

***LOTRONEX®(alosetron hydrochloride)
Tablets***

***Briefing Document for the Joint
Gastrointestinal Drugs Advisory Committee
and
Drug Safety and Risk Management Subcommittee
April 23, 2002***

Volume 1

Table of Contents

<i>Section</i>	<i>Description</i>	<i>Volume</i>	<i>Page</i>
I.	INTRODUCTION AND BACKGROUND	1	8
	1. Chronology of Events	1	9
	2. Organization of the Briefing Document	1	13
II.	OVERVIEW OF BENEFIT-RISKS	1	14
	1. Introduction	1	14
	2. Burden of Illness and Current Management of IBS	1	15
	3. Benefits	1	17
	3.1 Overview of Evidence Supporting Clinically Meaningful Benefits	1	17
	3.2 Rationale for Dose Selection	1	20
	3.3 Efficacy Results from Clinical Trials	1	23
	3.3.1 Adequate Relief of Abdominal Pain and Discomfort	1	23
	3.3.2 Bowel Urgency	1	26
	3.3.3 Stool Frequency	1	29
	3.3.4 Stool Consistency	1	31
	3.3.5 Global Improvement of IBS Symptoms	1	32
	3.3.6 Quality of Life	1	34
	3.3.7 Productivity	1	36
	3.3.8 Efficacy of Alosetron in Patients with Severe IBS Symptoms	1	37
	3.3.9 Efficacy in Men	1	48
	3.3.10 Summary of Benefits	1	48
	4. Summary of Safety Information	1	49
	4.1 Background: Understanding of Safety Data Prior to Product Withdrawal	1	49
	4.1.1 Adverse Events of Special Interest at the Time of Approval Constipation, Ischemic Colitis, Hepatic Abnormalities	1	49
	4.1.2 Post-Marketing Adverse Events Leading to a Second ADCOM	1	52
	4.1.3 Adverse Events Leading to Product Withdrawal	1	53
	4.2 Overview of Currently Available Safety Data	1	54
	4.2.1 Extent of Exposure in Clinical Trials	1	55
	4.2.2 Estimate of Market Exposure	1	56
	4.3 Adverse Events of Special Interest	1	57
	4.3.1 Constipation	1	57

Table of Contents

<i>Section</i>	<i>Description</i>	<i>Volume</i>	<i>Page</i>
	4.3.1.1 Constipation - Clinical Trials Experience	1	57
	4.3.1.2 Serious Cases of Constipation and Complications of Constipation from Clinical Trials	1	60
	4.3.1.3 Serious Cases of Constipation and Complications of Constipation from Marketing Experience	1	67
	4.3.1.4 Possible Risk Factors for Constipation	1	71
	4.3.1.5 Strategies to Reduce Risks Associated with Constipation	1	72
	4.3.2 Overview of Ischemic Colitis and Mesenteric Ischemia	1	74
	4.3.2.1 Reports of Colonic Ischemia from Clinical Trials	1	77
	4.3.2.2 Onset, Risk and Incidence of Ischemic Colitis: Studies Evaluating Alosetron	1	79
	4.3.2.3 Reports of Ischemic Colitis from Marketed Experience	1	83
	4.3.2.4 Mesenteric Ischemia, Occlusion, or Infarction	1	86
	4.3.2.5 Strategies to Reduce Risks Associated with Colonic Ischemia	1	90
	4.4 Surgeries and Transfusion Associated with Serious GI Events	1	91
	4.5 Deaths	1	91
	4.5.1 Clinical Trials	1	91
	4.5.2 Marketed Experience	1	92
	4.6 Risks Associated with Alternative Therapies	1	93
5.	Summary of the Benefit-Risk Profile of Alosetron	1	94
6.	Conclusions	1	97
	• <u>Attachment I</u> : Epidemiology Studies	1	99
	• <u>Attachment II</u> : Complications of Constipation	1	113
	• <u>Attachment III</u> : Ischemic Colitis	1	119
III.	RISK MANAGEMENT PLAN	1	132
	1. Objectives of the GSK RMP for LOTRONEX	1	133
	2. Population for Whom Benefits Outweigh Risks	1	134
	3. Appropriate Prescribers	1	134

Table of Contents

<i>Section</i>	<i>Description</i>	<i>Volume</i>	<i>Page</i>
4.	Modified Labeling	1	135
5.	Modified Packaging	1	136
6.	Communication of Risk	1	137
7.	Definition of Risk	1	139
8.	Program Evaluation	1	140
9.	Enhancements of Safety Monitoring	1	141
10.	Post-marketing Commitments	1	141
11.	Promotional Activities	1	141
•	<u>Attachment 1</u> : Product Information and Medication Guide	1	142
•	<u>Attachment 2</u> : Patient-Physician Agreement for LOTRONEX	1	166
•	<u>Attachment 3</u> : A Twenty-four Week, Randomized, Double Blind, Placebo-Controlled, Crossover Study to Assess the Effect of Alosetron 1.0mg BID on Work/Main Activity Productivity in Female Subjects with Diarrhea-Predominant IBS	1	170
•	<u>Attachment 4</u> : A 12-Week, Randomized, Double-blind, Placebo Controlled, Dose-titration, Study of Alosetron in Female Subjects with Diarrhea-Predominant Irritable Bowel Syndrome	1	175
•	<u>Attachment 5</u> : A Twelve-Week, Randomized, Double-Blind, Placebo-Controlled Study to Compare Methods of Constipation Management in Female Diarrhea-Predominant Irritable Bowel Syndrome Subjects Treated with Open-Label Alosetron	1	180
•	<u>Attachment 6</u> : A Twelve-Week, Randomized, Double Blind, Placebo-Controlled, Study to Assess the Safety and Efficacy of 0.5mg BID and 1mg QD of Alosetron in Female, Diarrhea-Predominant, IBS Subjects	1	185
•	<u>Attachment 7</u> : LOTRONEX Utilization Study: A Cohort Study in the United Healthcare Research Database	1	189
•	<u>Attachment 8</u> : A Pharmacy-based Post Marketing Surveillance Study of LOTRONEX	1	228
•	<u>Attachment 9</u> : Voluntary Expedited Reporting of Post-marketing, Spontaneous Adverse Events	1	239

Table of Contents

<i>Section</i>	<i>Description</i>	<i>Volume</i>	<i>Page</i>
IV	SUMMARY AND OVERALL CONCLUSIONS	1	242
Appendix 1	TABLE OF CLINICAL TRIALS	1	244

References

<i>Ref. No.</i>	<i>Description</i>	<i>Volume</i>	<i>Page</i>
1.	Thompson WG, Longstreth GF, Drossman DA, et al. Functional bowel disorders and functional abdominal pain. <i>Gut</i> ;1999;45(suppl II):143-147.	2	4
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6.	Klein K. Controlled Treatment Trials in the Irritable Bowel Syndrome: A Critique. <i>Gastroenterology</i> 1988;95:232-241.	2	55
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References

<i>Ref. No.</i>	<i>Description</i>	<i>Volume</i>	<i>Page</i>
14.	Grennwald DA, Brandt LJ. Colonic ischemia. Journal of Clinical Gastroenterology 1998;2:22-28.	2	132
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I. INTRODUCTION AND BACKGROUND

This Briefing Document has been compiled for the members of the joint Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management Subcommittee for the April 23, 2002 Advisory Committee Meeting. The Briefing Document provides information that is pertinent to the understanding and discussion of the data provided in Supplemental Application, NDA 21-107/S-005, for LOTRONEX® (alosetron hydrochloride) tablets.

LOTRONEX, a selective antagonist of 5HT₃ serotonin type receptors, was approved by FDA on February 9, 2000 for the treatment of irritable bowel syndrome (IBS) in women with the predominant bowel symptom of diarrhea. The approved dosage was 1 mg, BID. The product labeling also included two warnings; the first stated that ischemic colitis had been infrequently reported in clinical trials and that the relationship to LOTRONEX was unknown and the second advised prescribers of the frequency and the nature of constipation reported in clinical trials.

On November 28, 2000, GlaxoSmithKline (GSK) withdrew LOTRONEX from the US market and terminated all ongoing clinical trials. This action resulted from concerns regarding post-marketing reports of ischemic colitis and of complications of constipation and from the inability of GSK and FDA to reach agreement on a mutually acceptable Risk Management Plan that would have allowed for the continued marketing of LOTRONEX.

On December 7, 2001, GSK submitted a Supplemental Application (NDA 21-107/S-005) for LOTRONEX. This Supplemental Application seeks FDA approval to allow the re-introduction of LOTRONEX Tablets, under modified conditions of use and with restrictions imposed by an appropriate Risk Management Plan (RMP), for women with diarrhea predominant IBS who have failed on conventional therapy. The Supplemental Application contains a clinical trials safety database of 11,874 alosetron treated patients; a four-fold increase over the number of patients included in the original NDA. Thus, the Supplemental Application has a substantial body of new information that was not available for Agency review at the time LOTRONEX was withdrawn in November 2000.

The regulatory events and key activities in the history of LOTRONEX are summarized in the chronology of events that follows.

1. Chronology of Events

- **June 29, 1999.** The New Drug Application (NDA) for LOTRONEX Tablets was submitted to FDA for the treatment of women with diarrhea-predominant irritable bowel syndrome (IBS). The Application was given Priority Review status.
- **November 16, 1999.** The NDA for LOTRONEX (NDA 21-107) was reviewed by the Gastrointestinal Drugs Advisory Committee. Constipation and ischemic colitis were two adverse events of special interest identified by FDA for attention during the Advisory Committee's deliberations.

Constipation was the most frequently reported AE in clinical trials of IBS patients treated with LOTRONEX 1 mg BID; 28% compared to 5% of the patients who received placebo. Approximately 80% of the events were reported during the first month of treatment. Constipation was primarily mild or moderate in severity; however, there were three reports of serious constipation among patients treated with LOTRONEX (N≅3000) and none among patients who received placebo (N≅1100). There were two patients (one who received LOTRONEX and one who received placebo) who developed complications of constipation.

There were four reports of possible *ischemic colitis* among patients treated with LOTRONEX and no reports among the placebo treated patients. All cases involved hospitalization and resolved without sequelae. Constipation was reported in only one of the four cases.

Based on both the efficacy and safety evidence presented, the Gastrointestinal Drugs Advisory Committee unanimously recommended approval of LOTRONEX for the treatment of women with diarrhea-predominant IBS.

- **February 9, 2000.** LOTRONEX, at the dose of 1 mg, BID, was approved for the treatment of women with diarrhea predominant irritable bowel syndrome. The product labeling carried two warnings. One warning stated that ischemic colitis had been infrequently (defined as 1/100 to 1/1000 patients) reported in clinical trials and that the relationship with LOTRONEX was unknown. The second warning advised prescribers of the frequency and nature of constipation reported in clinical trials.
- **June 27, 2000.** Following the launch of LOTRONEX in mid-March of 2000, new cases of ischemic colitis and complications of constipation were reported in both the ongoing clinical trials being conducted by GSK and in post marketing spontaneous

reports. Meetings to discuss the safety of LOTRONEX were held between GSK and FDA, and GSK was asked to develop a Risk Management Plan.

On June 27, 2000, FDA convened the Gastrointestinal Drugs Advisory Committee to review the benefit-risk assessment of LOTRONEX. The Agency also asked the Advisory Committee to consider methods by which the safety profile of LOTRONEX could be optimized through a Risk Management Plan. In general, the Advisory Committee accepted the GSK proposed Risk Management Plan, with the added recommendation that a Medication Guide be instituted as part of the labeling changes.

