rate of ischemic colitis for subjects treated with Lotronex[®] (18/11,874 or 1 in 660 subjects) materially different from that calculated by GSK.

FDA's statistical analyses of incidence rates of ischemic colitis may be found in tab 3, appendix 4 (*Re-evaluation of the Risk of Ischemic Colitis* by Dr. Zili Li) and in tab 4 (*Statistical Perspective* by Dr. David Hoberman). These reviewers used several approaches to evaluate the rates of ischemic colitis, including evaluation of study-specific incidence rates and rates derived from pooling studies.

a. Study-specific incidence rates:

For his principal analyses, Dr. Li identified the controlled studies of Lotronex[®] that were performed in the target population: U.S. women with irritable bowel syndrome. Fourteen such studies were identified; three of these studies were excluded because they had less than 50 study subjects in the Lotronex[®] group. Dr. Li explains why it may not be appropriate to pool the remaining 11 studies. Instead, he identifies a "representative study" (study S3B30020). Of the 11 studies, this study has the greatest exposure (in person-years) to Lotronex[®]. As shown in table 4 of his review, this study yields a study-specific incidence rate of ischemic colitis of 16.9 per 1000 person years for the Lotronex[®]-treated patients and 0 per 1000 person years for the patients in the control group (traditional therapy).

b. Pooled incidence rates:

- i. By pooling data from 86 studies, GlaxoSmithKline calculates an incidence rate of ischemic colitis of 5.6 cases per 1000 years of Lotronex[®] therapy (See part III and Appendix A of Dr. Li's review).
- ii. Dr. Hoberman performed a pooled analysis of the largest clinical studies (those with at least 100 patients who received Lotronex[®]). The twenty studies that met this criterion accounted for 99% of the person-time over all controlled studies. As shown in Table 2 of his review, these 20 studies yield a pooled estimate of the incidence rate of ischemic colitis of 1/1921 person-months (or 6.2 cases per 1000 person-years).
- iii. A pooled analysis by Dr. Li of the 11 studies performed in the target population yields an incidence rate of ischemic colitis of 9.2 cases per 1000 years of Lotronex[®] therapy (see table 2 of his review).

These analyses differ in details, but the conclusions are similar. The best estimates of excess risk come from placebo-controlled clinical trials. Most of the exposure was in studies of three months' duration. There is less information about the risk of longer exposure. The estimates of risk across trials vary, and there is no best way of taking this variability into account. However, the estimates of risk are all of the same order of magnitude with an uncertainty factor of two or three. The lack of agreement across studies

(and therefore between methods of choosing and combining studies) contributes some additional uncertainty, but not of an order of magnitude.

Dr. Brinker (tab 3, appendix 4 *Comments on Epidemiological Studies*) estimates that about 83% of spontaneous reports of ischemic colitis reported in association with Lotronex[®] can be attributed to Lotronex[®] and not to background disease. He arrives at this conclusion using a relative risk for ischemic colitis in association with Lotronex[®] of 5.9 (with wide confidence intervals) that was seen in the original NDA. Also, see tab 3, appendix 7: *Causality Assessment*.

2. Change in risk over time

For an assessment of whether risk of ischemic colitis changes over time, see tab 3, appendix 4 (*Re-evaluation of the Risk of Ischemic Colitis* by Dr. Zili Li) and tab 4 (*Statistical Perspective* by Dr. David Hoberman). An assessment of risk over time is important for several reasons. First, the cumulative risk after long exposure cannot be estimated precisely without information about how the risk varies with the time of exposure. Second, the variation over time could be important. If the risk per unit time increased with longer exposure, then patients in clinical practice would be exposed to greater risks than the risks seen in clinical trials. Conversely, if the risk per unit time decreased, then careful observation and treatment during the early period of greatest hazard might mitigate the overall risk. The analysis performed by FDA shows that there is insufficient statistical power to confirm changes in rates over time due to the wide range of 95% confidence intervals around the estimates (see Figure 1 in Dr. Li's review). These limited data suggest that the risk does not appear to increase over time. While the risk may decrease after the first month, the evidence to support such a conclusion is extremely limited.

3. Risk in subsets of patients

If more were known about who might be at risk of developing ischemic colitis, then therapy could potentially be tailored to reduce the risk. It might be avoided altogether in groups at most risk, or extra caution in the evaluation and treatment of high-risk patients might be recommended. GlaxoSmithKline's findings in this regard are negative. No groups at substantially higher or lower risk than others have been identified. Appropriate techniques were applied to search for them, but with the small number of cases of ischemic colitis observed, only very strong risk factors would have been detected.

B. RISK MANAGEMENT

An overview of risk management may be found in tab 5 (*Goals of Risk Management*). This document discusses options for Lotronex[®] risk management based on a model proposed in the May 1999 Report to the Commissioner by the Task Force on Risk Management. The document presents features of current restricted distribution plans, advantages and disadvantages of selected plan features, a description and critique of the plan proposed by GlaxoSmithKline, and

four plan options ranging from more restrictive to less restrictive. The GlaxoSmithKline plan to evaluate results is also briefly addressed.

FDA has provided this material to provide a framework for the Advisory Committee deliberations on risk management.

Victor F. C. Raczkowski, M.D.

**HIGHLIGHTS
OF
REGULATORY
HISTORY**

Highlights of the Regulatory History of Lotronex™, NDA 21-107

Paul E. Levine, Jr., R.Ph., Regulatory Project Manager

Review of Original NDA

The NDA for Lotronex (alosetron) was received from GlaxoWellcome on June 30, 1999, and given a priority 6-month review. Lotronex was granted priority review because of the possibility that the drug, if approved, would be a significant improvement compared to marketed products, in the treatment of IBS.

The pivotal clinical trials for Lotronex demonstrated drug efficacy for adequate relief of abdominal pain and discomfort (primary endpoint), as well as improvement of stool frequency, stool consistency and urgency. Two major adverse events were noted: dose-related constipation and ischemic colitis. No patients with constipation experienced serious complications. Four patients were reported to have experienced transient, self-limited ischemic colitis. However, no cases of ischemic colitis were reported in patients treated with placebo. These events were assessed as being self-limited and reversible upon discontinuation of Lotronex. In clinical trials, no deaths occurred in patients receiving Lotronex

First Gastrointestinal Drugs Advisory Committee - November 16, 1999

While the full impact of adverse events of ischemic colitis and constipation was not clear, concerns were raised about the possibility of increasing numbers and greater severity of adverse events in the larger, post-marketing patient population. These concerns were presented at the Gastrointestinal Drugs Advisory Committee on November 16, 1999, at which the diagnosis of ischemic colitis was debated. However, based on the available information, the committee unanimously recommended approval of Lotronex. After an independent review of the colonic pathology specimens (requested by FDA and received February 4, 2000), the Agency concluded that the four cases were most consistent with the diagnosis of ischemic colitis rather than other diagnoses. The company agreed to include a statement about the risk for ischemic colitis in the Warnings section of the drug's approved package insert.

Approval of Lotronex - February 9, 2000

Lotronex was approved on February 9, 2000, "*for the treatment of irritable bowel syndrome (IBS) in women whose predominant bowel symptom is diarrhea. The safety and effectiveness of LOTRONEX in men have not been established.*" The WARNING section of the approved labeling listed acute ischemic colitis as being infrequently reported (1/100 to 1/1000), and constipation as a frequent and dose-related side effect.

Post-Approval Reports of Adverse Events

After the marketing of Lotronex, FDA began receiving reports of serious complications of constipation and ischemic colitis associated with use of the drug. By June 1, 2000, FDA had received seven reports of serious complications of constipation, three of which required surgical intervention; and twelve new cases of ischemic colitis, none of which required surgery. No deaths were reported.

As a result of the increasing seriousness of post-marketing reports of gastrointestinal adverse events, FDA began extensive interactions with GlaxoWellcome to initiate a Risk-Management Plan that would significantly reduce the incidence of serious adverse events associated with the use of Lotronex. This included a request for GlaxoWellcome to include a Black Box Warning to the labeling.

Second Gastrointestinal Drugs Advisory Committee – June 27, 2000

On June 27, 2000, a second Gastrointestinal Drugs Advisory Committee convened to discuss issues related to the risks of serious adverse events associated with the use of Lotronex. Components of a Risk Management Plan that were discussed included (1) risk identification, (2) risk communication (dissemination of safety information), and (3) program monitoring and evaluation. The Committee concluded that both physicians and patients needed to be informed of the potentially serious adverse effects associated with the use of Lotronex. A Medication Guide, to educate patients about Lotronex, was discussed and supported by the Committee.

Subsequent Risk Management Communications

Following extensive communications between GlaxoWellcome and the FDA, the labeling for Lotronex was revised to highlight the risks associated with the drug. FDA approved “Dear Health Care Professional” and “Dear Pharmacist” letters, as well as Medication Guides for patients were distributed by GlaxoWellcome. Discussions continued for the remaining elements of the risk management plan. In an effort to increase public awareness of the new safety concerns, FDA issued press releases, and contacted professional organizations and patient advocacy groups.

On September 8, 2000, the Agency received a Citizen Petition by the Public Citizen Health Research Group requesting removal of Lotronex from the market due to the safety profile of the drug.

In September 2000, FDA received the first report of death associated with Lotronex. Within 6-8 weeks of that initial report, FDA received reports of four additional deaths and the first reports of ischemic colitis leading to surgical complications associated with the use of Lotronex. CDER staff questioned the adequacy of the existing risk management interventions to address the drug’s risks.

Withdrawal of Lotronex - November 28, 2000

On November 28, 2000, FDA met with GlaxoWellcome and proposed the following options: (1) voluntary withdrawal of Lotronex from the market with limited access under an Investigational New Drug application (IND), (2) temporary suspension of drug marketing pending a public advisory committee discussion of scientific issues related to the safe use of Lotronex, and (3) restricted distribution to patients currently receiving Lotronex who sign an informed consent form. After considering these options, GlaxoWellcome voluntarily withdrew Lotronex from the market. On November 28, 2000, GlaxoWellcome released a public announcement stating its decision to cease worldwide development and distribution of Lotronex. In a letter submitted December 21, 2000, the Agency was officially notified that GlaxoWellcome had ceased all sales and distribution of Lotronex.

Post-Withdrawal Communications

Following the withdrawal of Lotronex, GlaxoWellcome merged with SmithKline & Beecham to form GlaxoSmithKline (GSK).

Since withdrawal of Lotronex from the market, many patients have contacted the FDA seeking access to the drug. Many of these patients have described their suffering from the chronic and debilitating nature of their IBS symptoms, and have expressed frustration with their inability to successfully control their IBS symptoms with therapies other than Lotronex. These patients have indicated that they are desperate for access to Lotronex.

On April 9, 2001, the Lotronex Action Group, a patient advocacy group, submitted a citizen petition to the FDA requesting that Lotronex be returned to the market.

Since the withdrawal of Lotronex, FDA and GSK have had many communications about the possible options for making Lotronex available to appropriate IBS patients. Although GSK has declined to pursue the option of making Lotronex available to patients under an IND, the company has been willing to pursue the option of market access to patients under restricted conditions.

Also, since withdrawal, substantial amounts of new safety information from clinical trials have become available. Therefore, after discussions and meetings with the Agency, the sponsor agreed to submit a revised risk management plan, the new study data, and revised product labeling as part of a supplement to the NDA for the possible re-introduction of Lotronex to the market. The Agency asked that GSK submit for review all additional study data from the entire development plan for Lotronex, in order to better quantify the risks. The complete supplement was submitted on December 07, 2001, and is being expeditiously reviewed.

**FDA
PERSPECTIVES
ON SAFETY**

NDA 21-107/S-005

LOTRONEX[®] (alosetron hydrochloride)

Sponsor's submission of December 7, 2001

FDA Perspectives on Safety

Hugo E. Gallo-Torres, M.D., Ph.D.
**Medical Team leader, Division of Gastrointestinal
and Coagulation Drug Products, HFD-180**

LOTRONEX[®]
FDA Perspectives on safety
Tables of Contents

Executive Summary	3
I. Background/Introduction	7
II. ISCHEMIC COLITIS	9
A. Randomized Clinical Trial Experience	9
B. Incidence Rate of IC in RCTs	12
C. Alternative Approach to Reevaluate the Risk of Alosetron-Associated Ischemic Colitis	13
D. Post-Marketing Reports of Alosetron-Associated Ischemic Colitis	14
E. Ischemic Bowel Complications (Including Ischemic Colitis) Associated with Alosetron (LOTRONEX[®]) intake: A Clinical Perspective	15
F. Summary Comments on Epidemiologic Studies Pertinent to Ischemic Colitis	16
G. Possible Mechanisms by Which Ischemic Colitis due to Alosetron Occurs	17
III. SERIOUS COMPLICATIONS OF SEVERE CONSTIPATION	18
A. Randomized Clinical Trial Experience	18
B. Post-Marketing Reports of Alosetron-Associated Serious Constipation	19
C. Clinical Review of LOTRONEX (Alosetron)-Associated Serious Complications of Severe Constipation Reported Post-Marketing	20
IV. MESENTERIC ISCHEMIA	20
V. DEATHS	21
A. Summary of all Death Cases (Post-Marketing Experience)	21
B. Clinical Perspective: Deaths Reported in Association with the use of Alosetron	21
VI. CAUSALITY ASSESSMENT	22

LOTRONEX® FDA Perspectives on Safety

EXECUTIVE SUMMARY

The objective of this multidisciplinary review on alosetron safety is to consolidate these issues into a central document for the advisory committee members. The primary approach will consist of briefly highlighting important aspects of the safety reviews while providing the entire reviews in the form of appendices. Based on randomized clinical trial (RCT) data evaluations, Lotronex is, all in all, well tolerated. The most common group of alosetron-related disorders are confined to the gastrointestinal (GI) tract system. At the time of approval, the major adverse event (AE) in the clinical trials was constipation occurring in 26% to 30% of patients at the alosetron dose of 1 mg b.i.d., significantly greater than the 5% of patients on placebo. The constipation was dose-related and was the most frequent reason for patients to withdraw from clinical trials. Four cases of mild, acute, self-limiting ischemic colitis (IC) which resolved without overt sequelae were identified before approval. Prior to approval, there was no clear cut evidence for a causal relationship between the development of this ischemic colitis and alosetron. But alosetron's direct or indirect contribution in these initial 4 cases of IC could not be eliminated with certainty as none was seen among those patients taking placebo. Lotronex® was approved on February 9, 2000. Soon after marketing, a **significant shift** was noted related to the seriousness and severity of IC cases. Also reported were cases of serious complications of severe constipation ranging from fecal impaction to obstruction, toxic megacolon, perforation and gangrenous colitis. Some of these patients required hospitalization and surgical removal of part or even the entire colon. Following the November, 2000 voluntary withdrawal of LOTRONEX® from the market, many patients contacted the Agency seeking access to LOTRONEX®. In an sNDA submitted December 7, 2001 GSK is requesting re-marketing approval through 21 CFR 314 Subpart H under a Restricted Distribution Program.