- **July 2000 - November 2000.** Subsequent to the June Advisory Committee meeting, GSK and FDA worked toward refining the proposed Risk Management Plan, revising the patient prescribing information and developing the patient Medication Guide (approved in August 2000). In October 2000, GSK provided the Agency with updated safety information, which showed an increase in the number of spontaneous post-marketing reports that, was coincident with increased media attention. The Agency agreed that the publicity-related "spike in reporting" was a known phenomenon. Many of the spontaneous reports were submitted directly to FDA and not to GSK. In early November 2000, the Agency informed GSK of their having obtained hospital records that provided information that linked ischemic colitis to surgery and death. Consequently, because of the potential serious outcome of ischemic colitis, the Agency suggested that GSK voluntarily withdraw LOTRONEX from the market. Subsequent efforts between GSK and FDA to develop appropriate labeling and an appropriate Risk Management Plan were unsuccessful.
- **November 28, 2000.** After substantial discussion with FDA, on November 28, 2000, GSK voluntarily withdrew LOTRONEX from the US market. This decision was taken because of concern regarding the post-marketing reports of ischemic colitis and of complications of constipation and the inability of GSK and FDA to reach agreement on a mutually acceptable Risk Management Plan that would have allowed for the continued marketing of LOTRONEX. All ongoing clinical trials were terminated.
- **December 2000 – December 2001.** Following the withdrawal of LOTRONEX both GSK and FDA received an unprecedented number of communications from physicians, IBS patients and IBS patient advocacy groups requesting that the withdrawal of LOTRONEX be reconsidered. GSK and FDA resumed discussions in January 2001, to explore options that might allow for the re-introduction of LOTRONEX under a mutually acceptable Risk Management Plan. FDA and GSK agreed, in principle, on the following key issues:

- modification of the product labeling to include a black box warning prominently placed at the beginning of the label to describe the most important safety information, appropriate patients and prescribers, directions for monitoring constipation and ischemic colitis and a lower initial dose recommendation;
 - inclusion of a patient agreement document and physician attestation statement as elements of the Risk Management Plan;
 - conduct of additional research intended to better define the ideal treatment regimens, potential risk factors, and mechanisms for adverse events. Specifically, GSK agreed to conduct a functional outcome trial with a randomized withdrawal component and a dose titration trial to evaluate alternative dosing regimens;
 - a summary and report of preliminary results from the epidemiology studies;
 - re-introduction of LOTRONEX not limited to only those IBS patients who had been treated previously;
 - distribution of LOTRONEX through retail pharmacies, not centralized distribution.
- **December 7, 2001.** On December 7, 2001, GSK submitted Supplemental Application NDA 21-107/S-005 for LOTRONEX Tablets. This Supplemental Application was submitted to support re-introduction of LOTRONEX, under modified conditions of use and with restrictions imposed by an appropriate Risk Management Plan (RMP), for women with diarrhea predominant IBS who have failed on conventional therapy. FDA has granted priority review of the Supplemental Application.

For the Supplemental Application, safety data from 11,874 clinical trial subjects who received alosetron were available for integrated safety data analyses. This number represents a four-fold increase, an additional 9,118 subjects who had received alosetron since approval of the original NDA and prior to withdrawal of LOTRONEX from the market. A total of 10,805 IBS patients, who received BID doses of alosetron in 24 completed or terminated trials provided the primary safety data. This number included 988 patients who received alosetron, 1 mg BID, in two yearlong studies. A list of the clinical studies is included as Appendix 1 of the Briefing Document.

Constipation was the most frequently occurring adverse event in the expanded safety database provided in the Supplemental Application. Constipation was reported by 29% of the IBS patients who received LOTRONEX 1 mg BID, compared to 6% of

the IBS patients who received placebo. The frequency of constipation reported as a serious adverse event in the alosetron-treated IBS patients was 9/10,805 or 0.08%. Complications of constipation occurred in 7/10,805 (0.065%) of the IBS patients who received alosetron and in 3/2935 (0.1%) of IBS patients who received placebo. Ischemic colitis was reported by 16/11,874 (0.135% or 1 in 742) subjects who received alosetron and by 1/3500 (0.029%) subjects who received placebo. The frequency of ischemic colitis in subjects exposed to alosetron in clinical trials in the Supplemental Application was the same as that observed in the original NDA [1 in 750 (4 out of approximately 3000 subjects)].

As part of our Phase IV commitments, GSK initiated an integrated series of epidemiologic studies that were designed to investigate the incidence and risk factors for colonic ischemia, complications of constipation requiring hospitalization and bowel surgery. The epidemiological data were included in the Supplemental Application for the purpose of providing information about the incidence and risk factors of these events.

FDA has indicated to GSK representatives on a number of occasions that the efficacy of LOTRONEX is not in question. Accordingly, the primary intent of the new data is to provide the comprehensive safety database needed for an updated benefit-risk assessment. However, new study data are included that confirm the sustainability of the efficacy of LOTRONEX and demonstrate its efficacy in patients with debilitating IBS symptoms. These new benefit data are pertinent to a revised safety assessment for the patient population for whom the benefit-risk consideration is believed to be most favorable, namely, women with diarrhea-predominant IBS who have failed to respond to conventional therapy.

2. Organization of the Briefing Document

- The Briefing Document has four major sections:

Section I: INTRODUCTION AND BACKGROUND. This section provides a history of the key events associated with LOTRONEX from submission of the original NDA to submission of the Supplemental Application.

Section II: OVERVIEW OF BENEFIT-RISK. This section reviews the burden of the illness of IBS and the efficacy and safety of LOTRONEX. The safety review focuses upon adverse events of special concern, ischemic colitis and complications of constipation, and presents these events in terms of the clinical trials profile and post-marketing spontaneous reports.

Section III: RISK MANAGEMENT PLAN (RMP). The proposed RMP addresses: (1) the selection of appropriate informed patients for whom benefit outweighs risk; (2) the appropriate prescribers; (3) communication of the RMP; (4) monitoring and program evaluation; (5) modified labeling and packaging of LOTRONEX.

Section IV: CONCLUSIONS. The final section of the Briefing Document summarizes the evidence and rationale for re-introduction of LOTRONEX.

II. OVERVIEW OF BENEFIT-RISK

1. INTRODUCTION

The safety data from GlaxoSmithKline's comprehensive clinical trials program have now been assessed and available data from post-marketing surveillance thoroughly reviewed. In addition, data from epidemiological studies provide new insight on the burden of illness of IBS that is pertinent to the reassessment of the safety of alosetron. (For consistency, throughout Section II of the Briefing Document, the generic name alosetron is used rather than the brand name, ALOSETRON®.)

In reassessing the benefit-risk profile today, several differences and considerations exist that support a favorable balance:

- Identification of a restricted, more narrow intended patient population, i.e. the population for whom the benefit-risk profile is most favorable: women with diarrhea-predominant IBS who have no suitable alternative treatment options.
- Reintroduction under different conditions of use; restrictions formalized under the provisions of 21 CFR 314 Subpart H.
- New benefit data which add to the information available at the time of NDA approval. These new data demonstrate benefit in patients with debilitating IBS symptoms, clinically relevant measures of outcome such as quality of life, productivity, global improvement and the durability of the effect through 48 weeks.
- Data derived from a five-fold increase in the number of IBS patients treated with alosetron in clinical trials reveal that the nature and relative frequency of ischemic colitis cases have remained generally consistent.
- Influencing prescribers to recognize and to avoid inappropriate patient uses is not an expected challenge for reintroduction, since alosetron, presently, is not marketed and was available to the market for only a short period of time.

This section of the Briefing Document provides an overview of the comprehensive body of information that supports the benefits and risks of alosetron treatment in women with diarrhea-predominant IBS who have failed to respond to conventional therapy. The document summarizes all available information, including new safety and efficacy data from all clinical trials, ongoing epidemiologic studies, and post-marketing surveillance.

Benefit-risk assessments are invariably influenced by subjective and objective factors. Prominent influences critical to the benefit-risk evaluation of alosetron therapy include the ability to accurately gauge the:

- underlying burden of illness associated with IBS
- impact of the condition on the lives of women with diarrhea-predominant IBS
- effect of alosetron therapy on IBS symptoms and IBS-associated disability
- magnitude of risks associated with alosetron therapy
- benefits and risks of alternative therapy
- potential for prescribers to manage treatment-associated risks.

Accordingly, an examination of the current body of information, as related to each of the above factors, is provided below.

2. BURDEN OF ILLNESS AND CURRENT MANAGEMENT OF IBS

Irritable bowel syndrome (IBS) is characterized by the Rome committee as “a functional bowel disorder in which abdominal pain is associated with defecation or a change in bowel habit, with features of disordered defecation and distention”¹. These changes in bowel function may manifest as diarrhea, constipation, or alternating diarrhea and constipation. Diarrhea-predominant IBS is estimated to affect 5-10% of the population, with females representing 80% of sufferers. More than 75% of IBS cases occur in persons between 25 and 64 years of age. The disorder accounts for 20-50% of referrals to gastrointestinal clinics and 5-10% of primary care visits. Further, it is estimated that 5-10% of patients with IBS has severe and debilitating symptoms interfering with their work and social activities on a daily basis²⁻⁴.

The high prevalence of IBS contributes to substantial, national and medical costs, estimated at close to \$2 billion in 1998. In the US, IBS accounts for about 4 million physician visits, 2 million prescriptions and countless OTC drug purchases^{2,4}. Unnecessary diagnostic tests, inappropriate management and unnecessary surgery account for some of the costs³. Significant among these is the cost associated with absenteeism and lost productivity due to the inability to work. Although it is difficult to estimate with precision, this has been calculated at approximately \$20 billion in 1998². Health related quality of life of IBS sufferers is significantly impaired compared to that of the normal US population as measured by the SF-36, and is similar to that of patients with other chronic disorders (GERD, clinical depression, diabetes mellitus and end-stage renal disease)⁵. The multiple symptoms of IBS and their recurrent and unpredictable nature account for the disability experienced by many

sufferers. This is particularly true for patients with diarrhea-predominant IBS, where, in addition to pain, bowel urgency occurs frequently. These symptoms have been shown to be most bothersome for patients and are responsible for a significant component of the disability of IBS.

Emerging epidemiologic data suggest that IBS is associated with serious gastrointestinal comorbidities (**see synopses in Attachment I**). While these data are preliminary, they provide a perspective on the burden of illness not previously described in the published literature. In the Phase IV observational study of over 5 million patients in United Healthcare (EPI-40060), patients with IBS studied before the introduction of alosetron were at a substantially elevated risk for developing colon ischemia and complications of constipation and for having bowel surgery compared to patients without IBS. While these studies are ongoing, they suggest that IBS is not the benign disease it was previously believed to be.

Until recently, the complex nature of IBS and limited understanding of the underlying pathophysiology resulted in a poor overall quality of clinical research^{4,6}. As a result, novel therapies directed at the multiple symptoms of IBS were not developed. Dietary modification, behavioral changes and education are useful adjuncts, and may be sufficient for patients with mild and intermittent symptoms. For the majority of IBS patients seeking healthcare, however, these approaches are unsatisfactory and lead to the use of pharmacotherapy.

The wide variety of conventional therapies used to treat IBS is a reflection of the lack of effectiveness of any one approach as well as an underlying unmet need experienced by patients. In the US, a small number of drugs are indicated to treat IBS or as adjunctive therapy. Approval for these medications occurred many years ago and was based on clinical trials that did not offer convincing evidence of effectiveness in treating the IBS symptom complex^{4,6}. Recent reviews of meta-analyses have concluded that some treatments are useful for diarrhea (but not pain) and others are superior to placebo for pain (but not bowel function)⁷⁻¹⁰.

Therapeutic recommendations have included the use of NSAIDs, COX-2 inhibitors and opioid analgesics to treat the pain component of IBS. Opiates are recognized as being effective, but chronic use is not encouraged. NSAIDs and COX-2 inhibitors are perceived as being equi-efficacious, but not consistently or adequately so, as evidenced by the frequent switching between drugs within this class. Anti-spasmodic medications have been approved for the treatment of IBS or as adjunctive therapy and, although they may have uses for the short-term relief of cramping, the overall impact is sub-optimal. The effect wears off over time and anti-cholinergic side effects occur frequently. Anti-diarrhea medications are

effective in the short-term management of diarrhea. However, they do not treat the overall symptom complex of diarrhea-predominant IBS since they do not treat pain. Chronic use of anti-diarrhea agents is not without risk. This risk includes ileus, obstipation, obstruction and bowel perforation. Given the paucity of effective therapy, patients also have resorted to psychotherapeutics (anxiolytics and anti-depressants) based on the rationale that these drugs may mitigate the central nervous system interpretation of afferent nociceptive signals emanating from the viscera. These drugs are not indicated for the treatment of IBS, but have been used off-label for some patients. They too are not without risks, some of which may be substantial.

In summary, for many patients, the IBS burden of illness is not alleviated with available therapy, resulting in a significant negative impact on daily functional status and quality of life. Conventional IBS therapy often is dependent on unapproved approaches with undefined benefit-risk profiles. Therefore, there is a significant unmet medical need associated with IBS, resulting in a) the inability to address patients' debilitating symptoms and b) significant costs to the healthcare system.

3. BENEFITS

3.1 Overview of Evidence Supporting Clinically Meaningful Benefits

In contrast to available agents, the efficacy of alosetron has been confirmed in multiple, large, randomized controlled trials. The original NDA included 53 completed studies, five of which were repeat dose studies involving 1903 alosetron-treated IBS patients (1552 female; 351 male). In the two pivotal 12-week studies, alosetron provided consistent benefit in diarrhea-predominant female IBS patients for the most bothersome symptoms of IBS: pain, bowel urgency and stool frequency. As a single agent, alosetron consistently improved all of these symptoms throughout the treatment period. Upon discontinuation of therapy, symptoms returned within one week.

The recently submitted Supplemental NDA (sNDA) contains 93 completed or terminated studies including 24 IBS trials involving a total of 10,805 alosetron-treated patients, a five-fold increase since the time of approval, and 2,935 placebo-treated controls. Also included in these 24 trials are three studies involving 1,661 patients treated with comparative agents, i.e., 390 mebeverine, 382 trimebutine, and 889 traditional therapy. Mebeverine and trimebutine are antispasmodic agents commonly used outside of the U.S. for treatment of IBS. The substantial body of new information includes controlled trials that have confirmed the efficacy described in the original application. In addition, new studies have demonstrated that alosetron is effective in patients with debilitating IBS symptoms at

baseline, affords substantial global improvement of IBS symptoms, and improves measures of quality of life and productivity. In addition, efficacy that has previously been established for 12 weeks, has now been shown to be maintained for up to 48 weeks. These data provide clinically meaningful evidence for the therapeutic benefits of alosetron as a treatment for female patients with diarrhea-predominant IBS and support the proposed, new, narrower, target population, those patients who have failed conventional therapy.

Specific findings include the following as related to each identified efficacy measure (new studies included since the original NDA approval are designated with bold print):

- **Relief of IBS Pain and Discomfort:** In five placebo-controlled studies (S3BA2001, S3BA3001, S3BA3002, **S3B30006**, **S3B30013**) and two active-controlled comparative studies (**S3BB3001**, **S3BB3002**), alosetron 1mg BID consistently provided significantly greater adequate relief of IBS pain and discomfort than either placebo, mebeverine, or trimebutine in women with diarrhea-predominant IBS. A significant treatment effect was typically seen in the first few weeks of treatment and persisted as long as subjects were on treatment, from 12 to 48 weeks.
- **Bowel Urgency:** In seven (four completed since NDA approval) placebo-controlled studies (S3BA2001, S3BA3001, S3BA3002, **S3B30006**, **S3B30013**, **S3B30011**, **S3B40031**) and an active-controlled comparative study of alosetron vs. mebeverine (**S3BB3001**), alosetron 1mg BID either significantly reduced or provided greater satisfactory control of urgency than placebo or mebeverine in women with diarrhea-predominant IBS. A significant improvement in urgency was typically seen in the first two weeks of treatment and persisted as long as subjects were on treatment, from 12 to 48 weeks.
- **Global Improvement of IBS Symptoms:** Two large, placebo-controlled IBS trials (**S3B30011** and **S3B40031**) demonstrated independent replication of statistically significant improvement in female IBS patients with debilitating IBS symptoms (i.e. satisfactory control of bowel urgency on less than 50% of days at baseline). Both studies, as well as an open-label trial vs. traditional IBS therapy (**S3B30020**), also showed statistically significant efficacy (substantial or moderate improvement) on global improvement scores; a patient-rated measure related to clinical and quality of life-associated dimensions of IBS.
- **Productivity:** In two placebo-controlled studies (**S3B30011**, **S3B40031**) and one open-label comparison study vs. traditional IBS therapy (**S3B30020**), alosetron 1mg BID

significantly improved productivity compared to placebo or traditional therapy in women with diarrhea-predominant IBS.

- **Quality of Life:** In four placebo-controlled studies (S3BA3001, S3BA3002, **S3BA3003**, **S3B30006**), two active-controlled comparative studies (**S3BB3001**, **S3BB3002**), and one open-label comparison study vs. traditional IBS therapy (**S3B30020**), alosetron 1mg BID significantly improved quality of life (QoL) ratings on one or more scales of the IBSQoL questionnaire compared to placebo, mebeverine, trimebutine, or traditional therapy in women with diarrhea-predominant IBS. Although safety/effectiveness data for studies S3BA3001, S3BA3002, and S3BA3003 were included in the original NDA, the QoL analyses for these trials were submitted subsequent to the NDA approval at FDA's request.
- **Improvement of IBS Symptoms in Patients with Severe Baseline Symptoms:** At the request of the FDA, further analyses revealed the following:

The weekly adequate relief data from the six placebo-controlled studies (S3BA2001, S3BA3001, S3BA3002, **S3B20023**, **S3B30006**, **S3B30013**), stratified by baseline pain severity, urgency, stool frequency, and stool consistency showed that alosetron 1 mg BID provided greater adequate relief than placebo in patients who, at baseline, either: 1) averaged moderate to intense pain; 2) had urgency 100% of the time; 3) averaged > 4 stools per day; or 4) averaged loose to watery stools every day.

Significantly more alosetron-treated patients with lack of control of urgency on at least 70% of days at baseline (**S3B30011**, **S3B40031**) reported satisfactory control of urgency on at least 85% of days during treatment.

The five placebo-controlled 12-week studies that utilized the IBS QoL (S3BA2001, S3BA3001, S3BA3002, **S3B30013**, and **S3B20023**), revealed that the proportion of severe patients at baseline who subsequently reported 'none' or 'mild' symptoms following treatment was significantly greater in alosetron-treated patients than placebo-treated patients for 15 IBS specific QoL measures.

Following its introduction into the US market, alosetron established itself as an effective remedy in clinical practice for women with diarrhea-predominant IBS as demonstrated by the number of prescriptions written, and by the proportion of patients seeking refills. In addition, the unprecedented and sustained demand by patients and physicians to reintroduce alosetron is further testimony that it satisfied an unmet medical need.

3.2 Rationale for Dose Selection

Two placebo-controlled dose-ranging Phase II trials were conducted to determine the optimal dose of alosetron for the treatment of patients with IBS in Phase III clinical trials, S3B-P12 and S3BA2001.

S3B-P12

S3B-P12 was a randomized, double-blind, placebo-controlled, multicenter study conducted in 43 centers in 9 countries in Europe and Canada. The study consisted of 4 parallel treatment groups: placebo BID, alosetron 0.1mg BID, alosetron 0.5mg BID, or alosetron 2.0mg BID given for 12 weeks. Female and male subjects diagnosed with IBS and having symptoms meeting the Rome Criteria for 6 months were eligible for enrollment into a 2-week screening phase to collect baseline symptoms. IBS subjects with all 3 subtypes of IBS, i.e., diarrhea-predominant, constipation-predominant, or alternating diarrhea and constipation, were allowed to participate.

During screening, subjects recorded their IBS symptoms (abdominal pain or discomfort, stool consistency and frequency) each day using diary cards. At the end of the 2-week screening period, subjects were randomized with equal allocation to one of the four treatment groups; placebo BID, or alosetron 0.1, 0.5, or 2.0mg BID. Subjects continued to record daily symptoms and returned to the clinic at Weeks 2, 4, 8, and 12 for assessments.

A total of 467 male and female subjects were randomized to treatment; 73% of the subjects were female. Randomized patients were evenly distributed by IBS sub-type; 1/3 each being constipation-predominant, diarrhea-predominant, or alternators between diarrhea and constipation.

The results of the study showed that alosetron 2mg BID was the most efficacious of the 3 alosetron doses studied. More specifically, improvement of abdominal pain or discomfort and percentage of pain-free days was most consistently found in the 2mg BID group for female IBS subjects with loose/watery stools at baseline compared to either other dose groups, male subjects, or subjects with firmer stools.

S3BA2001

S3BA2001 was a randomized, double-blind, placebo-controlled, multicenter study conducted in 68 centers predominantly in the US but also in Europe and Canada (315 out of 370

patients were randomized from the US). The study consisted of 5 parallel treatment groups: placebo BID, alosetron 1mg BID, alosetron 2mg BID, alosetron 4mg BID, and alosetron 8mg BID given for 12 weeks. Female and male subjects diagnosed with diarrhea predominant or alternating diarrhea and constipation IBS and having symptoms meeting the Rome Criteria for 6 months were eligible for enrollment into a 2-week screening phase. Subjects recorded their IBS symptoms each day using an electronic touch-tone phone system. At the end of the 2-week screening period, patients reporting at least 4 days of moderate pain and mean stool consistency scores ≥ 2.5 (1=very hard, 2=hard, 3=formed, 4=loose, 5=watery) were randomized with equal allocation to one of the five treatment groups: placebo BID, or alosetron 1.0, 2.0, 4.0, or 8.0mg BID. Subjects continued to record daily symptoms and also weekly responses to whether they had received adequate relief of their IBS pain and discomfort over the previous 7 days. Subjects returned to the clinic at Weeks 4, 8, and 12 for assessments.

Three hundred seventy (370) male and female patients were randomized to treatment; 70% of the patients were female. Fifty-six percent (56%) of randomized patients were diarrhea-predominant, 8% were constipation-predominant, and 36% were alternating diarrhea/constipation. Treatment groups were similar with respect to duration of IBS symptoms and distribution of investigator-rated IBS subtypes.