In this review, the risks associated with LOTRONEX® administration are further characterized. Summary discussion is focused on **serious adverse events** including ischemic colitis, mesenteric ischemia/infarction, serious complications of constipation and deaths. For each of these topics, data from the RCT experience and initial and follow-up reports from the spontaneous reporting system (AERS) are considered. Also added, where applicable, are discussions on epidemiological issues, approaches to calculate incidence rates and on possible mechanisms by which colonic ischemia/ischemic colitis due to alosetron occurs. The present summary concludes with an appraisal on the available evidence supporting a causal association for LOTRONEX® with these SAEs.

ISCHEMIC COLITIS (Overall Summary Table)

When collectively analyzed, in all RCTs a total of 19 cases of ischemic colitis were reported, 18 in patients treated with alosetron and one in a patient treated with placebo:

Ischemic Colitis			
<u>ALOSETRON mg b.i.d.</u> [n=18/ 11,874]			PLACEBO b.i.d. [n=1/ 2,935]
0.5	1.0	2.0	
[n=1] ^a	[n=16] ^b	[n=1] ^c	[n=1] ^d
a. Study S3B20023 b. 10 of 16 cases in Study S3B30020 c. Study S3BA2001 d. Study S3BA3003			

Overall Summary Table
Lotronex-Associated Serious Adverse Events

Selected Outcomes	Ischemic Colitis	Serious Complications of Severe Constipation
-------------------	------------------	--

I. Pre-Approval (November 1999) n= 633

Cases	4	1
Hospitalization	4	1
Surgery	0	0
Deaths	0	0

II. Overall RCT Experience (Clinical Study Reports)^a (December 7, 2001)

n = 11,874

Cases	18	12
Hospitalization	7	11
Surgery	1	1
Deaths	0	0

III. OPDRA/ODS Post-Marketing Safety Review^b

Use estimated at 275,000 patients and 534,000 prescriptions^c

Cases^d	85	107
Hospitalization	52	78
Surgery	9	30
Deaths	2^e	2^f

- a. In all patients experiencing IC, the test medication was discontinued and the patient was eventually withdrawn from the trial.
- b. Data as of **December 31,2001**. Included are initial and follow-up reports from AERs, the spontaneous reporting system.
- c. GlaxoSmithKline, "Briefing Document for the Joint Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management Subcommittee April 23, 2002", Section 4.2.2, page 56. *Data from March 13, 2000 (product launch) through December 31, 2000.*
- d. Hospitalization, surgery and death may be included in multiple categories; therefore cannot be added together to equal the total.
- e. Assessed as PROBABLY related to alosetron
- f. Assessed as PROBABLY related to alosetron

Just as the 4 original cases, the newly described patients in the subsequent RCTs had a clinical syndrome characterized by a) bloody stool/bloody diarrhea occurring in association with abdominal pain (sometimes 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 sometimes confirmation on histopathological examination.

- The IC in RCTs, 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** because the patient responded well to **drug discontinuation**. The event usually resolved within 2 weeks with no overt sequelae. But, at this point in time, there are no long-term follow-up endoscopic data demonstrating that the colonic mucosa has fully recovered.
- Results from Study **S3B30020**, (reviewed by Dr. S. Kress, Clinical Reviewer, HFD-180) a 24 week randomized, **open-label** study are discussed in detail because in this trial, IC occurred as a serious adverse event (SAE) in 10 alosetron-treated patients (total n= 1,828) and none in the 899 treated with traditional therapy. In this study nearly all patients experiencing IC (like in most cases in other RCTs) reported use of concurrent medications such as antidepressants, NSAIDs and estrogens but, as it is repeatedly stated, risk factors for IC in -30020 and other trials, are yet to be identified.
- Two approaches to calculate incidence rates of IC in RCTs are described. One, documented in Tables 1 and 2 of Dr. Hoberman's statistical review (Tab 4), consists in pooling the information from pertinent clinical trials. Using this approach an overall incidence on 1/1921 person-months over 20 studies (see more details in Dr. D.Hoberman's Statistical Review) is obtained and this is similar to the incidence rate of IC seen at the time of approval. The other, proposed by Dr. Z. Li (Medical Epidemiologist, HFD-430) consists of identifying the "most representative" study – **30020**, considered the most reasonable and reliable estimate for the risk of IC among female IBS patients in the United States. With this alternative approach the calculated rate of 16.9 cases per 1,000 person years is ca. **3 times higher** than the 5.6 per 1,000 person years calculated by GSK. See table 4 of Dr. Li's review (Appendix 2).
- The Post-Marketing reports of alosetron-associated IC are summarized in the Overall Summary Table. Of the **85** patients who developed IC in association with the use of alosetron, **52** required hospitalization and **9** required surgery; **2** reported deaths were in **probable association** with the use of the drug. With regard to presenting symptoms for possible early detection of serious outcomes, the post-marketing data showed that bloody stool and abdominal pain are neither sensitive nor specific to IC.
- Dr. M. Barreiro (Clinical Reviewer, HFD-180)'s appraisal of all IC cases allowed the conclusion that **83%** of the alosetron-associated ischemic bowel disease cases were of reversible, mild forms that resolved spontaneously and left no apparent sequelae upon discontinuation of the drug while **17%** of the cases represented **severe forms** of the disease. There is an ever-increasing list of drugs associated with ischemic colitis.
- Several conclusions were reached by Dr. A. Brinker (Epidemiology Team Leader, HFD-430) from his analysis of results of 10 epidemiology studies pertinent to IC (Appendix 4). Among these conclusions were that during initial U.S. marketing, the majority of LOTRONEX[®] prescribers were not gastroenterologists. Clinicians may utilize IBS as an interim diagnosis or, in the absence of colonoscopic/sigmoidoscopic evidence misdiagnose other, more serious conditions (e.g. inflammatory bowel disease, ischemic colitis, etc.) as IBS. The data and analysis based on the Ingenix Research Database support a "background" rate of IC among U.S. IBS patients, a finding that needs to be validated. Dr. Brinker concluded that the best estimate of an association between LOTRONEX[®] and IC will be derived from randomized, double-blind, placebo-controlled trials of the drug in IBS patients. The relative risk for IC in association with LOTRONEX[®] of 5.9 [with 95% CI (logit) of 0.3 to 114] was used to determine that most (83%) spontaneous reports of IC reported in association with LOTRONEX[®] can be attributed to LOTRONEX[®] and not background disease.
- An initial hypothesis to explain how does alosetron-induced ischemic bowel disease/ischemic colitis occur is proposed by Dr. M. Barreiro (HFD-180). Based on this proposal, it is suggested that, as part of the risk management plan (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 evaluations**. It is further recommended to ask GSK to perform a retrospective study of genetic and coagulation factors in patients who have had any form of alosetron-associated ischemic bowel disease during the RCTs or, if possible, during the post-marketing period up to November 28, 2000.

SERIOUS CONSTIPATION

- Selected outcomes of the 12 cases of serious complications of severe constipation (SCSC) occurring as part of the overall RCT experience are listed in the Overall Summary Table. Of the 12 cases of SCSC, 11 required hospitalization and 1 required surgery. The patient that required surgery (from study – **30020**) had developed toxic megacolon, fulminant secondary ischemic, gangrenous (**transmural**) colitis and septicemia; a total colectomy and ileostomy was performed in this patient. Once again, of special interest are results from study –30020 because in this trial 6 of the alosetron-treated patients but none of those given traditional therapy developed SCSC. Nearly all patients reported use of concurrent medications; the most common groups were anti-depressant (30%, specifically SSRIs), NSAIDs (13%) and estrogens (30%).
- An update of the OPDRA/ODS post-marketing safety data is given in the Overall Summary Table. Of the **107 cases** of SCSC, **78** were hospitalized and **30** required surgery; **2** reported deaths were in **probable association** with the use of the drug. As in the case of IC, an examination of the available data allows the conclusion that there is not enough evidence to determine which patients with SCSC will progress to more serious outcomes.
- In a clinical appraisal of the SCSC cases reported post-marketing, Dr. S. Kress (HFD-180) identified a set of patients who apparently **did not report constipation** even though they already **were impacted**. This type of event represents a further challenge to the management of alosetron-induced complications of constipation.

MESENTERIC ISCHEMIA

A review of all cases of alosetron-associated IC, carried out by Dr. M. Barreiro (HFD-180), revealed that in 5 cases [3 of mesenteric vein thromboses (MVT) one of colonic gangrene (CG) and one of transient ulcerated ischemic colitis (TUIC)] there was strong suspicion that a hypercoagulable state (HCS) might have played a role in the development of alosetron-associated ischemic bowel disease. In his review Dr. M. Barreiro (HFD-180) notes that MVT and CG are among the most serious, life threatening forms of ischemic bowel disease.

DEATHS

- The RCT experience did not include reports of deaths (Overall Summary Table).
- The OPDRA/ODS report reveals that, as of August 17, 2001, there were a total of 13 deaths in patients receiving alosetron. Of these 13, 7 deaths showed a strong association with alosetron: 2 cases of IC, 2 of complications of serious constipation (Overall Summary Table) and 3 (not included in the Overall Summary Table) of small bowel ischemia.
- In agreement with the above-summarized OPDRA/ODS conclusions on deaths, Dr S. Kress (HFD-180) reported that of the 13 deaths, 3 were probably related to alosetron usage and 2 were possibly related to alosetron usage, 2 were determined to be probably related to an alternate cause, although alosetron usage was a possible contributor. It was also noted that in some of the patients that died there were multiple reasons that could explain the patient's death. It was further noted that, based on the available information, none of the remaining 6 deaths could be attributed to alosetron usage.

CAUSALITY ASSESSMENT

From his appraisal on causality, based on an analysis of the **totality of evidence**, Dr. Z. Li (Epidemiologist reviewer, HFD-430) concludes that there is support for the hypothesis that alosetron can cause constipation and ischemic colitis, which may lead to **rare but serious complications** (Appendix 7). It is emphasized 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. This established association does not mean that all reported cases of constipation, ischemic colitis and their complications among alosetron users are necessarily the result of alosetron use.

LOTRONEX[®]

FDA Perspective on Safety

I. BACKGROUND/INTRODUCTION

NDA 21-107 for LOTRONEX[®] (alosetron hydrochloride) tablets was received from Glaxo Wellcome (GW) on June 30, 1999 and given priority review status. The main evidence of efficacy¹ consisted of two adequate and well-designed 12-week trials comparing alosetron 1 mg b.i.d. to placebo. The drug was, all in all, well tolerated in the trial setting. The most common group of alosetron-related disorders were confined to the gastrointestinal (GI) tract system. The major adverse event (AE) was constipation, occurring in 26% to 30% of patients at the alosetron dose of 1 mg b.i.d., significantly greater than the 5% of patients on placebo. The constipation was dose-related and was the most frequent cause for patients to withdraw from the trials. Before approval, four alosetron-treated patients, each participating in a separate randomized clinical trial, experienced episodes of ischemic/infectious colitis.

A review of all the available information, including clinical summaries and pathology assessment, demonstrated that all 4 patients had a clinical syndrome of **ischemic colitis (IC)**. This clinical impression was consistently confirmed on endoscopic examination but was not always confirmed on histopathological evaluations. This ischemic colitis can be described as mild (meaning superficial, **non-transmural**), acute, self-limiting and to resolve without overt sequelae. NDA 21-107 was presented to the GI Drugs Advisory Committee (AC) on November 16, 1999². At that time, there was no clear cut evidence for a causal relationship between alosetron treatment and the development of this ischemic colitis. On the other hand, the direct or indirect contribution of alosetron use in these initial 4 cases of ischemic colitis could not be eliminated with certainty since none was seen among those patients taking placebo. Lotronex was approved on February 9, 2000³.

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 the previous experience with the drug in clinical trials.

¹ Efficacy in NDA 21-107 was reviewed by Dr. R. Prizont. In both trials, the primary endpoint of efficacy, adequate relief of IBS pain and discomfort, showed 10 to 15% therapeutic gain (over placebo) as well as similar improvement on stool frequency, stool consistency and urgency.

² The AC found the generally understood benefit-risk relationship acceptable and recommended unanimous approval of the drug.

³ This Regulatory Action was taken only when the Agency judged that Lotronex[®]'s benefits 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 and further review of these IC cases.

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)⁴. The sponsor subsequently submitted several versions of a RMP⁵ but it was clear that the Agency did not find the sponsor's RMPs entirely satisfactory⁶.

At a 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 disabling** nature of their IBS symptoms⁷.

Early in 2001, upon reconsideration of two possible options for patient access to Lotronex, 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 addressed in a separate document by Dr. Toni Piazza-Hepp (Tab 5). In the present multidisciplinary review, FDA perspectives on safety are given.

The risks associated with LOTRONEX[®] administration are further characterized by reviewing and analyzing data from two main sources: the randomized clinical trial experience and initial and follow-up reports from the spontaneous reporting system. To this information, an epidemiological appraisal is added. This discussion is focused on serious adverse events including ischemic colitis, mesenteric infarction, serious complications of severe constipation and deaths. Initial approaches to calculate incidence rates of ischemic colitis, especially the opportunities and constraints encountered when pooling vs. non-pooling information from randomized clinical trials, are discussed. Also included is a discussion by Dr. M. Barreiro on the possible mechanisms by which ischemic colitis due to alosetron occurs. The present document concludes with a summary appraisal by Dr. Z. Li on the available evidence supporting a causal association for Lotronex with SAEs.

⁴ 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 AE associated with the use of Lotronex. The need for a Medication Guide was discussed and supported by the Committee.

⁵ The sponsor began 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.

⁶ This situation was compounded because of the significantly increasing use of the drug: during a 9-month period, over 300,000 patients filled more than 450,000 prescriptions of the drug. At the time of the drug's withdrawal from the market, the number of prescription may have been more than 600,000 (according to data provided by the Sponsor).

⁷ 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.

NOTE: Not included in the current document are more complete analyses dealing with time-to-event, cumulative risk, and whether the hazard rates change over time which are addressed in a separate document by Dr. D. Hoberman (Biometrics). Likewise, results of analyses of possible risk factors including sex, age, race/ethnicity, dose, treatment duration, cumulative dosage, treatment with Lotronex for a diagnosis other than for DP-IBS, concomitant medications (e.g. estrogen, beta-blockers) are not included in this review as GSK has not submitted results of these requested evaluations to the Agency.

The materials addressed in the following sections of the present review are the result of contributions from many individuals. Under the various sections and subsections you will find some text highlighting the main findings and when possible, arriving at conclusions. The reader is then referred to the corresponding Appendix, at the end of the document, for a more complete evaluation (review) of the subject matter.

II. ISCHEMIC COLITIS

A. Randomized Clinical Trial Experience (Appendix 1)

- The total number of alosetron patients exposed (Table 4 in Appendix 3) is 10,960. The RCT experience included 12 studies with concurrent placebo control, 4 open-label, and 3 in which indications other than IBS (i.e. anxiety, non-cardiac chest pain, non-ulcer dyspepsia) were studied (Table 1 in Appendix 3); 13 of the trials were completed, while the other 13 were terminated early. Most of the trials included only females while in 5 the study population consisted of males and females. One study randomized only male patients. In most trials the duration of treatment was 12 weeks but ranged from 14 days to 1 year. The bulk of the trials was randomized, double-blind.