The results of the study, illustrated in Figure 1, showed that alosetron 1mg BID was the most efficacious dose in female subjects and that no dose of alosetron demonstrated consistent improvement over placebo in male subjects (for which the sample size was recognizably limited).

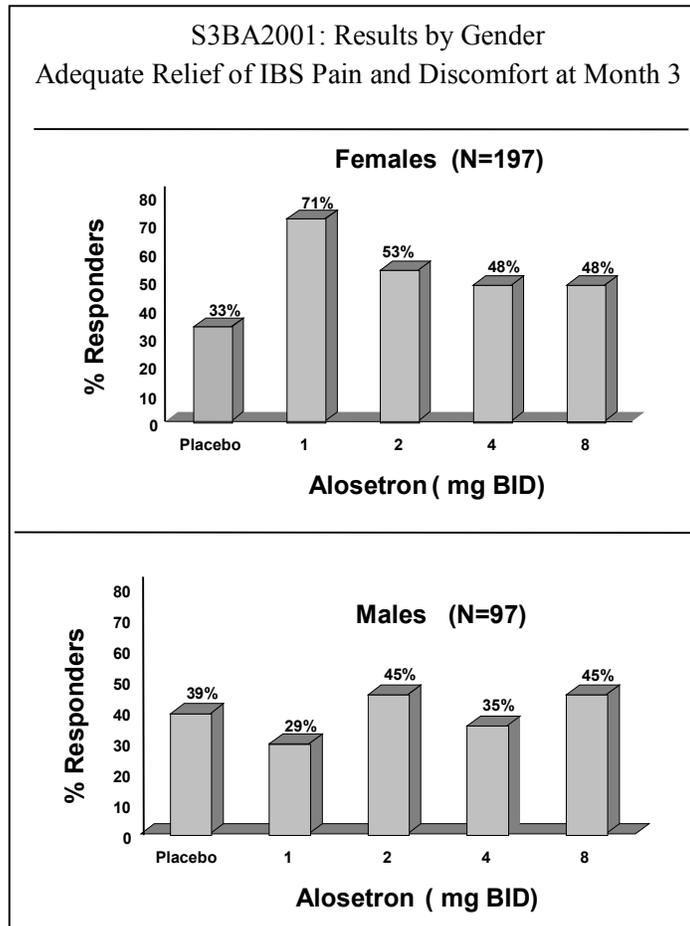


Figure 1. Adequate Relief Responders by Dose and Gender

In female patients, alosetron 1mg BID was also the most efficacious dose on other endpoints, including the proportion of pain/discomfort free days and the percentage of days with urgency.

The conclusions from the two dose-ranging studies was that alosetron 1mg BID was the most efficacious dose with respect to pain relief and bowel function improvement in female patients. In men, no consistent trend for improvement in pain and discomfort was seen with any dose of alosetron. Significant improvement in females was also seen in urgency, stool consistency, and frequency during alosetron treatment, while males showed no consistent improvement in stool frequency or urgency. In S3BA2001, alosetron 1mg BID was the most efficacious dose of the doses of studied, including 2, 4, or 8mg BID. In S3BP12, alosetron 2mg BID was more effective than alosetron 0.1mg BID or 0.5mg BID; however, the effect of alosetron 2mg BID did not appear to be as strong as that observed with alosetron 1mg BID in S3BA2001. Therefore, alosetron 1mg BID was chosen as the dose for progression into subsequent trials of IBS in female subjects.

3.3 Efficacy Results from Clinical Trials

Clinical surveys of non-constipated females with IBS (S3BA2001, S3BA3001, S3BA3002, S3BB3001, S3BB3002) identified the three most bothersome symptoms of diarrhea-predominant IBS as abdominal pain and discomfort, bowel urgency, and stool frequency. Stool consistency was also a bothersome symptom for some patients. Data presented in this section provides compelling evidence of the benefit of alosetron for the most bothersome and debilitating symptoms suffered by females with diarrhea-predominant IBS.

Also provided in this section are data from clinical trials completed subsequent to the NDA approval which confirm the consistent effect of alosetron on the relief of IBS symptoms and demonstrate this effect to be sustained over 12 months of therapy. New data further demonstrate the global relief of IBS symptoms not only in the original population studied, but also for patients with debilitating disease (i.e., patients with daily bowel urgency on at least 50% of days). Data from these recently completed clinical trials also demonstrate that alosetron provides benefits in terms of humanistic outcomes including quality of life and productivity. Finally, results are presented from a study of male patients and from analyses of patients with more severe IBS symptoms at baseline.

3.3.1 Adequate Relief of Abdominal Pain and Discomfort

The efficacy of alosetron 1mg BID in females with diarrhea-predominant IBS was established in the original NDA through the results of two adequate and well-controlled Phase III trials (S3BA3001 and S3BA3002) which demonstrated the effectiveness of alosetron as a novel pharmacological treatment for a significant proportion of IBS patients. Alosetron provided significant improvement in the relief of abdominal pain and discomfort within one to four weeks of treatment initiation. Beneficial effects persisted throughout treatment with no evidence of tolerance with continued therapy. Symptoms returned rapidly upon stopping therapy, although no exacerbation was observed. Figure 2 represents weekly adequate relief of IBS abdominal pain and discomfort for the two treatment groups in both studies.

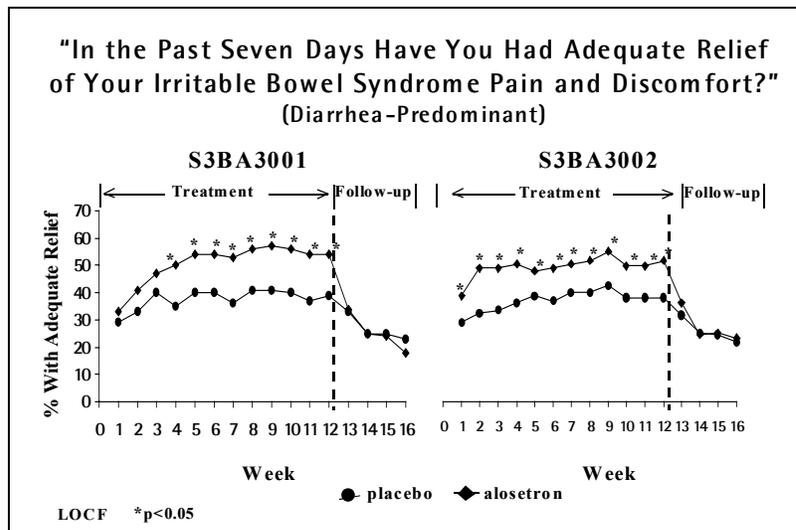


Figure 2. Relief of IBS Pain and Discomfort as Reported in the Original NDA

The prospectively defined primary endpoint in both studies was “adequate relief of IBS pain and discomfort”, which represents a patient-assessed, scientifically validated endpoint that has been shown to be significantly correlated with improvements in the following IBS symptoms: abdominal pain severity, pain-free days, bowel urgency, stool frequency, and stool consistency¹¹; these findings have been replicated in numerous clinical trials of IBS patients.

Data to support the significant benefit of alosetron 1mg BID in the relief of IBS pain and discomfort in women with diarrhea-predominant IBS have been demonstrated consistently in five placebo-controlled studies (two of the studies were completed after NDA approval (S3B30006, S3B30013)) and in 2 active-controlled comparative studies (S3BB3001, S3BB3002). The latter two studies compared alosetron to either mebeverine or trimebutine. Figure 3 illustrates the replication of the pivotal trial results as demonstrated in S3B30013. This study enrolled subjects with an average baseline pain score of 1 (mild), as well as average stool frequency of at least two stools per day and an average stool consistency of at least 3 (where 3 = formed and 4 and 5 = loose and watery respectively). As in the pivotal trial population, significant benefit was achieved within 2 weeks and was maintained throughout the treatment period. Pain rapidly returned after discontinuing therapy.

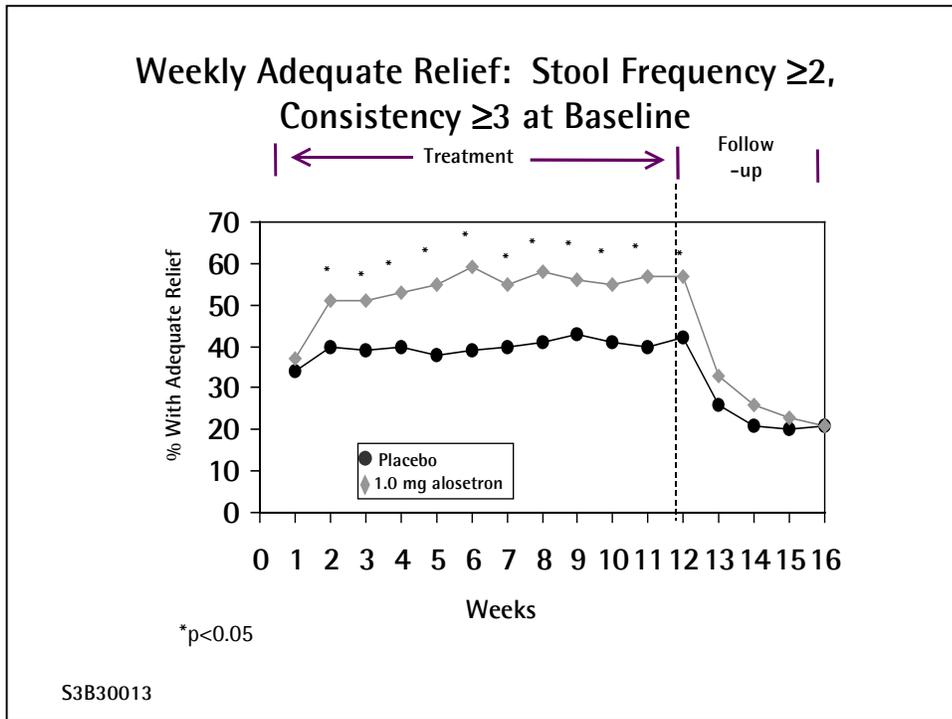


Figure 3. Proportion of Patients with Relief of IBS Pain and Discomfort in Women with Stool Frequency ≥ 2 and Stool Consistency ≥ 3 at Baseline

Alosetron's effect on relief of IBS pain and discomfort has been demonstrated to be consistent and long lasting. Figure 4 illustrates that the benefits of alosetron treatment persist throughout 48 weeks of therapy in female patients with diarrhea-predominant IBS (S3B30006). This study also confirmed that efficacy dissipates upon withdrawal of therapy.

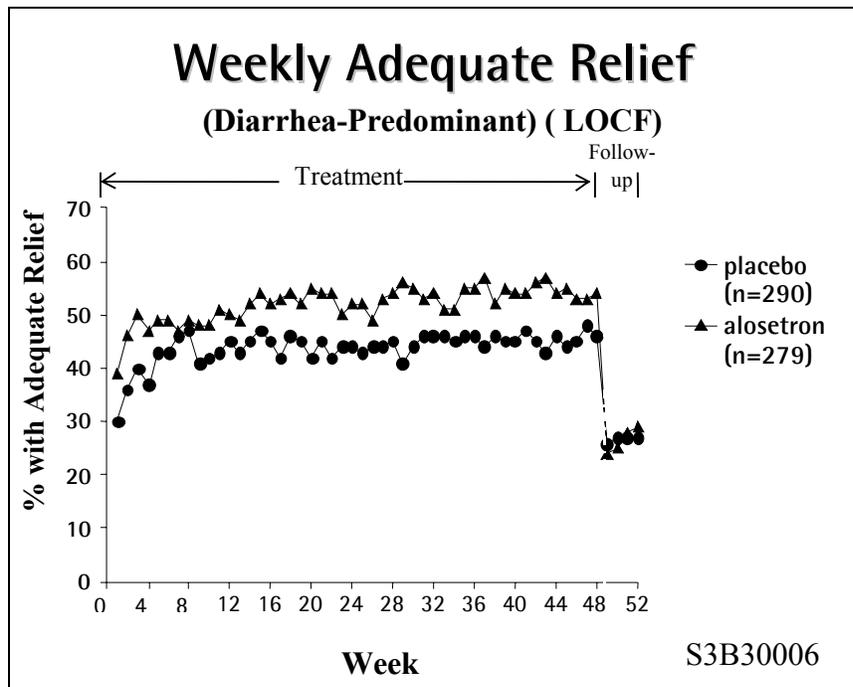


Figure 4. Weekly Adequate Relief Over 48 Weeks of Treatment

3.3.2 Bowel Urgency

Bowel urgency or urgency to defecate is a significant and burdensome symptom in females with diarrhea-predominant IBS. This is a prominent symptom that “ties the patient to the bathroom”. In seven placebo-controlled studies (S3BA2001, S3BA3001, S3BA3002, S3B30006, S3B30013, S3B30011, S3B40031) and an active-controlled comparative study vs. mebeverine (S3BB3001), alosetron 1mg BID either significantly reduced or provided greater ‘satisfactory control’ of urgency than placebo or mebeverine in women with diarrhea-predominant IBS. A significant improvement in urgency was typically seen in the first 2 weeks of treatment and persisted as long as subjects were on treatment, from 12 to 48 weeks.

As illustrated in Figure 5, patients in the two pivotal studies (S3BA3001 and S3BA3002) exhibited bowel urgency on approximately 70% of days during the two-week screening period. This decreased to less than 40% of days during treatment with alosetron.

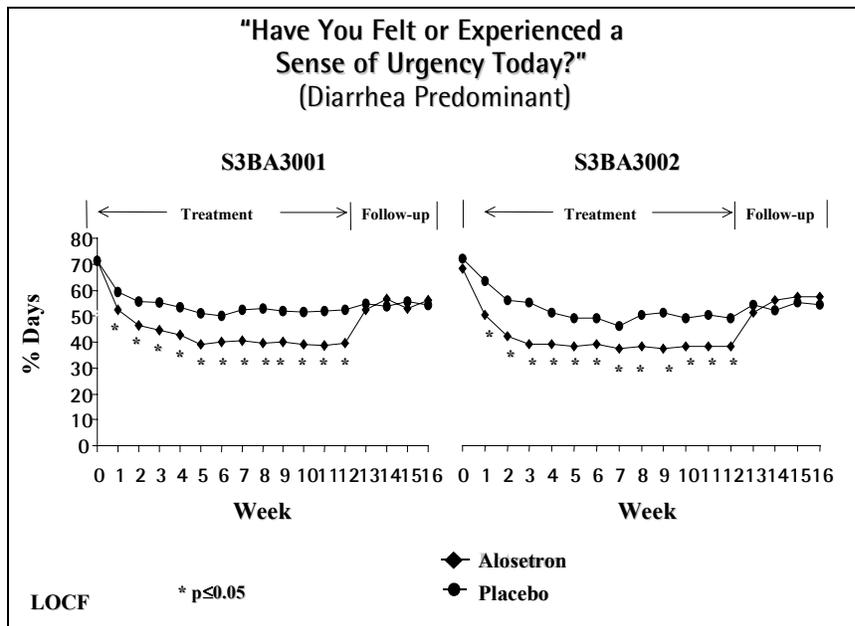


Figure 5. Proportion of Days with Bowel Urgency From Two Pivotal Studies Reported in Original NDA

Figure 6 illustrates the reproducibility of these results in a study involving women with baseline stool frequency ≥ 2 and stool consistency ≥ 3 and Figure 7 illustrates the sustained benefit over 48 weeks of treatment.

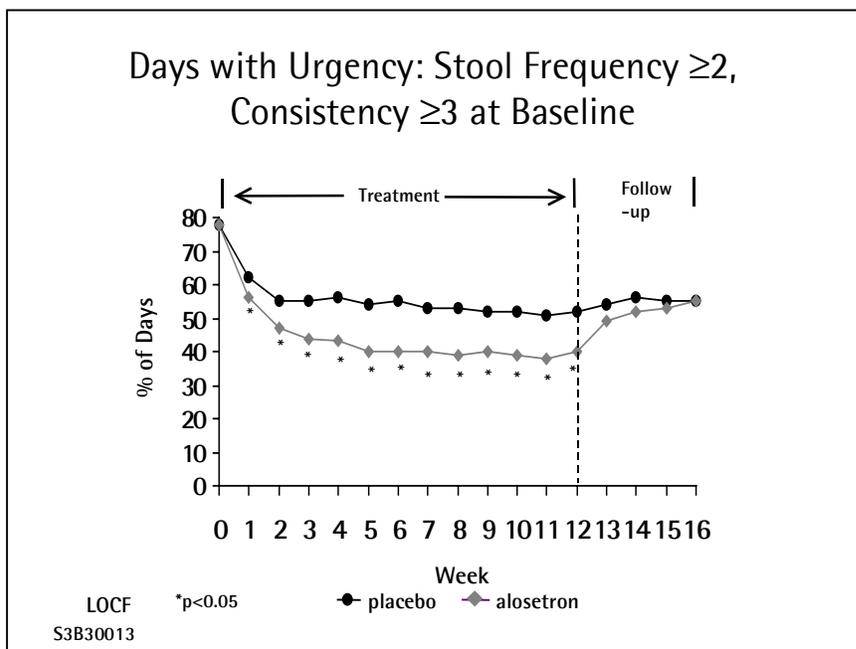


Figure 6. Proportion of Days with Urgency in Women with Stool Frequency ≥ 2 and Stool Consistency ≥ 3 at Baseline

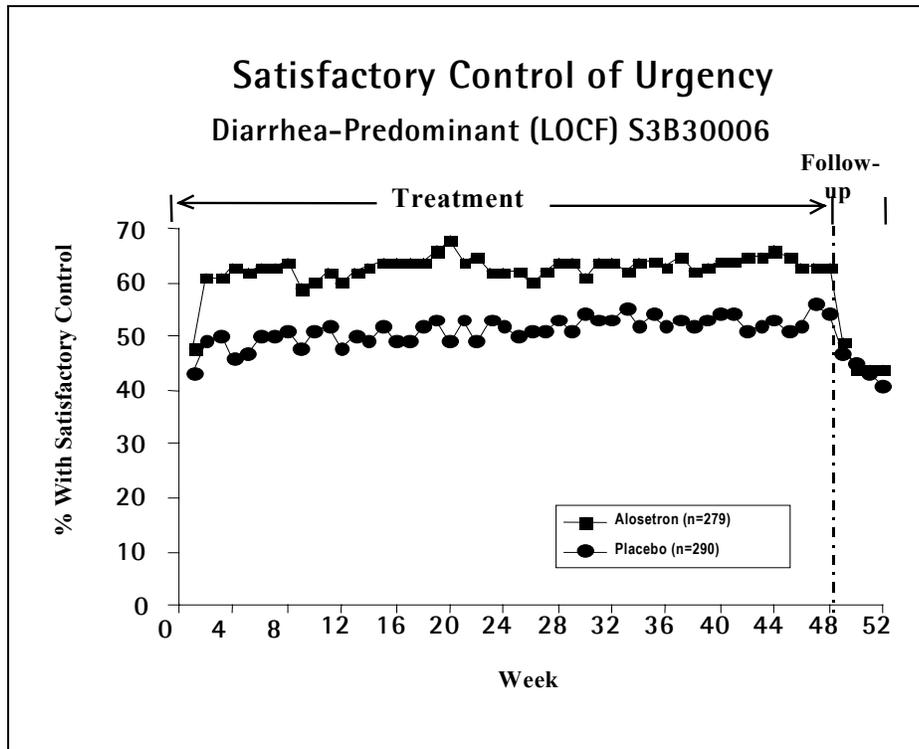


Figure 7. Satisfactory Control of Urgency Over 48 Weeks

The benefit of alosetron on this debilitating IBS symptom was further illustrated in studies S3B30011 and S3B40031, both completed after approval, which demonstrated that alosetron significantly increased from baseline the percentage of days with satisfactory control of urgency compared to placebo. Only patients substantially debilitated by urgency, i.e., those with bowel urgency on greater than 50% of days during the baseline period, were eligible to enter these studies. Enrolled patients in both studies experienced, on average, a lack of satisfactory control of bowel urgency on approximately 80% of days at baseline. Figure 8 illustrates the percentage of days with satisfactory control of urgency during the treatment period for the two treatment groups from both studies.

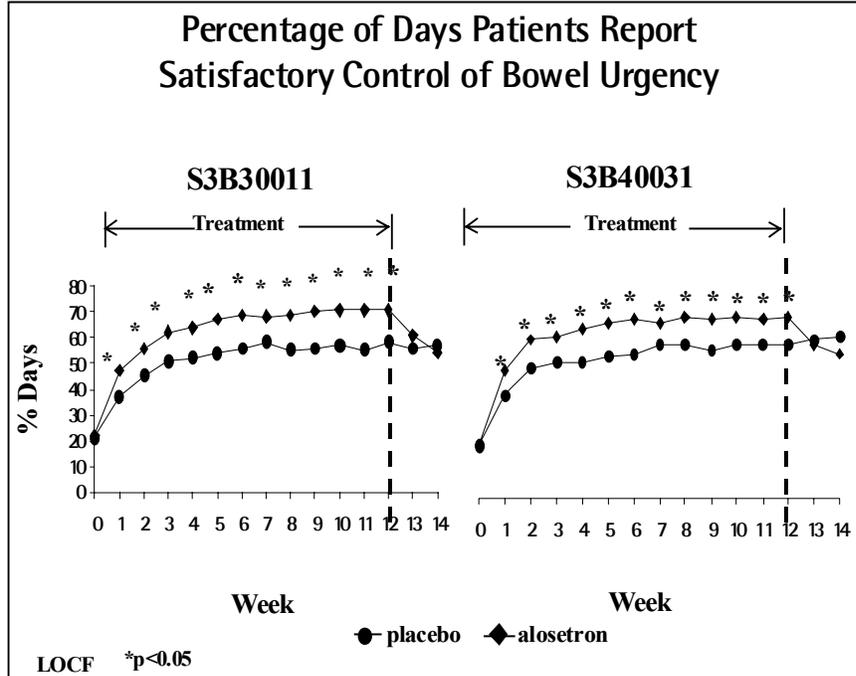


Figure 8. Percentage of days with Satisfactory Control of Urgency for Patients with Urgency on $\geq 50\%$ of days at baseline.