Trials of special interest include: **S3BA3001** and **-3002** the 2 pivotal trials submitted in the original NDA; **S3B30011** and **-40031 bowel urgency trials** demonstrating effectiveness in patients with **severe** IBS; the two completed active concurrent control trials (**S3BB3001**=mebeverine; **-3002**=**trimebutine**); the two long-term trials, **S3BA3003** (which enrolled M & F patients) and **S3B30006**; and finally, **S3B30020**; 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.

All in all, a total of 19 cases of ischemic colitis were reported out of 11,874 alosetron-treated study patients and 2,935 placebo-treated patients with the following distribution:

Ischemic Colitis [Total n=19]			
<u>ALOSETRON mg b.i.d. [n=18/ 11,874]</u>			<u>PLACEBO b.i.d. [n=1/ 2935]</u>
0.5	1.0	2.0	
[n=1]^a	[n=16]^b	[n=1]^c	[n=1]^d
a. Study S3B20023 b. 10 of 16 cases in Study S3B30020 c. Study S3BA2001 d. Study S3BA3003			

- In **Table 3** (of Appendix 1), 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. The case summaries for each of the patients experiencing IC are given in Appendix 1.
- Just as the 4 original cases, the newly described patients have 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.
- Detail of the outcome of these cases of ischemic colitis are given below. Seven of the 18 cases had to be hospitalized, one (from Study **S3B30020**) underwent **surgical intervention** because of IC, but no patient died.

Lotronex-Associated Ischemic Colitis

The Randomized Clinical Trial Experience

Selected Outcome	Ischemic Colitis
Cases	18
Hospitalization	7
Surgery	1 ^a
Death	0

- a. This patient (from Study-30020) developed a colonic perforation, peritonitis and sepsis and required a sigmoid resection and colostomy. She subsequently suffered a stroke. IC was reported by the patient's attorney to be present on pathological review of excised tissue.

- The ischemic colitis 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. The event usually resolved within 2 weeks with no overt sequelae.
- Results from Study **S3B30020**, a 24-week randomized, open label trial that evaluated 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%). IC occurred as a SAE in 10 alosetron-treated patients and none of the 899 treated with traditional therapy. Although 6 of the 10 patients developing IC required hospitalization, in 9 the event resolved with **conservative treatment**. In Study - 30020 nearly all patients experiencing IC (like in most cases in other RCTs) reported use of concurrent medications, such as antidepressants, NSAIDs and estrogens but, at this point in time, risk factors for IC in -30020 and other trials, are yet to be identified.

B. Incidence Rate of IC in RCTs: Pooled Data

- An approach documented in Tables 5 and 6 of Appendix 1, is to pool the information from pertinent clinical trials.

Table 6
sNDA 21-107/S-005
Overall Estimate of the Incidence
Density based on pooling all
20 Trials^a

<u>Study</u>	<u>Incidence density (/per-month)</u>
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

^aComputations by Dr. D. Hoberman (Biometrics)

The conclusion derived from this approach is that the newly appraised (overall RCT) experience yields similar incidence rates of ischemic colitis to those already included in the ALOSETRON[®] labeling.

C. Alternative Approach to Reevaluate the Risk of Alosetron-Associated

Ischemic Colitis: Most Representative Study (Appendix 2)

Dr. Z. Li, a Medical Epidemiologist from the Drug Risk Evaluation Division (HFD-430), has carried out an analysis 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.

Dr. Li's analysis focused on 11 of 86 clinical studies that 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 reviewer believes that 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 in an open-label design. 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.

Dr. Li notes that 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, Dr. Li 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. He notes that the rate of 16.9 cases per 1,000 person years, while being consistent with a previous FDA 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.

It is also noted that 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 uses were not associated with the development of IC among alosetron-treated patients.

It is further noted that, at this point, strategies to reduce the risk of IC are lacking, 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.

In conclusion, Dr. Li suggests that the risk of IC may be three times higher than that presented in GSK's current submission.

D. Post-Marketing Reports of Alosetron-Associated Ischemic Colitis (Appendix 3)

The Adverse Event Reporting System (AERS) is a passive surveillance system that is subject to underreporting.

In their memorandum in Appendix 3, which uses a cut-off date of **August 17, 2001**, Mrs. A. Corken Mackey (Safety Evaluator) and Dr. Z. Li (Medical Epidemiologist) analyzed post-marketing reports of patients who developed ischemic colitis in association with the use of alosetron to assess probable etiology and risk factors. They note that during the 9 month period during which the drug was available in the market, a total of 534,000⁸ alosetron prescriptions were dispensed in the United States.

- An update, using a cut-off date of **December 31, 2001**, is given below.

Lotronex-Associated Ischemic Colitis ODS Post-Marketing Safety Review^a Data as of December 31, 2001

Selected Outcomes	Ischemic Colitis
Case	85
Hospitalization	52
Surgery	9
Death	2^b

- a. Estimated 534,000 prescriptions for 275,000 patients - GlaxoSmithKline, "Briefing Document for the Joint Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management Subcommittee April 23, 2002", Section 4.2.2, page 56. *Data from March 13, 2000 (product launch) through December 31, 2000.*
- b. Deaths are addressed in Section V of the current review.

⁸ GlaxoSmithKline, "Briefing Document for the Joint Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management Subcommittee April 23, 2002", Section 4.2.2, page 56.

These reviewers point out that postmarketing data can be used to capture information that clinical trials for alosetron were not able to capture. Among the 4 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 severe complications of ischemic colitis requiring surgery (colectomy), including 2 cases of death. Of the [total] 161 patients who experienced ischemic colitis or complications of serious constipation as described by these reviewers, 6 (4%) were male, at least 15 (9%) of patients using alosetron had contraindication 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 sumatriptan 2 (3%). With regard to presenting symptoms for possible early detection of serious outcomes, postmarketing data found that 47 (62%) of patients with ischemic colitis had bloody stool, 12 (16%) had constipation, and 56 (74%) had abdominal pain. These could be symptoms of ischemic colitis or manifestations of other conditions. Therefore, these symptoms are considered neither sensitive nor specific to ischemic colitis.

The reviewers concluded that there is not enough evidence to determine which patients with ischemic colitis will progress to more serious outcome.

E. Ischemic Bowel Complications (Including ischemic colitis) Associated With Alosetron (LOTRONEX[®]) intake: A Clinical Perspective

Dr. M. Barreiro (Medical Officer, HFD-180) reviewed the clinical appraisal of the ischemic bowel disease cases reported in the RCTs and the AERS system. Among the interesting conclusions from this review are a) 83% of the alosetron-associated ischemic bowel disease was the reversible, mild form that resolved spontaneously and without apparent sequelae, upon discontinuation of alosetron therapy; and b) 17% of the cases represented the severe form of the disease (see section IV. of the current review).

F. Summary Comments on Epidemiologic Studies Pertinent to Ischemic Colitis (Appendix 4)

Dr. A. Brinker, Epidemiology Team Leader, Division of Drug Risk Evaluation (HFD-430) addresses relevant and novel information in 10 epidemiologic studies pertinent to ischemic colitis and the possible re-introduction of Lotronex[®] to the U.S. market place. Dr. Brinker concluded that the 10 epidemiological studies support the following positions:

1. During initial U.S. marketing, the majority of Lotronex prescribers were not gastroenterologists.
2. The diagnosis of IBS is sometimes uncertain and therefore problematic. Clinicians may utilize IBS as an interim diagnosis or in the absence of colonoscopic/sigmoidoscopic evidence, underdiagnose other, more serious conditions such as inflammatory bowel disease, ischemic colitis, etc. as IBS.
3. Although the data and analysis based on the GSK's submitted Ingenix Research Database support a "background" rate of ischemic colitis among U.S. patients given a diagnosis of IBS in clinical practice, this important finding 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, 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. There is an (apparent) heterogeneity of an "IBS" diagnosis and an established concern for ischemic colitis in association with Lotronex. Additional examination of this association in retrospective, observational settings for regulatory purposes is impractical and is 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.

G. Possible Mechanisms by Which Ischemic Colitis due to Alosetron Occurs (Appendix 5)

The mechanism (s) by which alosetron induces ischemic colitis is not know. At the first meeting of the Gastrointestinal Drugs Advisory Committee on alosetron, Dr. M. Gershon (Columbia University), one of the GW consultants, commented that alosetron would not be involved in inducing IC because there are no 5-HT₃ receptors in the wall of the intestinal vessels and therefore a pharmacological effect of the drug, such as vasoconstriction, is not pathophysiological possible. However, others have stated that to conclude that an AE is due to a drug it is not necessary to elucidate the mechanism. Indeed, with the scant available information, one can only speculate on the mechanism of the ischemia⁹.

In Appendix 5, an initial hypothesis to explain how does alosetron-induced ischemic bowel disease/ischemic colitis occur is proposed by Dr. M. Barreiro (HFD-180). Dr. Barreiro hypothesizes that a small but significant proportion of the population is genetically different in one of two possible ways:

- They metabolize alosetron differently when in presence of other drugs metabolized by same CYP 450 enzyme system. 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 alosetron-associated ischemic bowel disease that may range in severity from the usually seen mild, acute, self-limiting IC, to more serious thrombotic events. Candidates for these untoward effects are patients with a history of deep vein thrombosis (DVT), those on birth control pills, complicated pregnancies, myeloproliferative disorders, malignancies, etc.

Based on these assumptions, Dr. Barreiro suggested that, as part of the risk management program, 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. He further recommends that a retrospective study be performed of genetic and coagulation factors in patients who have had any form of alosetron-associated ischemic bowel disease, during the RCTs or, if possible, during the post-marketing period up to 28 November 2000.

⁹ D. Friedel and R.S. Fisher.
Ischemic colitis during treatment with alosetron.
Gastroenterology 120:557-560 (2001)

III. SERIOUS COMPLICATIONS OF SEVERE CONSTIPATION (SCSC)

A. Randomized Clinical Trial Experience (Appendix 1)

In Table 7 of Appendix 1, 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. Also given in Appendix 1 are the case summaries for each of the patients experiencing serious complications of severe constipation. Details of the 12 cases of alosetron-associated SCSC are summarized below. Eleven of the 12 cases had to be hospitalized, one (from study **S3B30020**), underwent surgical intervention, but no patient died.

Lotronex-Associated Serious Complications of Severe Constipation (SCSC)

The Randomized Clinical Trial Experience^a n = 11,874

Selected Outcomes	SCSC
Cases	12
Hospitalization	11
Surgery	1 ^b
Death	0

- a. In the overall RCT experience, a total of 15 patients (alosetron=12; placebo=3) experienced SCSC.
- b. This patient (from Study -30020) developed toxic megacolon, fulminant secondary ischemic gangrenous (**transmural**) colitis and septicemia and required a **total colectomy and ileostomy**.

- Once again, results from study **S3B30020** are of interest. 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 when the RCT overall experience is considered. SAEs of severe constipation were reported in 6 patients randomized to alosetron (details in Appendix 1) and none of the traditional therapy patients. All 6 of the patients experiencing SCSC had to be hospitalized. One of these patients (# 67694) required a **total colectomy and ileostomy**. But no patient died. As already mentioned, nearly all patients reported use of concurrent medications (**Appendix 1**) the most common groups were anti-depressants (30% specifically SSRIs), NSAIDs (13%) and estrogens (30%).

- It is worth noting that although in this review, emphasis is put on the occurrence of serious complications of severe constipation, in reality, 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).

B. Post Marketing Reports of Alosetron-Associated serious Constipation (Appendix 3)

In their memorandum which uses a cut-off date of **August 17, 2001**, Mrs. A. Corken Mackey (Safety Evaluator) and Dr. Z. Li (Medical Epidemiologist) analyzed post-marketing reports of patients who developed complications of serious constipation in association with the use alosetron to assess probable etiology and risk factors.

- An update, using a cut-off date of **December 31, 2001**, is given below.

Lotronex-Associated Serious Complications of Severe Constipation (SCSC) ODS Post-Marketing Safety Review^a Data as of December 31, 2001

Selected Outcome	SCSC
Cases	107
Hospitalization	78
Surgery	30
Death	2^b

a. Estimated 534,000 prescriptions for 275,000 patients - GlaxoSmithKline, "Briefing Document for the Joint Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management Subcommittee April 23, 2002", Section 4.2.2, page 56. *Data from March 13, 2000 (product launch) through December 31, 2000.*

b. Deaths are addressed in Section V of the current review.

- As in the case of ischemic colitis, an examination of the available data, allows the conclusion that there is not enough evidence to determine which patients with complications will progress to more serious outcomes.

C. CLINICAL REVIEW OF LOTRONEX (ALOSETRON)-ASSOCIATED SERIOUS COMPLICATIONS OF SEVERE CONSTIPATION REPORTED POST-MARKETING (Appendix 6)

The major goal of the detailed clinical analysis of the epidemiological data is an attempt to characterize the alosetron-associated SAEs of severe constipation as much as possible from the spontaneous reporting information. This assessment was carried out by Dr. S. Kress, Medical Officer, HFD-180. As of August 22, 2001, 77 cases of alosetron-associated serious complications of severe constipation had been reported to OPDRA/ODS. The majority, 86% (66/77) of these patients required hospitalization and 30% (23/77) required surgery. The reviewer noted that although constipation (per se) was a presenting complaint in 63 patients, constipation was not the presenting complaint in the additional 14 patients. 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 constipation¹⁰.

Further analysis of the data by Dr. Kress, 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, both higher than those with serious complications of severe symptomatic constipation among alosetron users¹¹.

IV. MESENTERIC ISCHEMIA

A clinical review of spontaneous adverse event reports of ischemic colitis by Dr. M. Barreiro identified 7 cases of vasculopathy [3 of mesenteric vein thrombosis (MVT), 2 of mesenteric artery thrombosis (MAT), 1 of colonic gangrene (CG) and 1 of transient ulcerated ischemic colitis (TUIC)]. There was strong suspicion that a **hypercoagulable state (HCS)** might have played a role in the development of alosetron-associated ischemic bowel disease. Dr. Barreiro emphasized that

¹⁰ In these individuals the benefit achieved (end of diarrhea) may be indistinguishable from the risk (development of impaction).

¹¹ More experience is needed. However, if this newly identified group actually represents patients who experienced serious complications of constipation **without prodromal manifestations**, prevention and treatment of the SAE among some alosetron users may be more difficult to achieve than previously suspected.

MVT and CG are amongst the most serious, life-threatening forms of ischemic bowel disease¹².

V. DEATHS

A. Summary of all Death Cases [Post-Marketing Experience]

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 of small bowel ischemia, and 2 cases of complications of serious constipation).

B. Clinical Perspective: Deaths reported in Association with the use of Alosetron

Dr. Kress [Medical Officer, HFD-180] reviewed the Post-Marketing deaths occurring among patients treated with Lotronex[®]. The patients received alosetron for between 5 and 60 days.