3.3.3 Stool Frequency

Alosetron 1mg BID significantly reduced or provided greater satisfactory control of stool frequency than placebo in women with diarrhea-predominant IBS in seven placebo-controlled studies. Three of these studies were reported in the original NDA (S3BA2001, S3BA3001, S3BA3002) and four were completed subsequent to the NDA approval (S3B30006, S3B30013, S3B30011, S3B40031). In addition to the placebo-controlled studies, this benefit was demonstrated in two active-controlled comparative studies involving mebeverine (S3BB3001) and trimebutine (S3BB3002). A significant improvement in stool frequency typically was seen in the first week of treatment. The improvement persisted as long as subjects were on treatment as illustrated in Figure 9 for the pivotal studies from the original NDA and in Figure 10 for the study involving women with baseline stool frequency ≥ 2 and stool consistency ≥ 3 . Similar results were seen in the remaining five studies.

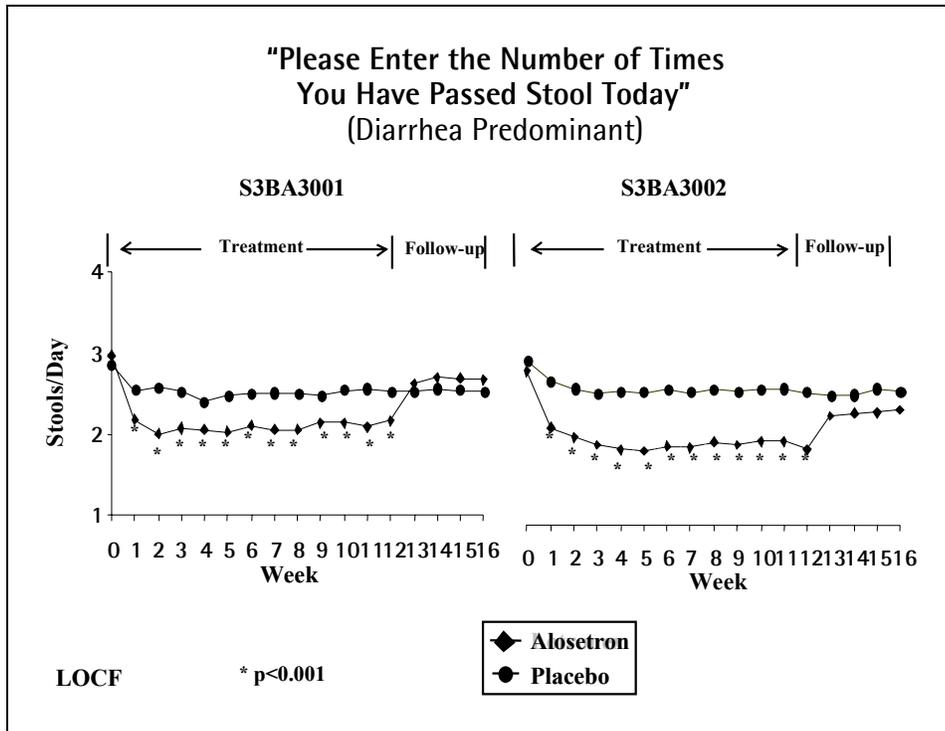


Figure 9. Weekly Average of Number of Stools/Day as Reported in the Original NDA

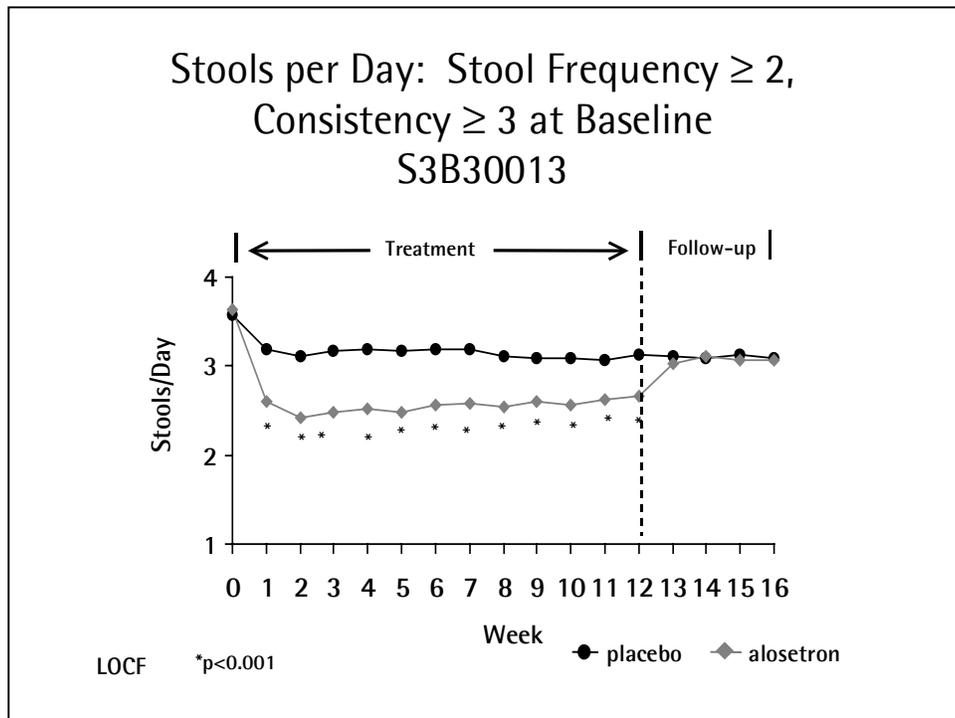


Figure 10. Weekly Average Number of Stools/Day in Women with Stool Frequency ≥ 2 and Stool Consistency ≥ 3 at Baseline

3.3.4 Stool Consistency

Alosetron 1mg BID significantly improved stool consistency as compared to placebo in women with diarrhea-predominant IBS in seven placebo-controlled studies. Three of these studies were reported in the original NDA (S3BA2001, S3BA3001, S3BA3002) and four were completed subsequent to NDA approval (S3B30006, S3B30013, S3B30011, S3B40031). In addition to the placebo-controlled studies, this benefit was demonstrated in two, active-controlled, comparative studies involving mebeverine (S3BB3001) and trimebutine (S3BB3002). A significant improvement in stool consistency was typically seen in the first week of treatment. The improvement continued as long as subjects were on treatment. This result is illustrated in Figure 11 for the pivotal studies from the original NDA and in Figure 12 for the study involving women with stool frequency ≥ 2 and stool consistency ≥ 3 at baseline. Similar results were seen in the remaining 5 studies.

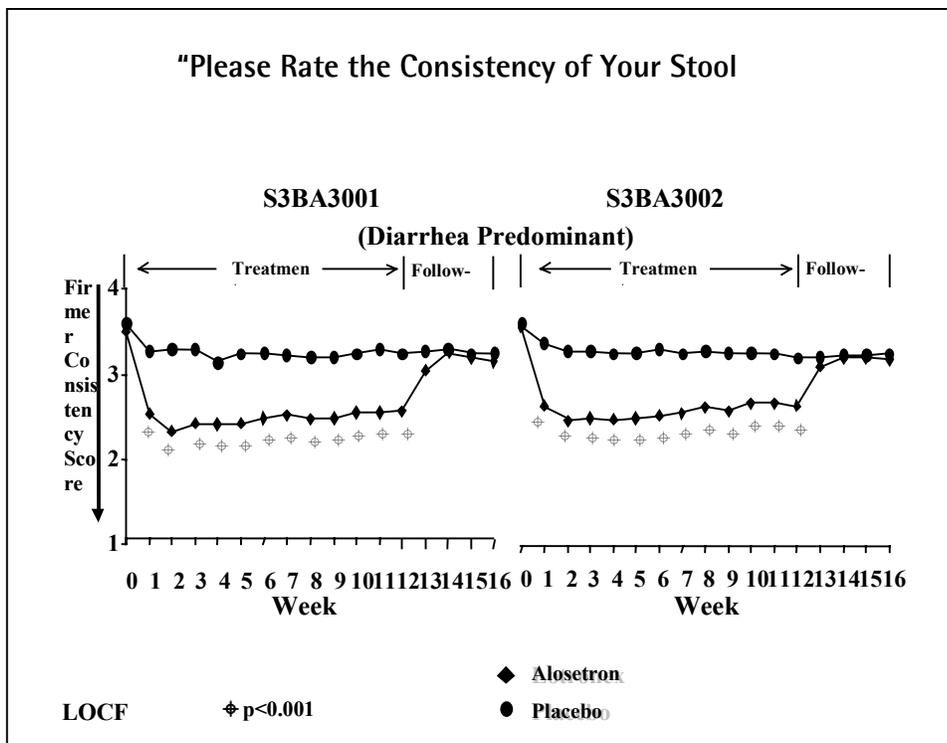


Figure 11. Change In Stool Consistency as Reported In The Original NDA

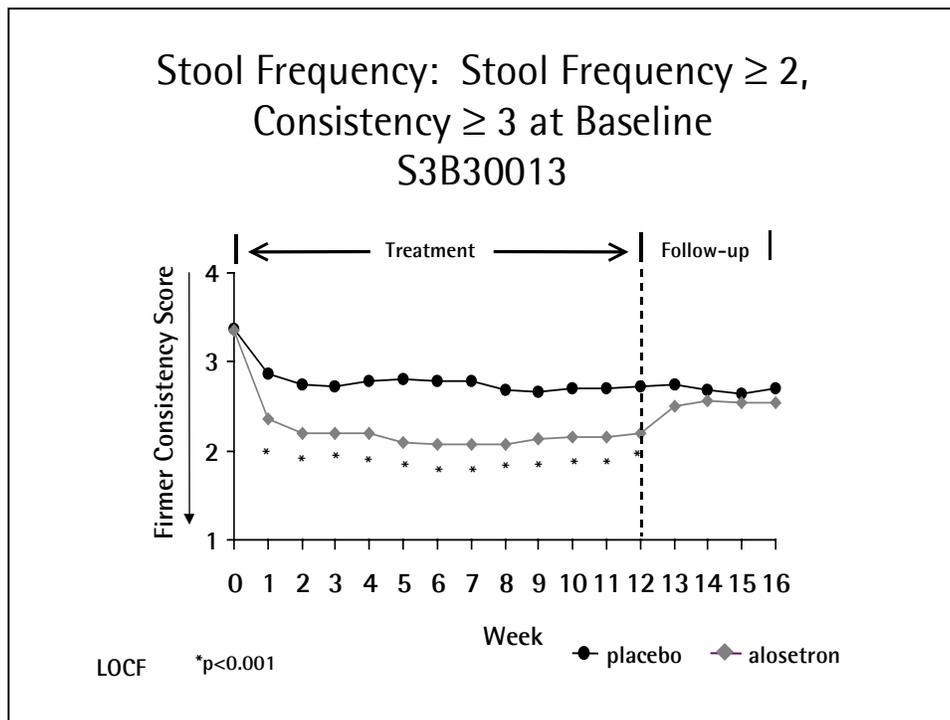


Figure 12. Change in Stool Consistency in Women with Stool Frequency ≥ 2 and Stool Consistency ≥ 3 at Baseline

As clearly demonstrated above and replicated in numerous studies, for females with diarrhea-predominant IBS, alosetron treatment significantly and consistently improved all three of the most bothersome symptoms identified by these patients, as well as stool consistency.