These deaths were classified as follows:

- 3 demonstrated **Probable** Evidence of Causality by alosetron
- 2 demonstrated **Possible** Evidence of Causality by alosetron
- 2 demonstrated **Alternative Explanations** with alosetron as a possible contributor.
- 3 demonstrated **Another** Obvious Alternative Explanation
- 3 demonstrated **insufficient information** to implicate alosetron

Among the five deaths considered as probably/possibly related to alosetron usage:

- 4 were related to intestinal perforation (#21, #69, #105, #157)
- 3 were related to colon perforation (#21, #69, #105)
- 2 were related to recto-sigmoid perforation (#21, #69)
- 2 were related to ischemic colitis (#21, #64)
- 1 was related to ischemic colitis and colon necrosis without perforation (#64)

¹² Dr. Barreiro suggests that identification of patients with thrombophilia or with risk factors for HCS may prevent the development of the more serious complications of alosetron therapy.

- 1 was related to recto-sigmoid perforation and diverticulosis (#21)
- 1 was related to severe constipation, fecal impaction, and recto-sigmoid perforation (diverticulitis was present) (#69)
- 1 was related to small bowel ischemic, necrosis, and perforation (#157)

It is obvious that in some of these patients there were multiple reasons that could explain the patient's death. For example, Pt. #157 experienced: intestinal perforation and small bowel ischemia. Pt. #21 experienced recto-sigmoid, colonic and intestinal perforation in addition to having diverticulosis. Pt. #69 experienced intestinal perforation, severe constipation, fecal impaction, and recto-sigmoid perforation (diverticulitis was present).

In conclusion, from the review of the GI Medical Officers, a consensus was agreed upon and their conclusions were compared to ODDRA/ODS's independent evaluation. Overall, the conclusions of both Divisions were almost identical: **3 deaths** were determined to be **Probably Related** to alosetron usage, and **2** were determined to be **Possibly Related** to alosetron usage; 2 were determined to be probably related to an alternate cause, although alosetron usage was a possible contributor. Based on the available information, none of the remaining 6 deaths could be attributed to alosetron usage.

VI. CAUSALITY ASSESSMENT (Appendix 7)

Dr. Z. Li's analysis is based on the totality of evidence. The current document incorporates summary statements from Appendix 7, reproduced below. A detailed discussion on causality is not given.

Definition

The word "causality" is not used 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 the word "causality" is used to address the issue on a population basis – and to answer the question: **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. In two pivotal clinical trials submitted before the drug's original approval, the proportion of patients who had developed constipation or had to discontinue treatment due to constipation was higher in alosetron-treated patients than in placebo-treated patients. The differences were statistically significant at $p < 0.001$ level¹². This statistical association is consistently

observed in additional studies submitted by GSK in its December 7, 2001 submission.

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 U.S. clinical trials with greater than 50 patients, 5,525 received alosetron and 2,905 placebo or traditional therapies. Dr. Li believes that 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 controls were treated and followed for up to 24 weeks. As shown in Table 1 (taken from Appendix 9), ten cases of ischemic colitis were observed among the 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 ($p < 0.001$)^{13,14}. 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 placebo¹⁵. 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, $p = 0.0012$). It is noted that incidence rates from these pooled studies may not represent the true risk of alosetron-associated ischemic colitis among female IBS patient in the U.S. given potential differences in trial designs, patient host factors and case ascertainment¹⁵.

Table 1 (from Appendix 7)

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	16.9 (6.4, 27.4)	
(95% CI)	p < 0.001	

Ischemic colitis cases reported during the post-marketing period provided additional 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 5HT₃ drugs¹⁶.

Necrosis or perforation of colon requiring surgical intervention: One case of toxic megacolon and one of colon perforation occurred in trial S3B30020 and both required a **surgical intervention**¹³. More than 30 cases of constipation-related or ischemic colitis-related complications requiring a surgical intervention among alosetron users in the U.S. have been reported to FDA during the post-marketing period¹⁷. 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. In other words since necrosis and perforation are known sequelae of constipation and ischemic colitis, it is reasonable to expect that these serious events will be rare, 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 re-emphasized 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.

-
- 12) John R. Senior. Medical officer's new drug application (NDA) review, October 15, 1999, FDA's Division Files System
 - 13) Sheldon Kress. Medical officer's review – Safety review of clinical reports for protocol S3B30020, March 2002
 - 14) Zili Li. Reevaluating the risk of ischemic colitis among female alosetron users with IBS in the U.S. March 15, 2002
 - 15) Hugo Gallo-Torres. Medical Team Leader's review, March 2002
 - 16) 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.
 - 17) 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.

APPENDIX 1

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
Research Triangle Park, N.C.

Drug: LOTRONEX[®] (alose tron hydrochloride)
Tablets for oral administration

Pharmacological Category: 5-HT₃ 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).

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.

All 40 new CSRs submitted in the sNDA of December 7, 2001.

Summaries from the Randomized Clinical Trials completed before approval of the original NDA.

Although the main emphasis is on safety, some information on efficacy is included.

Reviewer: Hugo E. Gallo-Torres, M.D., Ph.D.
Medical Team Leader, GI Drugs
HFD-180

LOTRONEX[®]:

The Randomized Clinical Trial Experience

Table of Contents

Executive Summary	3
I. Background/Approach to the Review.....	6
II. Clinical Trials.....	8
III. Ischemic Colitis.....	12
IV. Severe Constipation.....	19
V. Events of Rectal Bleeding, Bloody Stools/Diarrhea with Abdominal Pain/GI Pain in All IBS Trials.....	20
VI. Others SAEs.....	24
A. Other Intestinal SAEs.....	24
B. Extra-Intestinal AEs.....	25
VII. Notes on Efficacy.....	26
A. Urgency.....	26
B. Quality of Life.....	30
VIII. Appendices.....	33

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 in 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 formae 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.

^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 safety¹ and a secondary review² 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 studies³. 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.

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 findings⁴. 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 ischemia⁵ 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].

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:

<u>Treatment</u>	<u># of Patients</u>
Alosetron	10, 805
placebo	2,935
mebeverine	390
trimebutine	382
misc. IBS Tx	<u>889</u>
	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 1⁶.

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. Sheldon 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

COMPLETED 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	Fluoxetine Fluoxetine	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]			
<u>ALOSETRON mg b.i.d. [n=18]</u>			<u>PLACEBO b.i.d. [n=1]</u>
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 Vasculopathies	Miscellaneous GI Bleeding ^a	Hospitalization	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	<u>402</u>	<u>29,768</u>	12	-
	10,775	1,037,748		18

^aComputations 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

<u>Study</u>	<u>Incidence density (/per-month)</u>
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

^aComputations 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
<hr/>				
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
Considered	56	9	1
Serious ^b	3	2	0

^aPatient # 78134 [Study S3B30020] identified as probable or possible diagnosis of IC, is not included in the discussion that follows.
^bAll 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. bleeding⁷. 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.
- 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].
- 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.

^aThis 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

^aThis 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 established⁸.

- 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

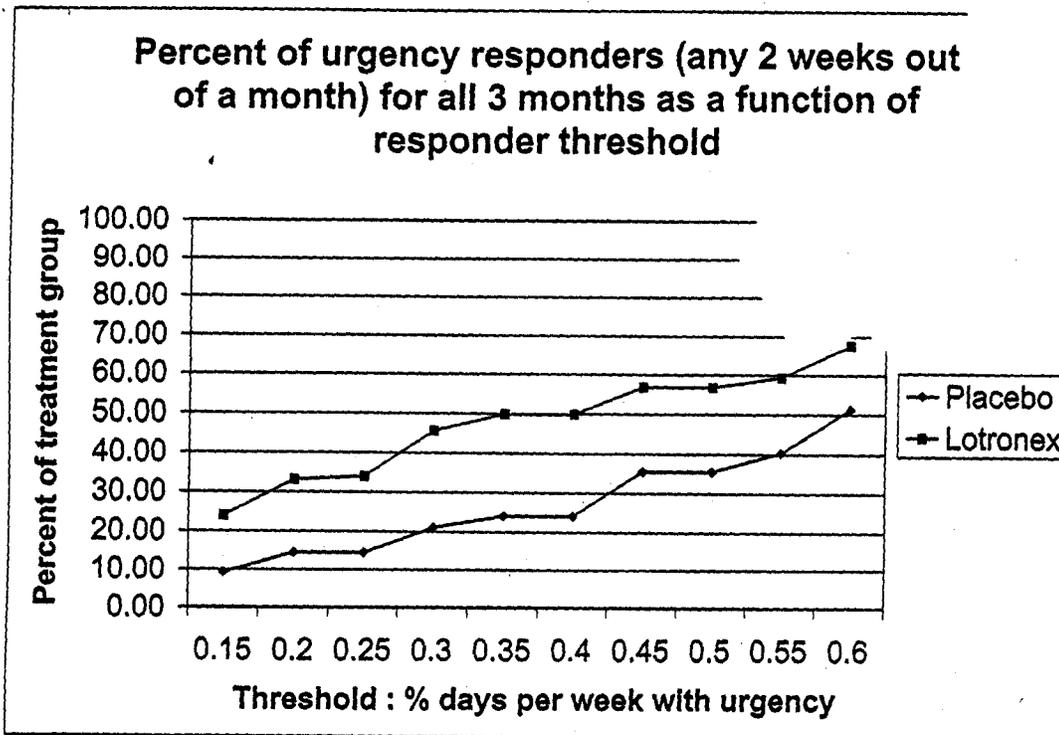
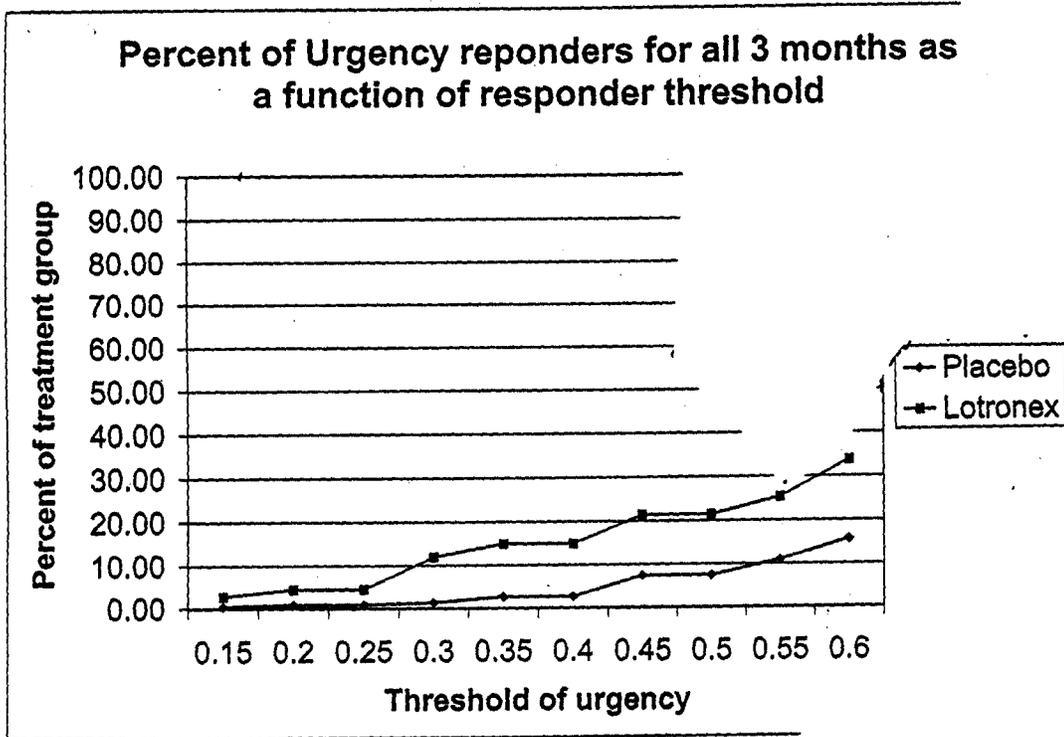


Fig. 1.- Proportion of Urgency Responders in the alosetron RCTs

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 symptoms⁹. This common disorder can be associated with significant disability and health care costs¹⁰. 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 scores¹¹ 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).

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.

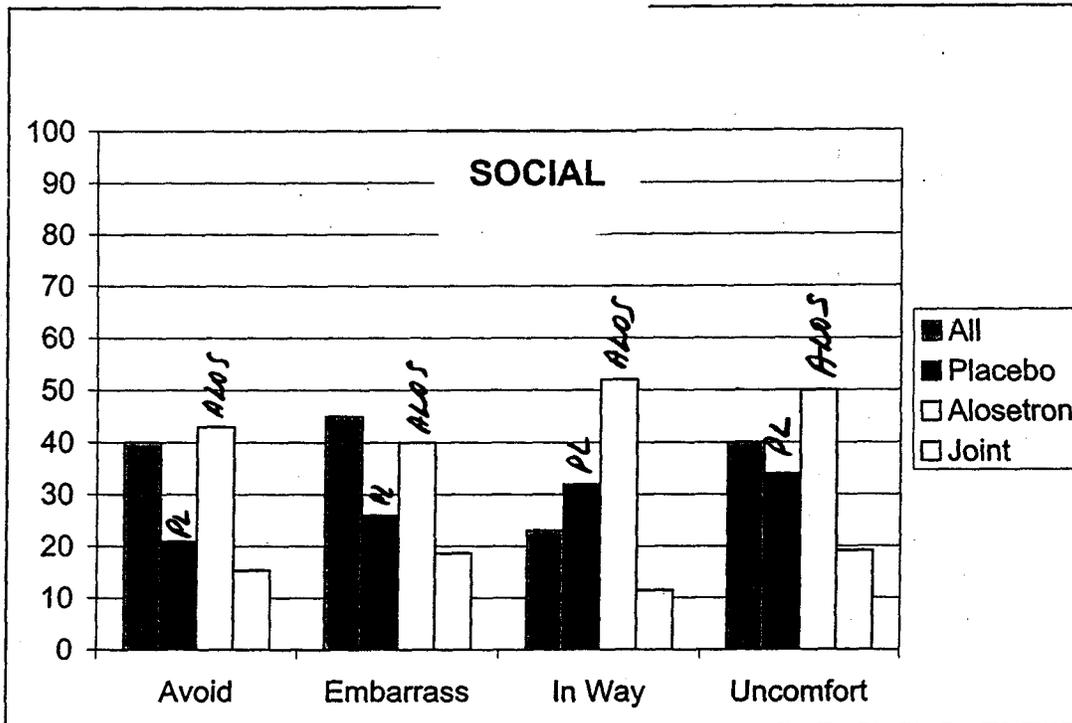
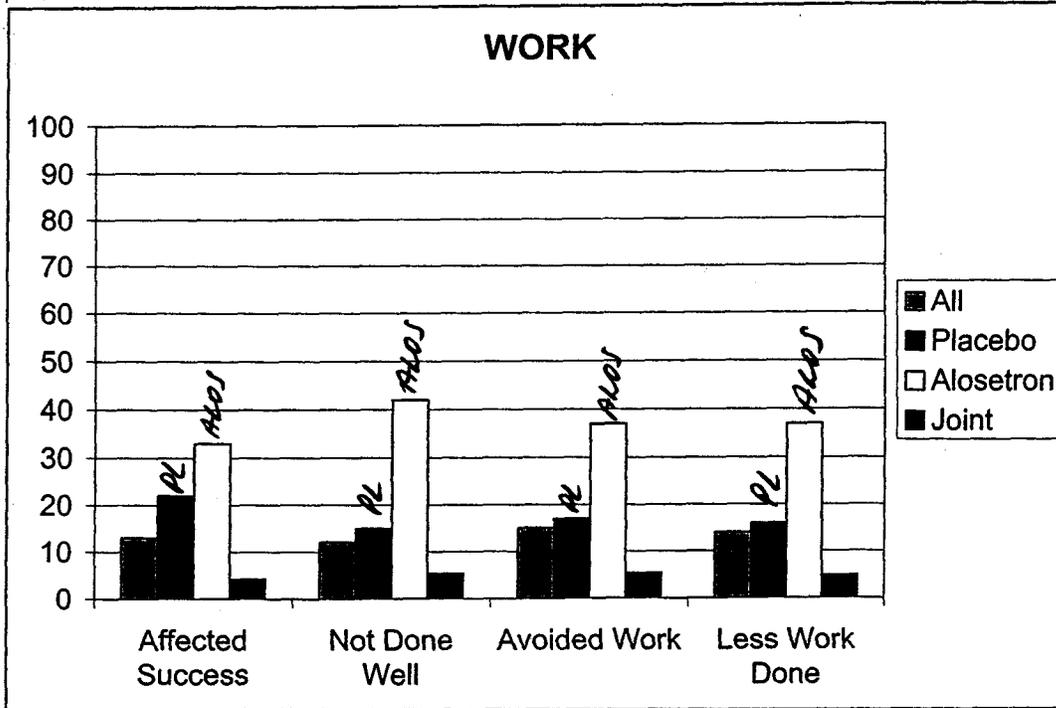


Fig.2.- Results of IBS-QoL-Social and Work Scales in Pivotal Studies S3B3001 and – 3002, as computer by Dr. David Hoberman (Biometrics).