3.3.5 Global Improvement of IBS Symptoms

In addition to improvement in the individual symptoms of IBS, results of studies completed since NDA approval further confirmed the ability of alosetron to provide global improvement of IBS symptoms in females with diarrhea-predominant IBS. Endpoints that provide an integration of patients' IBS symptoms are recommended by the Rome II working group on functional GI disorders as the most meaningful in representing overall treatment effects. The GIS endpoint measured the "Global Improvement of IBS Symptoms" compared to baseline on a 7-point scale ranging from "substantially worse" to "substantially improved" and has been shown to reflect both clinical and quality of life-associated dimensions of IBS¹².

In two placebo-controlled studies (S3B30011, S3B40031) and 1 open-label comparison study vs. traditional IBS therapy (S3B30020), a significantly greater proportion of women with diarrhea-predominant IBS treated with alosetron 1mg BID reported substantial or moderate improvement in IBS symptoms than did those treated with placebo or traditional therapy. Figure 13 illustrates the results of monthly measurements of Global Improvement in S3B30011 and S3B40031. The overall response rate on alosetron in S3B30011 was 67-74% compared to 41-44% on placebo. This magnitude of difference between placebo and alosetron (25-31%) demonstrates the robust efficacy of alosetron in this patient population. These findings were confirmed in a subsequent study, S3B40031.

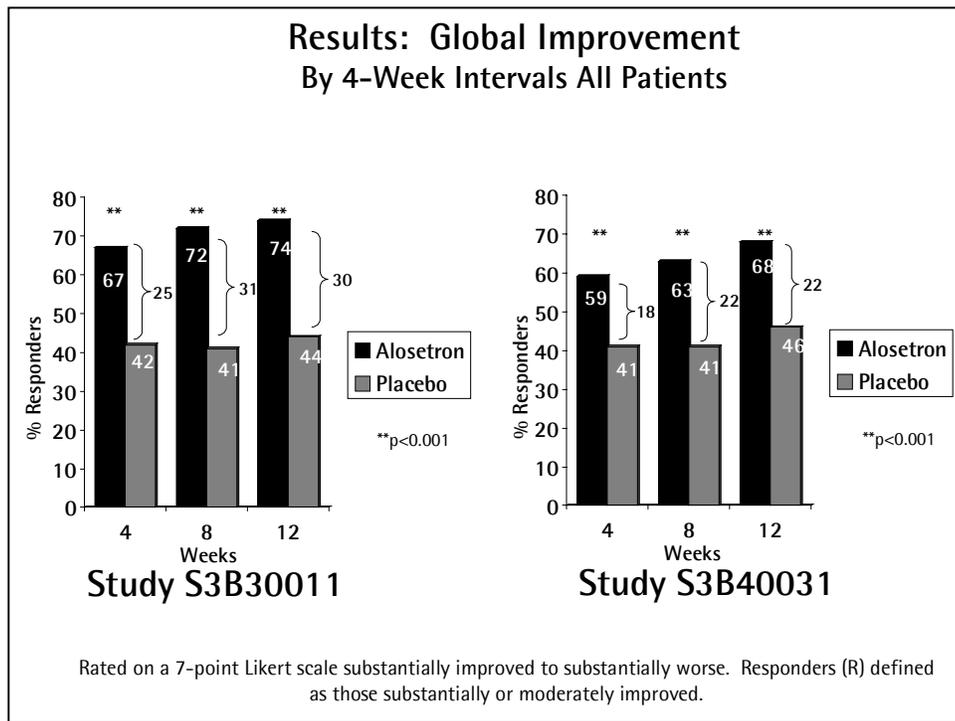


Figure 13. Global Improvement of IBS Symptoms; Alosetron vs. Placebo

Similar findings were seen in an open label study comparing alosetron 1mg BID with other IBS therapy prescribed by the investigator (traditional therapy) as illustrated in Figure 14.

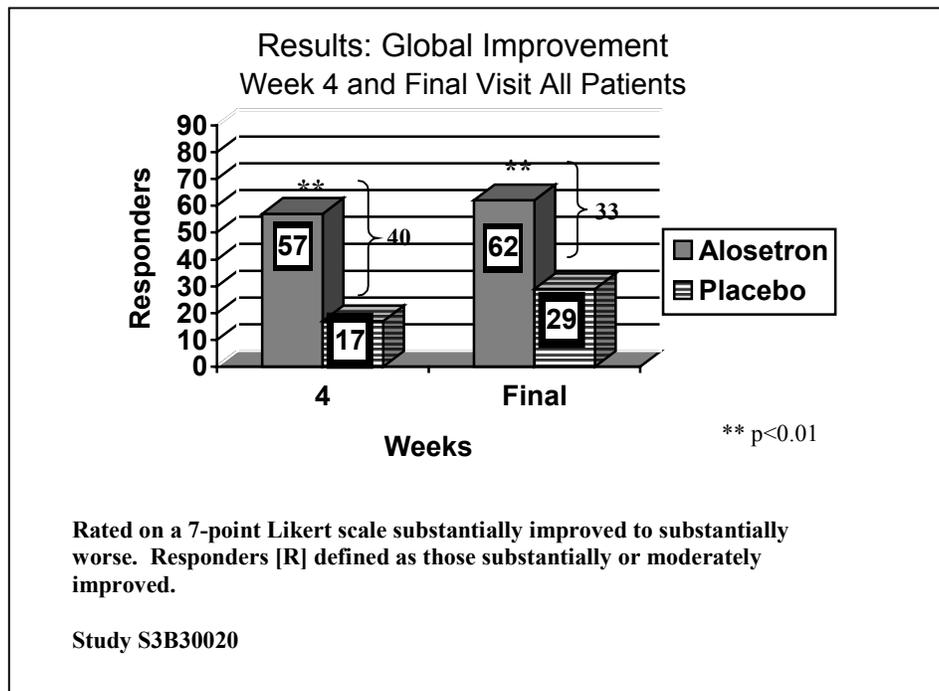


Figure 14. Global Improvement of IBS Symptoms; Alosetron vs. Traditional IBS Therapy

These results, along with demonstrated effectiveness against individual IBS symptoms, provide evidence of the clinically meaningful benefit of alosetron treatment for females with diarrhea-predominant IBS.

3.3.6 Quality of Life

Quality of life (QoL) for patients with IBS can be significantly diminished to the extent of other chronic illnesses⁵. A disease-specific QoL questionnaire (IBSQoL) has been developed to measure nine QoL domains important for patients with IBS. Using this measurement tool in numerous studies, alosetron has consistently produced positive improvements over baseline, active comparative agents, or placebo treatments in multiple domains. Specifically, data from the two pivotal trials (SBA3001 and S3BA3002) submitted to FDA subsequent to the NDA approval indicated that subjects treated with alosetron were significantly improved in each of the nine QoL domains in S3BA3001 and in 8/9 domains in S3BA3002. Since NDA approval, additional data from two long-term (48 week) studies (S3BA3003, S3B30006), two active-controlled comparative studies (S3B3001, S3BB3002), and one open-label comparison study vs. traditional IBS therapy (S3B30020), have demonstrated that alosetron 1mg BID produces positive changes from baseline in the majority of the nine domains. In addition to change from baseline, alosetron significantly improved QoL ratings

on one or more domains as compared to placebo, mebeverine, trimebutine, or traditional therapy in women with diarrhea-predominant IBS. The magnitude and sustainability of the response to alosetron is illustrated in Figure 15 utilizing the results of S3BA3003 showing positive changes in all nine domains upon dosing for 48 weeks, with the differences being statistically significant for six of the domains. The benefit of alosetron over traditional IBS therapy in quality of life is illustrated in Figure 16.

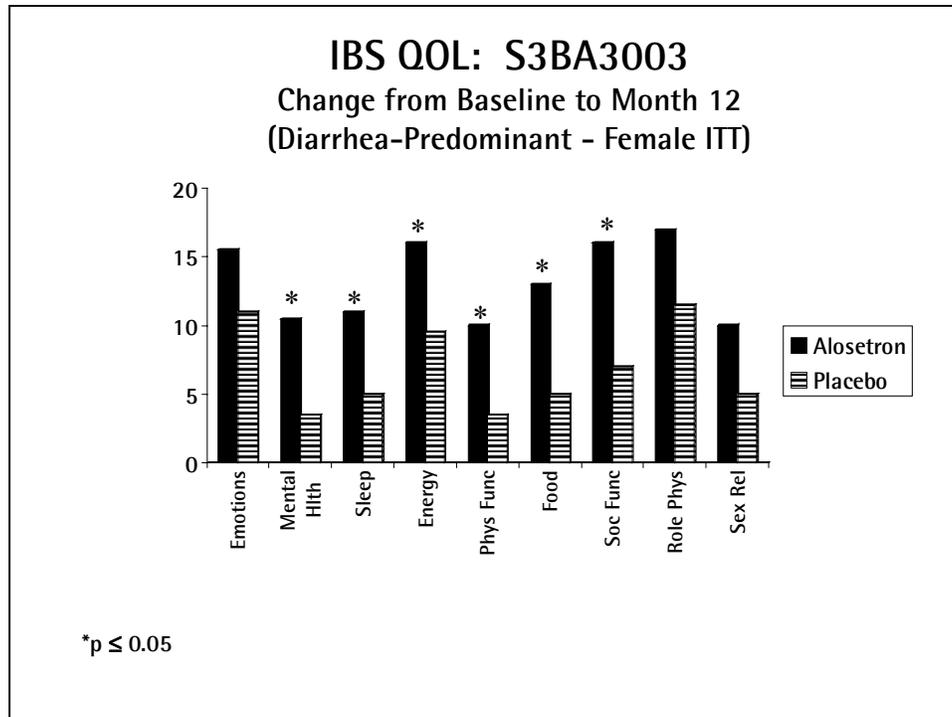


Figure 15. Change from Baseline to Month 12 in the Nine Domains of IBS QoL

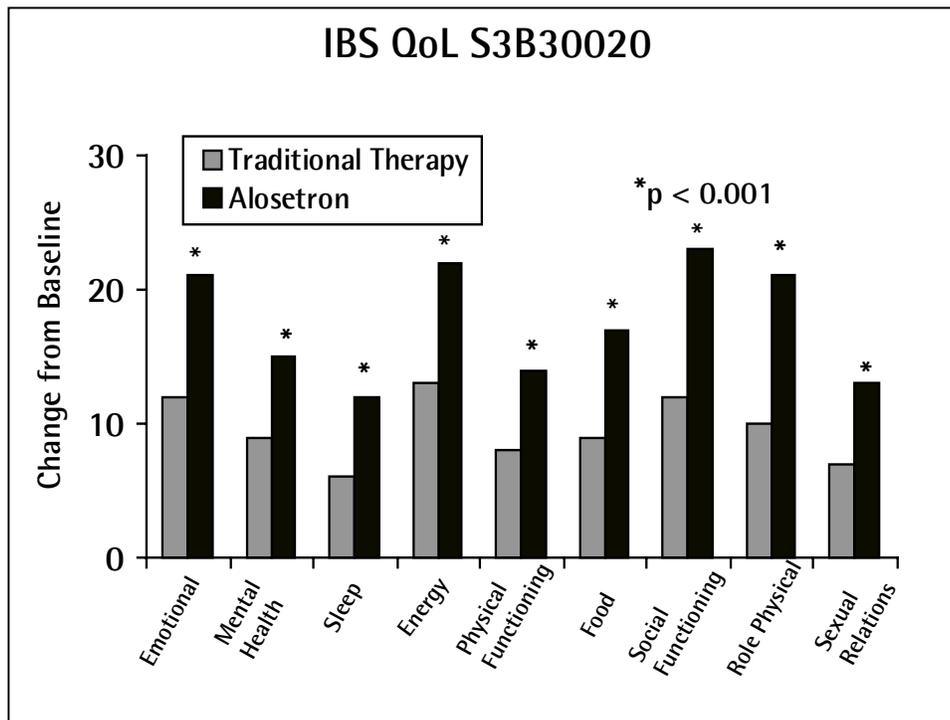


Figure 16. Change From Baseline in IBS QoL; Alosetron vs. Traditional Therapy

3.3.7 Productivity

The symptoms of IBS can be severe and result in limited functional productivity for the individual at work or in the conduct of main activity. The therapeutic goal of IBS treatment is to reduce abdominal pain and discomfort, as well as normalize bowel function. Successful treatment should allow individuals to be more socially and functionally productive. In both pivotal studies (S3BA3001 and S3BA3002), a significantly greater proportion of patients treated with alosetron experienced meaningful improvements in freedom from dietary limitations, social functioning, and in their ability to carry out their work or main activity. This result has been substantiated in two placebo-controlled studies (S3B30011, S3B40031) and in one open-label comparison study vs. traditional IBS therapy (S3B30020). In these studies alosetron 1mg BID significantly improved productivity compared to placebo or traditional therapy in women with diarrhea-predominant IBS. As illustrated in Figure 17 for S3B30011, this resulted in recovery of over 20 hours of lost workplace productivity over the 12-week treatment period.