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	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)	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/Paracetam w ol)	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. Alosetron 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

<p style="text-align: center;">Pt. #2829 [S3BA2001] <u>The 1996 Case</u></p> <ul style="list-style-type: none">• 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 <p style="text-align: center;">Pt. #15687 [S3BA 3001] <u>The 1998b Case</u></p> <ul style="list-style-type: none">• 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 <p style="text-align: center;">Pt. # 40398 [S3B20023]</p> <ul style="list-style-type: none">• 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	<p style="text-align: center;">Pt. # 7195 [S3BA 3002] <u>The 1998a Case</u></p> <ul style="list-style-type: none">• 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 <p style="text-align: center;">Pt. # 34069 [S3BA30011] <u>The 1999 Case</u></p> <ul style="list-style-type: none">• 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<ul style="list-style-type: none">-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)<ul style="list-style-type: none">-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.
---	---

<p style="text-align: center;">Pt. # [S3B30031]</p> <ul style="list-style-type: none">• 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.	<p style="text-align: center;">Pt. # 32451 [S3B30013]</p> <ul style="list-style-type: none">• 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 <p style="text-align: center;">Pt. # 49203 [S3B30012]</p> <p>Little information available</p> <ul style="list-style-type: none">• 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 woman
- 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
- Sigmoidoscopy (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. # 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. # 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. # 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
<ul style="list-style-type: none">• 37 y-old Caucasian woman• Co-morbid Conditions: anxiety• 1 mg bi.d. alosetron• Concomitant meds: Paxil, Imodium• 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.• COLONOSCOPY 2 days later: segmental colitis with patchy erythema, erosions and edema of splenic flexure and mid-descending colon.• Biopsy: non-specific mild abnormalities suggestive of ISCHEMIC COLITIS; very mild, focal acute inflammation with focal superficial erosions and minimal focal glandular attenuation.• The Pt. was neither hospitalized nor underwent a surgical procedure.• The event resolved in 4 days.	<ul style="list-style-type: none">• 67 y-old woman• Co-morbid Conditions: diverticulosis colelithiasis, hypothyroidism, smoking, colonic polyps.• 1 mg bid alosetron• Concomitant meds.: estrogens• On Day 4 after the start of therapy Pt. was hospitalized because of rectal bleeding, lower abd. pain, hypotension, ventricular tachycardia.• Abd. CT scan: peritonitis, free air and intra abd. fluid.• Reason for hospitalization (duration = 8 weeks): perforation 2.8 cm colon, diverticulitis.• Surgical procedure: sigmoid colon resection, descending colon colostomy.• Developed sepsis, stroke, dysphagia, hemiparesis; life-threatening DIC; cardioversion.• Post-operative: tachycardia required cardioconversion• ICU: peritonitis, septic, methicillin-resistant staph. aureas, abd. wound infection infection, DIC, respiratory distress required intubation, stroke with right-side hemiparesis.• Extended Care Facility: rehabilitation 3 months• Outpatient physical therapy: 5 months.• This event did not resolve. It left permanent sequelae of hemiparesis, colostomy and personality changes. <p>^aThe 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.</p>

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

<p style="text-align: center;">Pt. # 65385 [S3B30020]</p> <ul style="list-style-type: none"> • 76 y-old woman • Co-morbid Conditions: coronary artery disease, diverticular disease, internal hemorrhoids • 1 mg bid alosetron • Concomitant meds: paroxetine, 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. 	<p style="text-align: center;">Pt. # 67694 [S3B30020]</p> <ul style="list-style-type: none"> • 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, amlodipine/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, hemocult positive gastric fluid, stool hemocult 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?)
<p style="text-align: center;">Pt. # 80655 [s3B30020]</p> <ul style="list-style-type: none"> • 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. 	<p style="text-align: center;">Pt # 83206 [S3B30020]</p> <ul style="list-style-type: none"> • 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. # 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. # 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. #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.

<p style="text-align: center;">Pt. # 3773 [S3BB3002]</p> <ul style="list-style-type: none">• 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. <p style="text-align: center;">Pt. # 176167 [S3B30025]</p> <ul style="list-style-type: none">• 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)	<p style="text-align: center;">Pt. # 174139 [S3B30017]</p> <ul style="list-style-type: none">• 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

<p style="text-align: center;">Pt. # 23647 [S3B3006]</p> <ul style="list-style-type: none">• 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. <p style="text-align: center;">Pt. # 6585 [S3BA3002]</p> <ul style="list-style-type: none">• 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.	<p style="text-align: center;">Pt. # 34911 [S3B30011]</p> <ul style="list-style-type: none">• 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 salpingoophorectomy
- 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 temazepam.
- 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.

APPENDIX 2

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-HT₃ 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 GSK¹ (Sponsor). In a letter to the GI review division², 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 studies³. 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 (alosectron 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) ($p < 0.001$)	

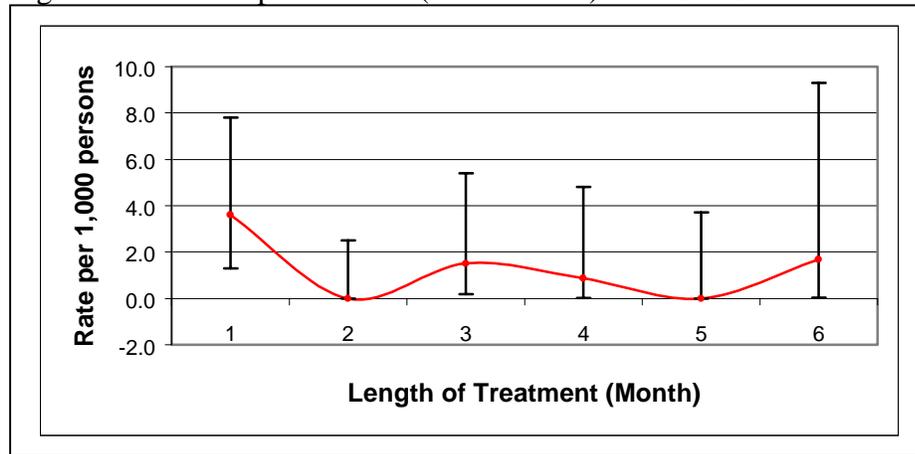
Risk constancy: Of the 10 IC cases in the study, 6 occurred within the first 30 days of alosetron treatment. The interval specific rate (hazard rate) during the first month of therapy was 3.6 per 1,000 persons, which appeared to be higher than rates observed during the ensuing five months

(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

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

Date of Report: November 2001

Sponsor Signatory: Vanessa Z. Ameen, MD
(and Medical Officer) 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 dyspepsia (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_sitel 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_sitel "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

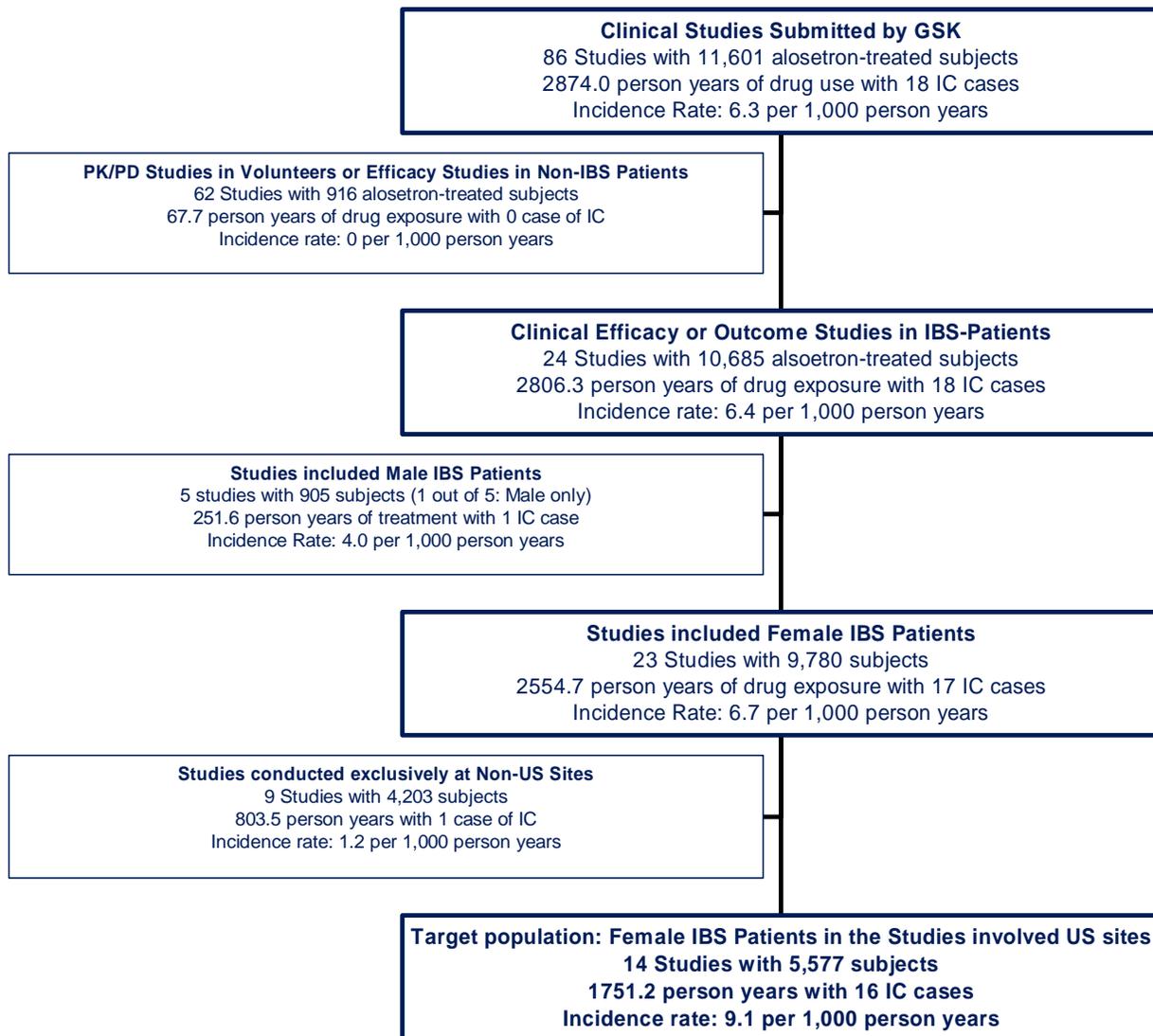
#	Variable	Type	Len	Pos	Format	Informat	Label
35	IC	Num	3	473			Ischemic Colitis Event Indicator (0=No,1=Yes)
22	MEDCODE	Char	6	311			Con. med. code variable
23	MEDTEXT	Char	59	317			Con. med. text variable
24	OCCUR	Num	8	376			No. of occurrences of AEs and con. meds.
2	PTID	Char	9	18			Protocol ID
15	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	

APPENDIX 3

MEMORANDUM

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 sumatriptan 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 Attachment 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 Prescription 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; $\geq 65 = 24$ (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; $\geq 65 = 33$ (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}

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 sumatriptan 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.

Signed 03-19-02

Ann Corken Mackey, R.Ph., M.P.H.
Safety Evaluator

Signed 03-19-02

Zili Li, M.D., M.P.H
Medical Epidemiologist

Concur:

Signed 03-19-02

Lanh Green, R.Ph., M.P.H.
Team Leader

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 stopped, 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 dicyclomine) 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 amitriptyline, 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.

^{*} This data was generated using computer printouts, and some of the numbers may reflect duplicate reporting.

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 typical, 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.

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

Paul Stolley, M.D., M.P.H.
Epidemiology Consultant

ATTACHMENT 1
WHAT IS KNOWN ABOUT THE RISK OF ALOSETRON

Ann Corken Mackey, Zili Li and Paul Stolley
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 Outcomes¹	Key Adverse Events¹			
	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 endoscopic evidence of ischemic colitis or ischemic change or necrosis	14	29%	29%
Endoscopic 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.

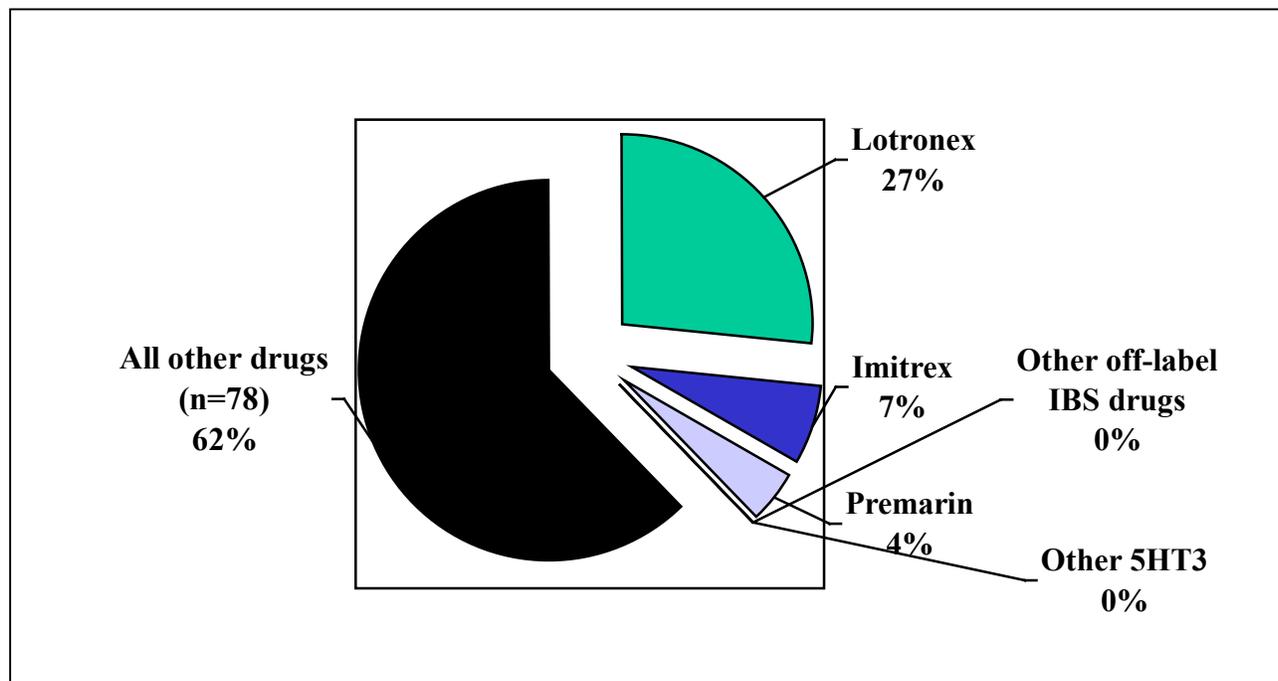
Table 2-2. Changes in severity of alosetron-associated surgical cases of ischemic colitis and severe constipation, United States, before and after Advisory Committee Meeting on June 27, 2000 (includes post-marketing, non-study cases only).

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-HT₃ 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 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.

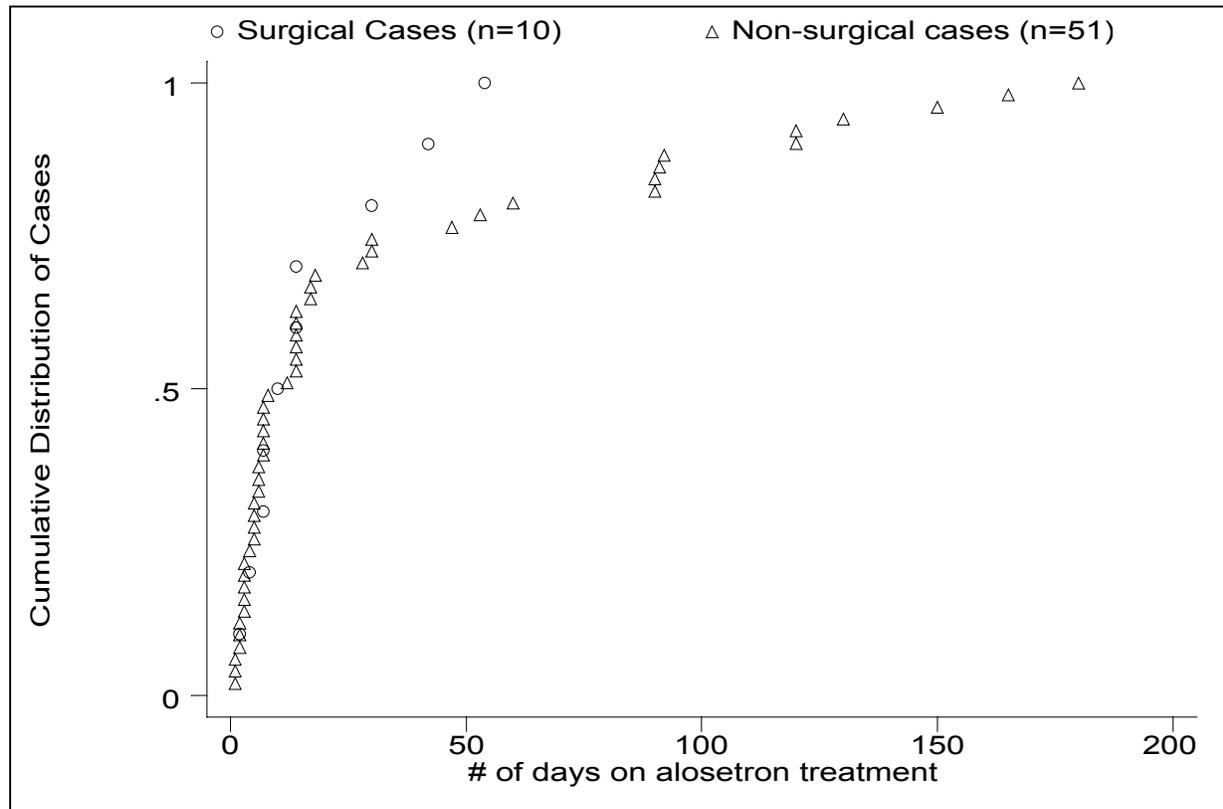
	Lotronex	Vioxx	Rezulin	Lotronex*
Date of Approval	2/9/00	5/20/99	1/29/97	2/9/00
Media Effect [†]	17 articles	--	213 articles	1 article
Reported Cases	49	5	1	23
Surgical cases	5			1
Estimated number of prescriptions (X 1,000) [§]				
Reported rate of ischemic colitis per million prescriptions				

* 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 be 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 episode of ischemic colitis at transverse colon that was supported by both colonoscopy 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 colonoscopy 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 ulcers on her right hip and abdomen. One week later, GI specialist also raised a possibility of 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.

This page intentionally left blank.

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 #69³	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 infarction	Not available	Perforated sigmoid colon and fecal material in the peritoneum	No sign of ischemic change of diverticulitis; 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 diverticulosis; 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)	Diverticulosis 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
Indication⁷	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	Sigmoid	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 colonoscopy before treatment	Negative	Diverticulosis, polyps	--	--	Negative	--	--	--	Diverticulosis	--
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				
PREFERRED TERM	LOPERAMIDE IMODIUM® AND OTHERS Approved 1976	AMITRIPTYLINE 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 (MEDDRA PREFERRED TERM)	LOPERAMIDE IMODIUM® AND OTHERS Approved 1976	AMITRIPTYLINE 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	Colonoscopy: 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 enteritis (5/12/00), small bowel and proximal colon with extensive hemorrhagic 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
Hypocoagulable 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 alossetron	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

**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 prescriber 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 article¹ 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

APPENDIX 5

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 associated with the use of **exogenous estrogenic agents** [Am J Surg Pathol 1995; 19(4):454-462]. **Pseudoephedrine** present

in nasal decongestants, because of its vasoconstrictive action may predispose perimenopausal 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-HT₁ 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-HT₃ receptor antagonist. The following points are relevant to our understanding of alosetron-associated ischemic bowel disease (AAIscBD):

- Agonists of 5-HT₃ 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 reviewer¹ had frank diagnosis or strong suspicion of a¹ 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 splanchnic 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 Raczkowski, MD

S. Kress, MD

Zili Li, MD, PhD

Julie B Meitz, MD

M. A. Barreiro, MD, MSc

APPENDIX 6

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.

TABLE of CONTENTS

	Page
1. Introduction to Review of Alosetron-Associated Serious Complications of Severe Constipation Reported Post-Marketing	4
2. Post-Marketing Experience- Recognition of Serious Enteropathies Associated with Alosetron Usage	6
3. Analysis of Patients with Lotronex (alosectron)-Associated Serious Complications of Severe Constipation With Symptomatic Constipation	10
4. Analysis of Patients with Lotronex (alosectron)-Associated Serious Complications of Severe Constipation With “Unreported” Constipation	13
5. Summary of All Patients Reported to Have Serious Complications of Severe Constipation	15
6. Clinical Summaries from Case Reports of Serious Complications of Severe Constipation Associated with Alosetron Usage With Resultant Death	25
7. Summary and Comparison of SAEs Among Two Groups of Patients With Serious Complications of Severe Constipation – Symptomatic and “Unreported”	27
8. Summary and Conclusions	31
9. GI Team Summary Risk–Benefit Assessment to Prevent SAEs Associated With Alosetron Usage	36
10. Agency’s Benefit-Risk Evaluation for Lotronex and Regulatory Actions	38
11. Expectations and Limitations of Possible Actions	40
APPENDIX	41

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-HT₃ 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-HT₃ 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).

CONSTIPATION: 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

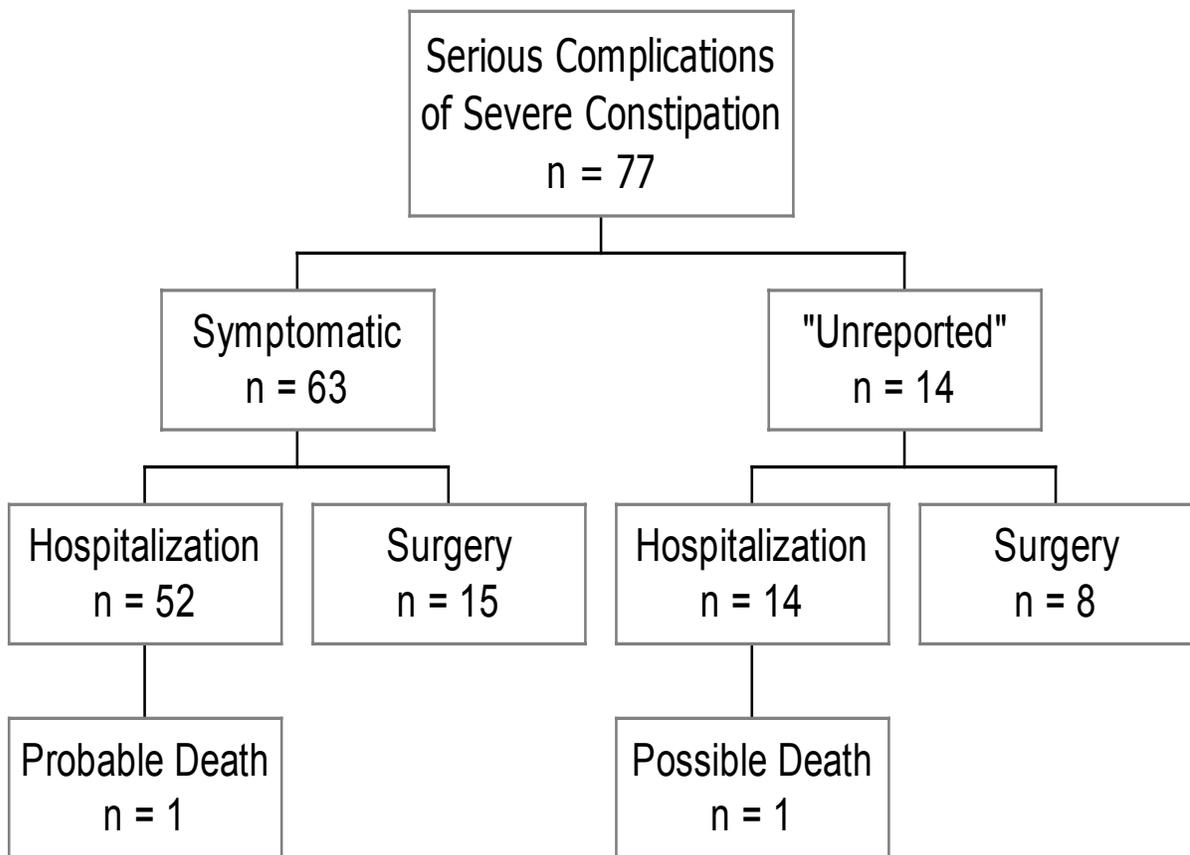
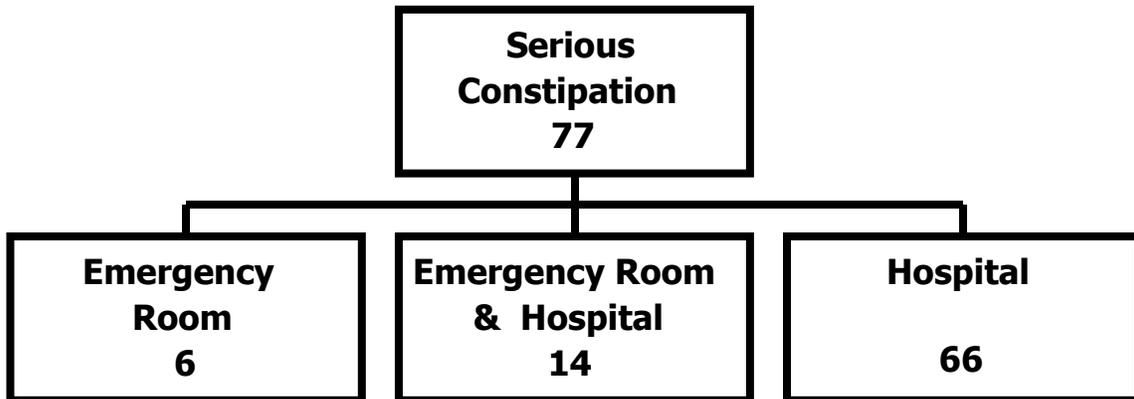


Table 2 classifies the reported cases by the site (local) where the more serious cases were treated. It should be immediately apparent, that these data lack complete accuracy. Whereas, practically all patients admitted to the hospital are admitted after evaluation in an Emergency Room, these data suggest 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.

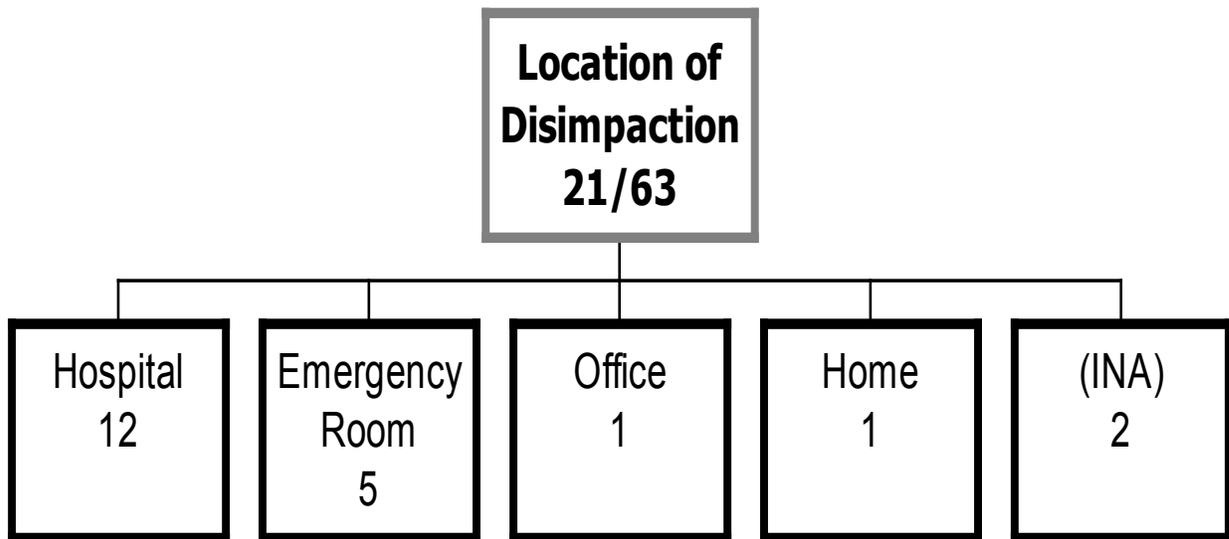
Table 2
Serious Complications of Severe Constipation
By Treatment Site



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 (alosectron)-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
Rectocele	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 rectocele	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

ID	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	Hospital
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

ID	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 Rectocele		Rectocele	
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

ID	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	ER
143	3610097	A0133184A	F	40	X			Rectal tear, bleeding		ER
144	3603435	A0138707A	F	64	X			F. impaction		ER
146	3605313	A0130764A	M	59	X				B. obstruction 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. obstruction 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

ID	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

ID	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	Laparotomy		
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 “Unreported” Constipation Alosetron-Associated Serious Complications of Constipation with “Unreported” Constipation

ID	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, hydrocodone
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		Cyanocobalamin, amitriptyline, Zolpidem, Methocarbamol, Nefazodone, Atorvastatin, Omeprazole, Buspirone,, Compazine, morphine
96	F	45	4 weeks	Bowel obstruction	Bowel resection		Unknown
97	F	79	?	Fecal impaction			Amiodipine, Lorazepam, rabeprazole, codeine, tramcinolone, 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)

ID	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 F - 4		Constipation 2	Total Hospitalization 5	Total Surgery Cases 4	Total Diagnoses 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 Probable Evidence of Certainty of Alosetron-Causality of Serious Complication of Severe Constipation and Death.

Case # 69 (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 4th 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
Rectocele	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 rectocele	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, rectocele, 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 1 Probable 2%	Case # 105 1 Possible 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
H-2 blockers

NSAIDs
proton pump inhibitors

antacids
antibiotics

antidepressants	anti-emetics	anti-diarrheals
chemotherapeutic agents	narcotics	amphetamines
anti-convulsants	diuretics	nitrites
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 preceding 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. (LOTROXEX 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

CC:

Florence Houn, M.D.

Victor Raczkowski, M.D.

Joyce Korvick, M.D.

Hugo Gallo-Torres, M.D.

Marcelo Barreiro, M.D.

Raymond Joseph, M.D.

Edvardas Kaminskas, M.D.

OPDRA (S Folkendt, M.D.; P Honig, M.D.;

J Senior, M.D.; L Zili, M.D.)

Tom Permutt

David Hoberman

Paul Levine

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
<p>The subject/patient did not receive the test drug. OR The temporal sequence of the AE onset relative to administration of the test drug is not reasonable. OR There is another obvious cause of the AE.</p>	<p>1 = Definitely not related to test drug.</p>
<p>There is evidence of exposure to the test drug. There is another more likely cause of the AE. Dechallenge (if performed) is negative or ambiguous. Rechallenge (if performed) is negative or ambiguous.</p>	<p>2 = Probably not related to test drug.</p>
<p>There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE could have been due to another equally likely cause. Dechallenge (if performed) is positive.</p>	<p>3 = Possibly related to test drug.</p>
<p>There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. Dechallenge (if performed) is positive.</p>	<p>4 = Probably related to test drug.</p>
<p>There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. Dechallenge (if performed) is positive. Rechallenge (if feasible) is positive. The AE shows a pattern consistent with previous knowledge of the test drug or test drug class.</p>	<p>5 = Definitely related to test drug.</p>

APPENDIX 7

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 $p < 0.001$ level¹. 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 placebo⁴. 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 ascertainment³.

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 5HT₃ drugs⁵.

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 intervention². 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 period⁶. 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. Sheldon 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

**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
3/27/02 09:19:31 AM
MEDICAL OFFICER

Julie Beitz
3/27/02 11:14:31 AM
DIRECTOR

STATISTICAL PERSPECTIVE

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., $3 \times 1/1921 = 1/640$ 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 4th 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

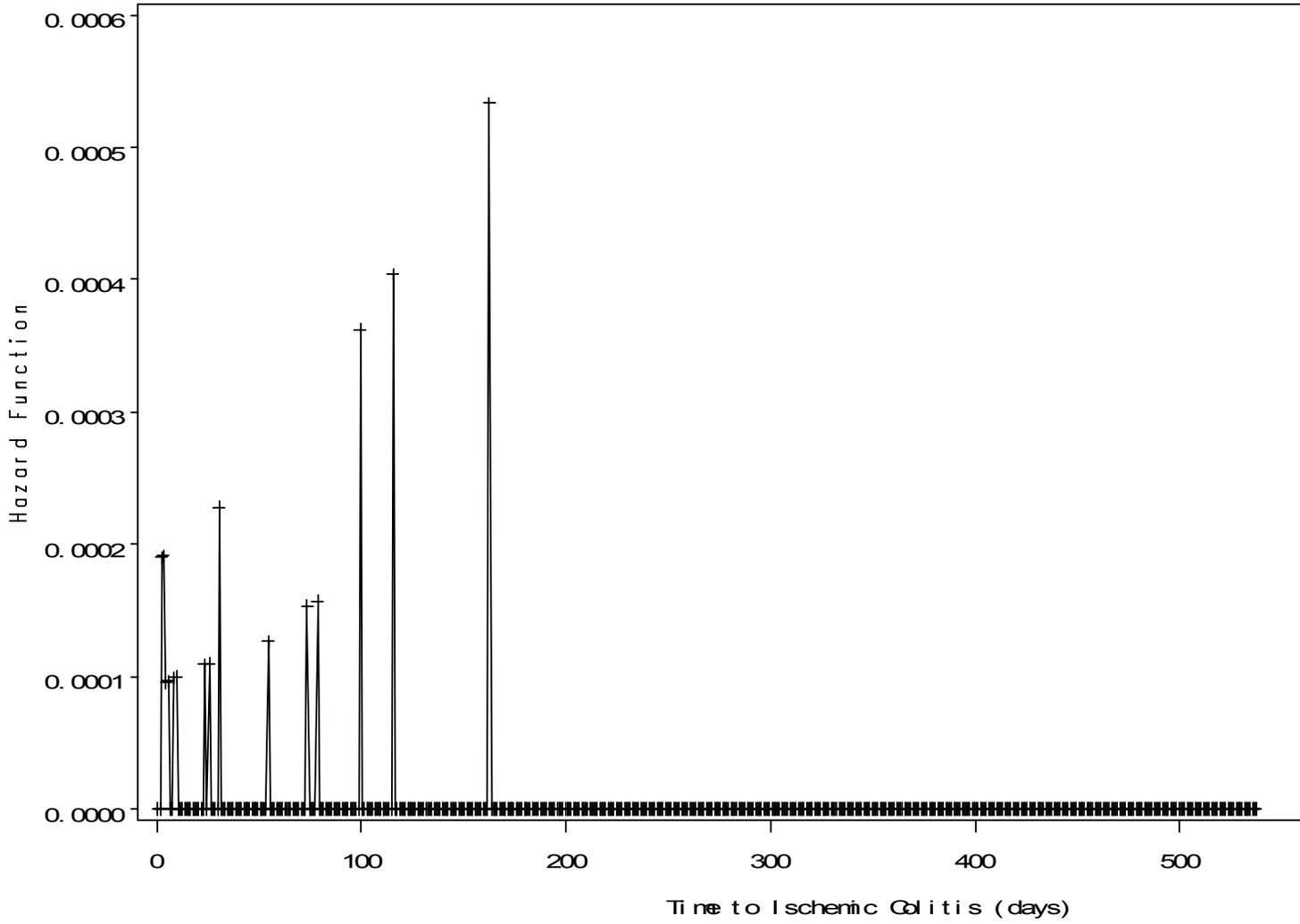


Table 1

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	<u>402</u>	<u>29,768</u>	<u>12</u>	<u>-</u>
	10,775	1,037,748		18

Table 2

Study	<u>Incidence Density</u> (/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)

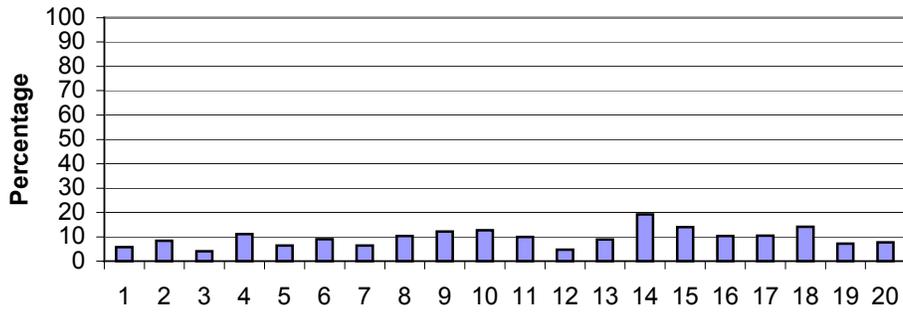


FIGURE 3

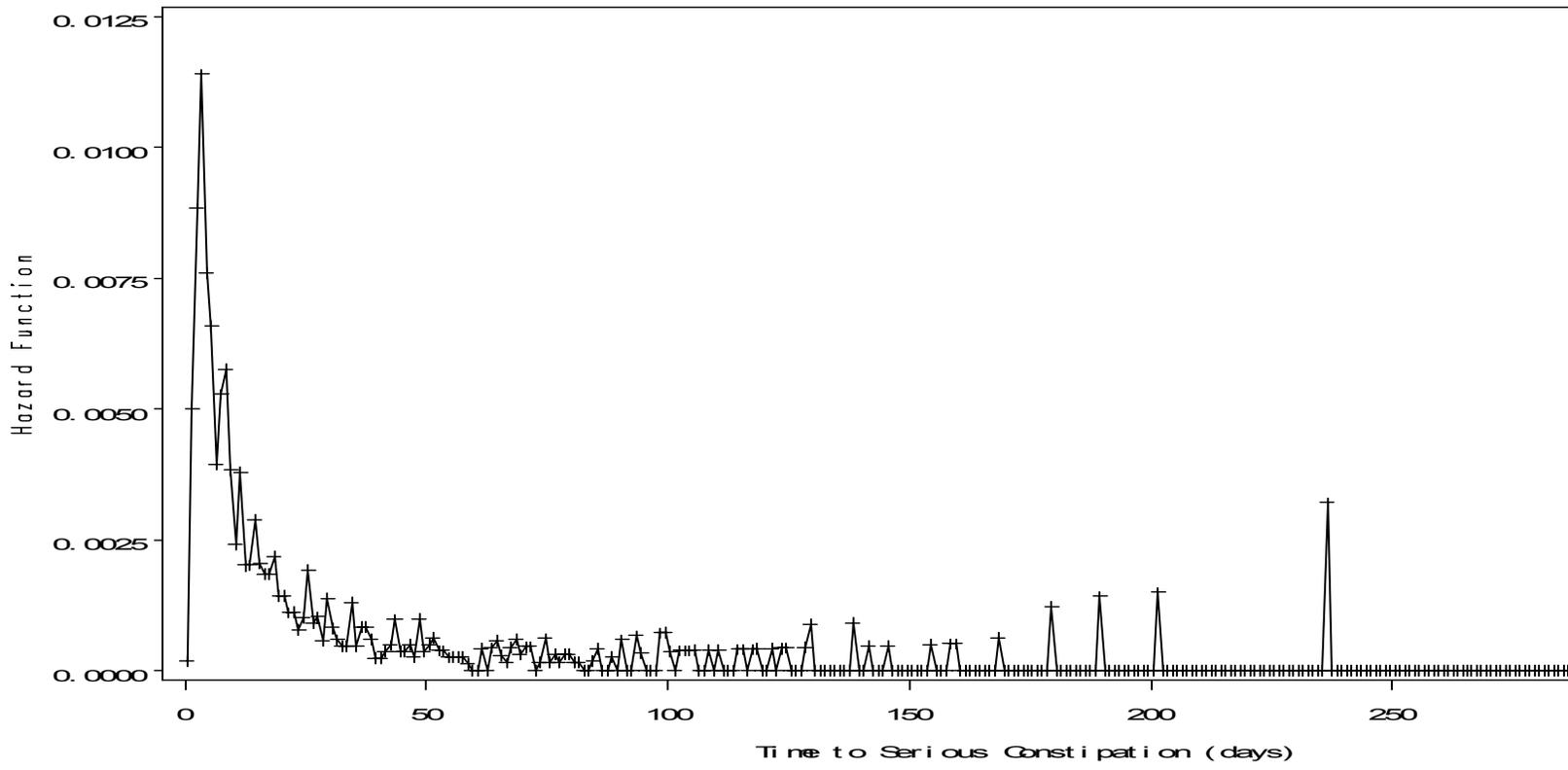
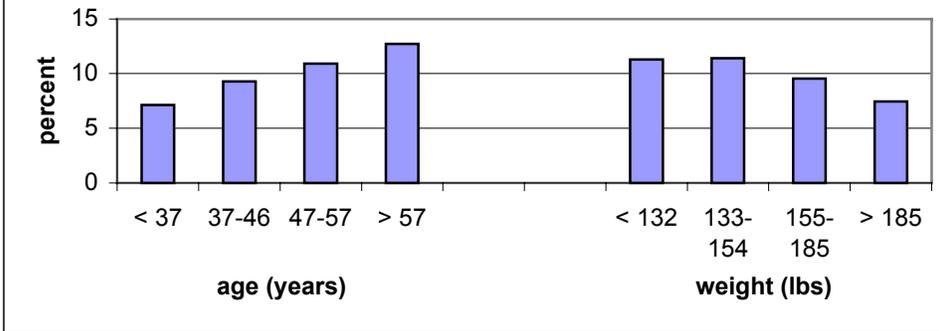


FIGURE 4: Percent of alosetron patients who had severe constipation as a function of age and weight



Urgency

TABLE 3

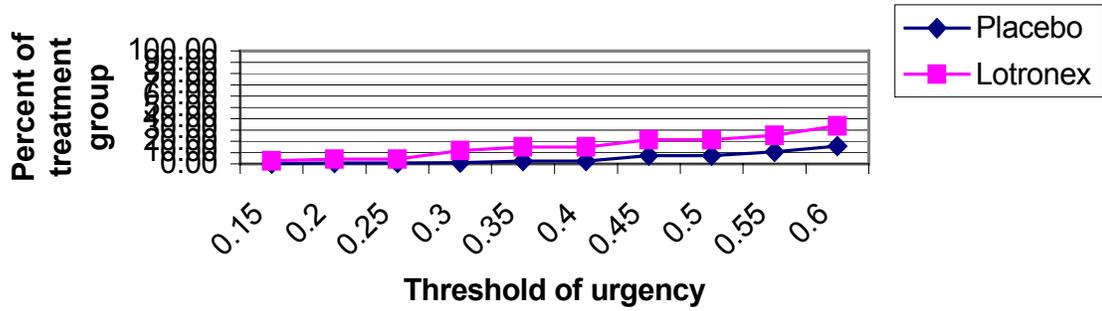
Percentages of groups who changed from at least 70% of days with urgency at baseline to no more than 15% of days with urgency for selected weeks in each pool of trials: 30011+30012 and 3001+3002.

		<u>30011+30012</u>					
		WEEK					
		1	2	3	4	...	12
Pbo		3.5	14	16	19		29
Lotr		11.4	23	33	37		50

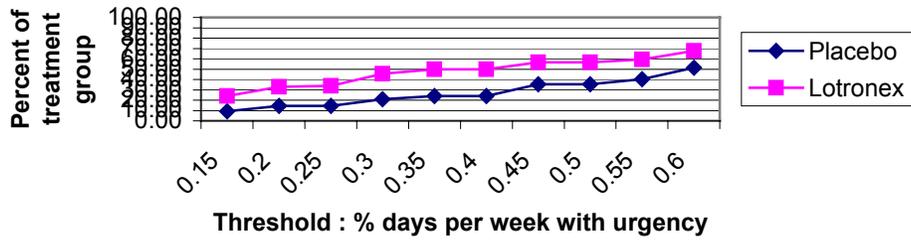
		<u>3001+3002</u>					
		WEEK					
		1	2	3	4	...	12
Pbo		3	8	9	10		19
Lotr		8	20	20	23		32

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 responders 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.

	<u>Placebo</u>				<u>Alosetron</u>			
	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

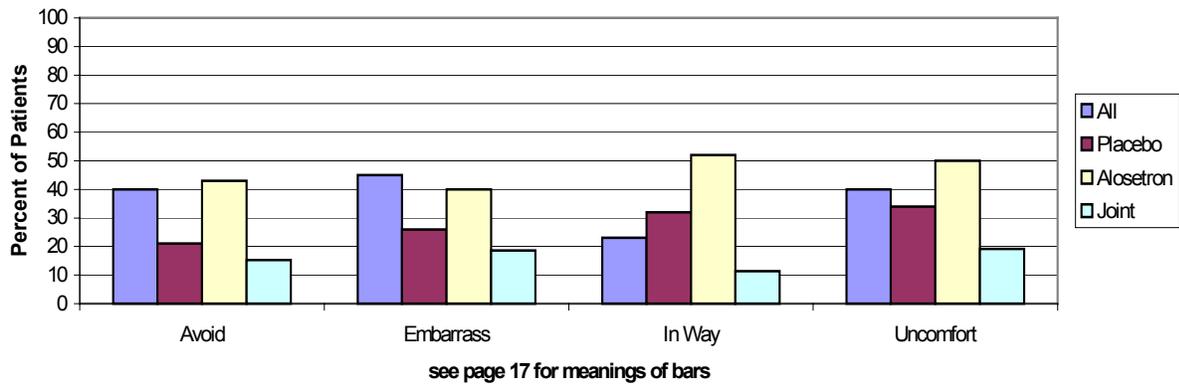
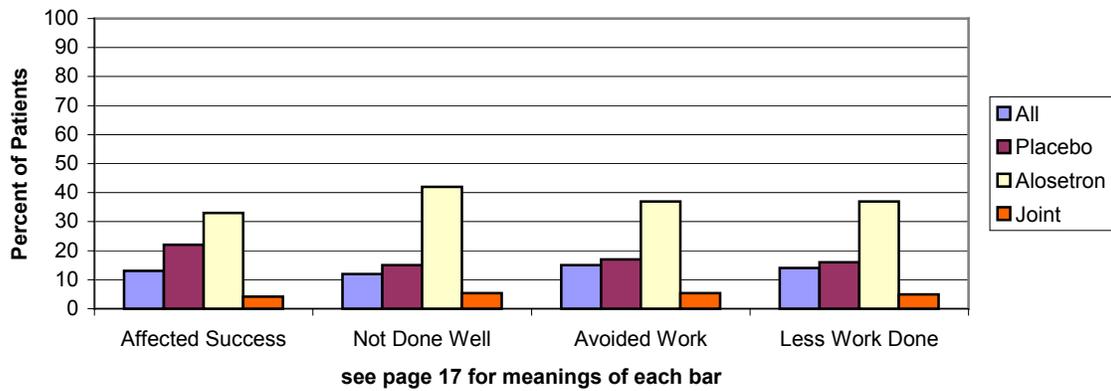


Figure 8: WORK



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

/s/

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.

GOALS OF RISK MANAGEMENT

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.

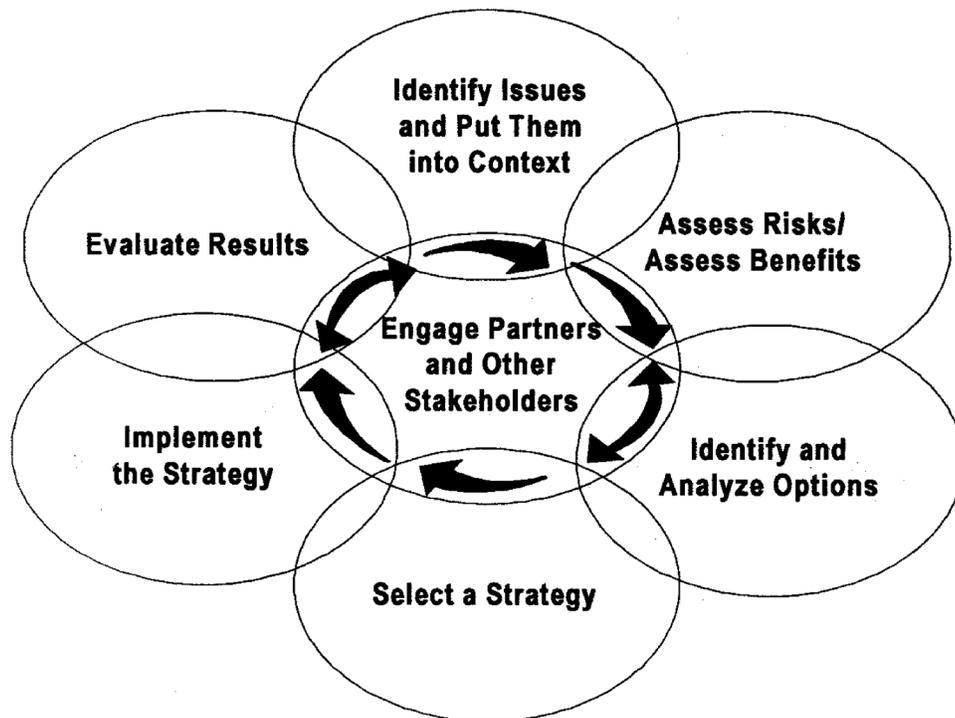
Compliance to the elements of the plan will probably be the most important measure of plan success. GSK should propose benchmarks for success of the risk management plan.

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 Commissioner¹ 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	<ul style="list-style-type: none"> •PROVIDES FOR REQUIRED EDUCATION ENHANCING PLAN-COMPLIANT PRESCRIBING •TARGETS GROUP FOR SURVEYS, CHART AUDITS, EDUCATION, CAPTURING ADVERSE EVENT DATA 	<ul style="list-style-type: none"> •BURDEN
REGISTRATION: PATIENT	<ul style="list-style-type: none"> •PROVIDES DENOMINATOR •PROVIDES INFORMED PATIENT •TARGETS GROUP FOR SURVEYS, EDUCATION 	<ul style="list-style-type: none"> •PATIENT PRIVACY •BURDEN
REGISTRATION: PHARMACIST	<ul style="list-style-type: none"> •PROVIDES FOR REQUIRED EDUCATION ENHANCING PLAN-COMPLIANT DISPENSING •TARGETS GROUP FOR SURVEYS, PRESCRIPTION AUDITS, EDUCATION 	<ul style="list-style-type: none"> •BURDEN
PRESCRIBING RESTRICTIONS AND DISPENSING RESTRICTIONS (GENERAL)	<ul style="list-style-type: none"> •LIMITS ACCESS TO ONLY PATIENTS WHO QUALIFY UNDER CONDITIONS OF THE PLAN 	<ul style="list-style-type: none"> •DECREASED DRUG ACCESS; MAY ENCOURAGE ALTERNATE SOURCING •BURDEN
AUTHORIZED PRESCRIBER CHECK MECHANISM	<ul style="list-style-type: none"> •ALLOWS RPH TO CONFIRM MD AS QUALIFIED/REGISTERED PRESCRIBER UNDER RMP 	<ul style="list-style-type: none"> •PRACTICALITY OF PHARMACIST AS GATEKEEPER •BURDEN
LIMITED SUPPLY / NO REFILLS	<ul style="list-style-type: none"> •LIMITS DRUG SUPPLY, ENSURING PT RETURNS FOR MD FOLLOWUP FREQUENTLY AND REGULARLY 	
SPECIAL PACKAGING	<ul style="list-style-type: none"> •CAN INCLUDE LIMITED DRUG SUPPLY •CAN PROVIDE SPECIAL SAFETY FEATURES •MEANS FOR REINFORCING MESSAGES AND INSERTS SUCH AS MEDGUIDE, SURVEYS, ETC. 	

PATIENT MONITORING BY PHYSICIANS (REGULAR INTERVALS)	<ul style="list-style-type: none"> •ASSURES PATIENT FOLLOWUP •OPPORTUNITY FOR REINFORCING EDUCATION •OPPORTUNITY FOR OBTAINING ADVERSE EVENT INFORMATION 	<ul style="list-style-type: none"> •ADDITIONAL DOCTORS VISITS OR OTHER MONITORING MEANS •BURDEN
SURVEYS VOLUNTARY	<ul style="list-style-type: none"> •MEASURE PLAN COMPLIANCE 	<ul style="list-style-type: none"> •INCOMPLETE DATA •REPRESENTATIVENESS QUESTION •BURDEN
SURVEYS MANDATORY	<ul style="list-style-type: none"> •MEASURE PLAN COMPLIANCE •COMPLETE DATA 	<ul style="list-style-type: none"> •BURDEN

LOTROXEX RISK MANAGEMENT PLAN

**Identify Issues
and Put Them
into Context**

**Assess Risks/
Assess Benefits**

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.

**Identify and
Analyze Options**

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.

LOTROXEX RISK MANAGEMENT PLAN PROPOSED DECEMBER 2001	
GSK PLAN: PROCESS	ODS SUGGESTED POINTS TO CONSIDER
STEP 1 ✎ MD receives patient-physician agreement kit (special stickers come with kit) upon request via 1-800 number or via sales reps ✎ MD education via written materials: Dear Healthcare professional letter, other materials in pt-MD kit, via GSK website, from sales force	<ul style="list-style-type: none">• Limit to gastroenterologists or physicians with significant gastroenterology training and experience or CME “certified” physicians• Register all physicians• GSK distribution of stickers and kits only to registered physicians
STEP 2 ✎ MD selects appropriate patient (Women with DP-IBS who have failed traditional therapy)	<ul style="list-style-type: none">• Subpart H by definition: “serious or life-threatening disease”- limit to serious / debilitating IBS (to be defined)• No treatment of “presumptive” or “interim” IBS diagnoses• Define “traditional therapy”

<p>STEP 3</p> <p>✎ MD signs attestation statement on “patient-physician agreement document” (of knowledge and experience in diagnosis and treatment of IBS and ability to diagnose and manage IC and CC)</p>	<ul style="list-style-type: none"> • Limit to gastroenterologists or or physicians with significant gastroenterology training and experience or CME “certified” physicians • Add MD agreement to report ischemic colitis and complications of constipation
<p>STEP 4</p> <p>✎ Patient signs “patient-physician agreement document”</p> <p>✎ Pt education via prescriber with review of benefits and risks of Lotronex</p>	<ul style="list-style-type: none"> • Regular pt. followup / monitoring by MDs missing (pt-MD agreement specifies pt. must initiate contact with MD if problems) • Define “constipation” • Register all patients
<p>STEP 5</p> <p>✎ Pt-MD agreement document: copy to pt. and placed in medical record</p>	<ul style="list-style-type: none"> • Register all physicians with GSK
<p>STEP 6</p> <p>✎ MD affixes special sticker to “initial” prescription (no samples)</p> <p>✎ 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</p>	<ul style="list-style-type: none"> • Allow no refills (new Rx with each fill) • Current plan allows for any MD to obtain sticker; could bypass all previous steps • Sticker only on “initial” Rx; thus legitimate Rxs (refill) exist without stickers, diminishing sticker utility
<p>STEP 7</p> <p>✎ Any pharmacy may dispense Lotronex IF: special sticker is affixed to <i>initial</i> prescription</p> <p>✎ Pharmacist education via Dear Healthcare Professional letter plus special attachment</p>	<ul style="list-style-type: none"> • All Rxs (new+refill) with sticker (“no sticker-no drug”) • No telephone or faxed Rxs • Inpatient allowance of no sticker while in hospital if ordered by gastroenterologist • Consider other means besides sticker method to check for authorized prescription
<p>STEP 8</p> <p>✎ Lotronex dispensed in special carton with 30 tab supply plus MedGuide</p>	<ul style="list-style-type: none"> • Reinforcing educational message (not to dispense unless sticker on Rx) on packaging • Assure that existing supplies of Lotronex (old packaging) do not remain in pharmacies
<p>STEP 9</p> <p>✎ Patient receives Lotronex supply</p>	<ul style="list-style-type: none"> • Regular pt. Followup / monitoring by MDs is missing (pt-MD agreement specifies pt. must initiate contact with MD if problems) • MD agreement to report ADRS: IC / CC
<p>STEP 10</p> <p>✎ 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.</p> <p>✎ Pt gets five dollars to participate in survey</p>	<ul style="list-style-type: none"> • GSK must demonstrate survey representativeness • Alternatively register all pts who would then participate in survey or MD solicit pt to participate in survey or include survey form in packaging
<p>SPONSOR ADR REPORTING: IC and CC will be reported expeditiously (15-day reports)</p>	
<p>ADVERTISING: Preapproval of promotional activities, no direct to consumer (DTC) ads</p>	

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 Rx

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.

	<u>A</u>	<u>B</u>	<u>C</u>	<u>D</u> 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

Select a Strategy

**Implement
the Strategy**

Evaluate Results

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% (1,700/55,000²) 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.).

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®) 1998	Thalidomide (Thalomid®) 1998	Bosentan (Tracleer®) 2001	Mifepristone (Mifeprex®) 2000
Approval date and indication for use	Breakthrough cancer pain in opioid tolerant pts	Erythema nodosum leprosum	Pulmonary artery hypertension	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
Physician Agrees to Reporting of ADRs		X	Specialty Distributor	
Dispensing of Drug- Centralized				
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 Registrations(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

	Clonazepam (Clozaril®, generic)	Isotretinoin (Accutane®)	Dofetilide (Tikosyn®)	Fentanyl (Oralcel®)	Trovafoxacin (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
Physician 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 Registratation(s)	X				
• Physician Specialty					
• Physician “Qualifications”					
• Indication for Drug Use					
• Presence/Absence of Patient Risk Factors	X				
• Authorized Prescriber Check Mechanism		Sticker	“Confirmed Participant” 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			