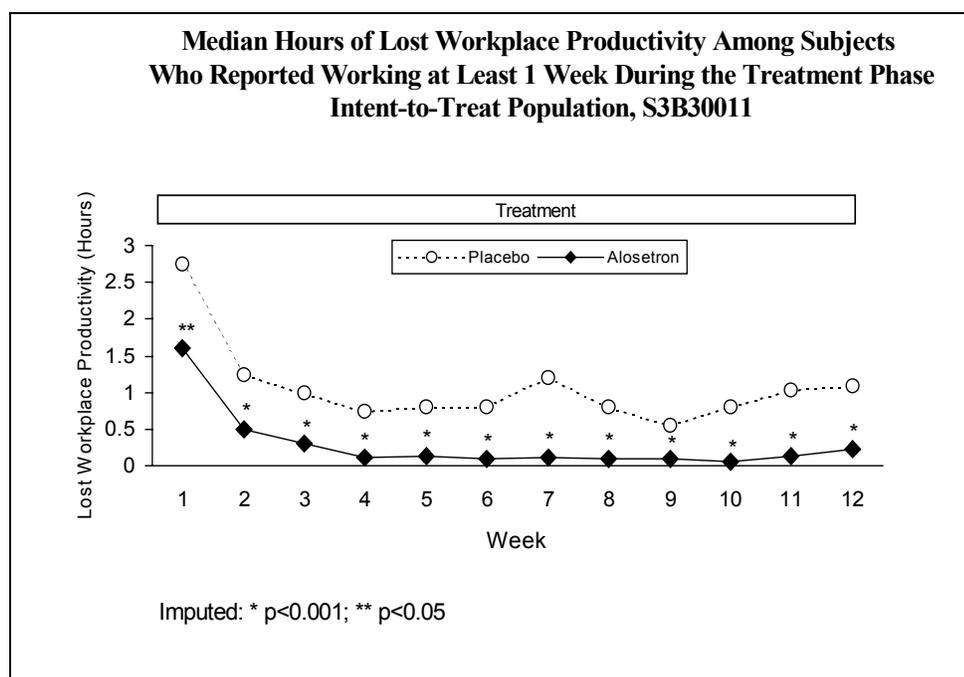


Figure 17. Median Hours of Lost Workplace Productivity

3.3.8 Efficacy of Alosetron in Patients with Severe IBS Symptoms

Relief of Pain and Improvement in Bowel Functions in Patients with Severe IBS Symptoms

In the pivotal studies forming the basis of the NDA, alosetron provided benefits in diarrhea-predominant female IBS patients who at baseline had symptoms that ranged from moderate to severe. Evidence that alosetron provides adequate relief in patients with severe IBS has been provided as part of a recent response to an FDA request. Figures 18 through 25, which follow, summarize weekly adequate relief data from the six placebo-controlled studies that collected adequate relief data (S3BA2001, S3BA3001, S3BA3002, S3B20023 [males], S3B30006 [weeks 1-12], S3B30013) stratified by increasing severity of baseline pain, bowel urgency, stool frequency, and stool consistency. These results show that alosetron 1mg BID also provides greater adequate relief than placebo in severe patients who, during their 14 day baseline period, either:

- 1) averaged between moderate and intense to severe abdominal pain every day; (Figure 19)
- 2) had urgency every day; (Figure 21)
- 3) averaged >4 stools per day; or (Figure 23)
- 4) had loose or watery stools every day. (Figure 25)

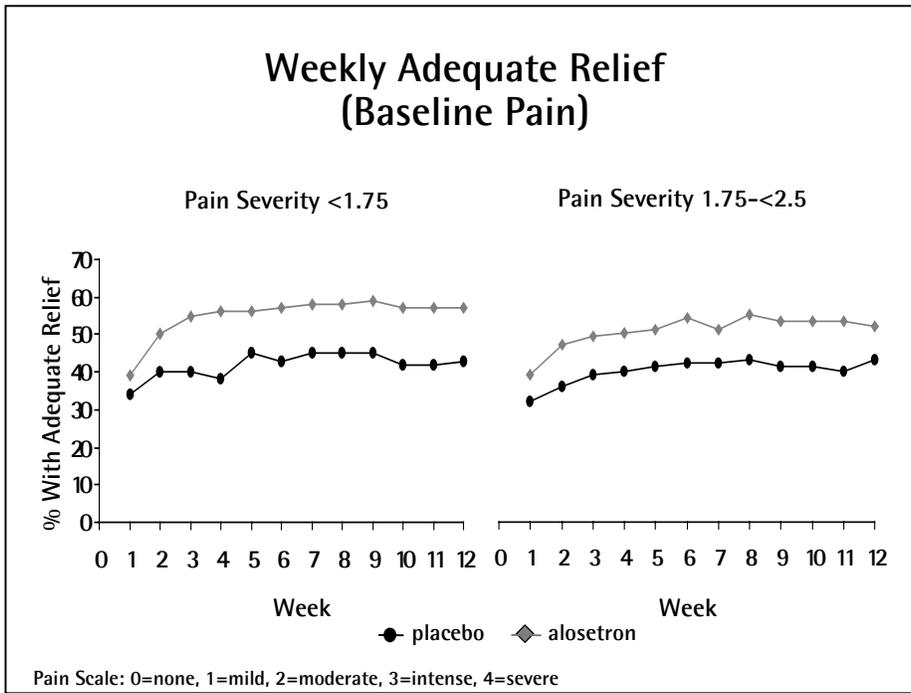


Figure 18. Weekly Relief of Pain in Patients Who Averaged Mild to Between Mild and Moderate Pain at Baseline

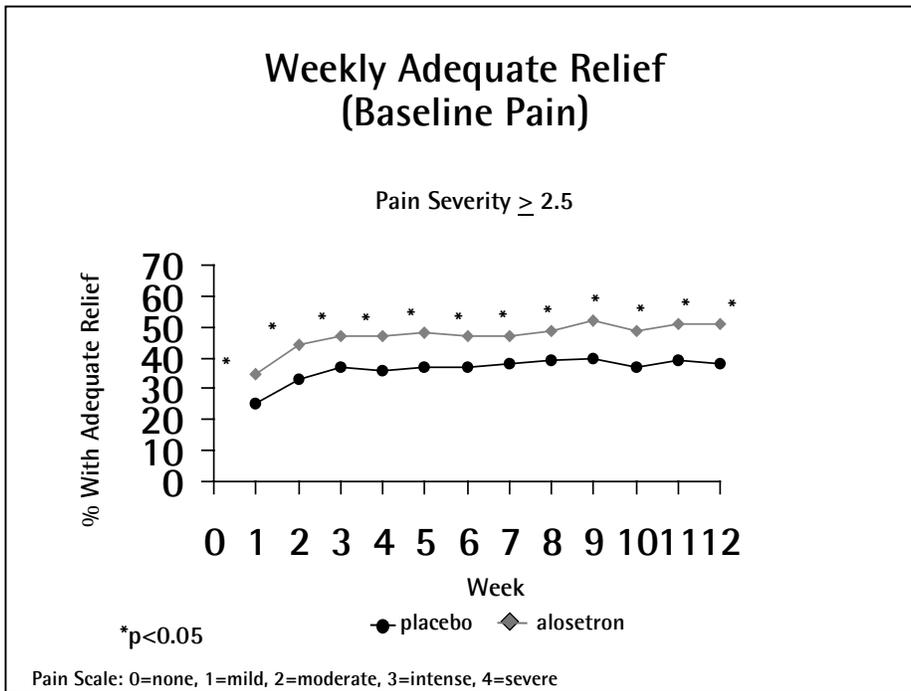


Figure 19 Weekly Relief of Pain in Patients Who Averaged between Mild and Moderate to Severe Pain at Baseline

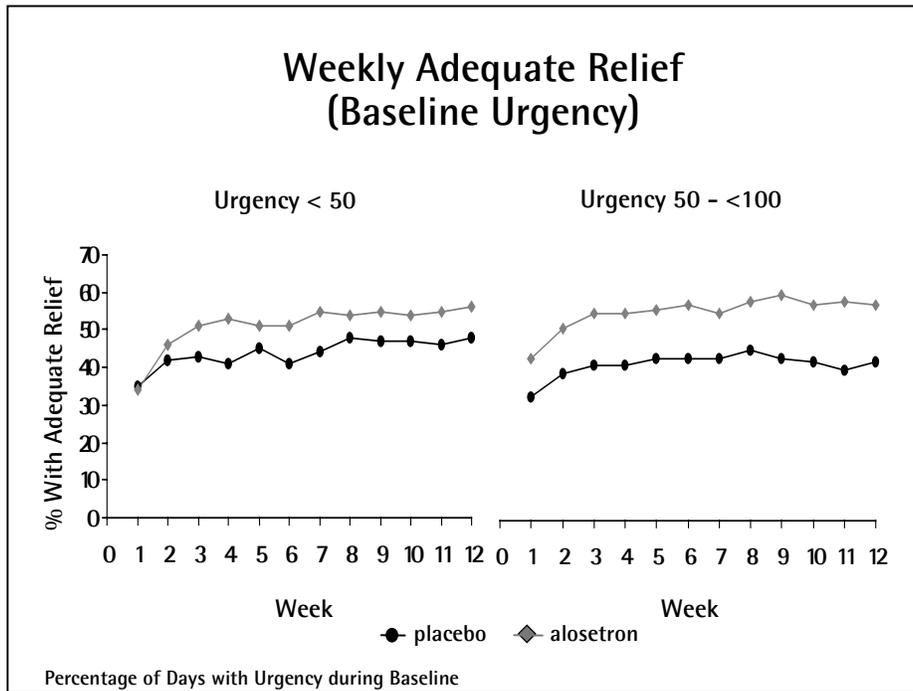


Figure 20 Weekly Relief of Pain in Patients Who Averaged < 50% and <100% Days with Urgency at Baseline

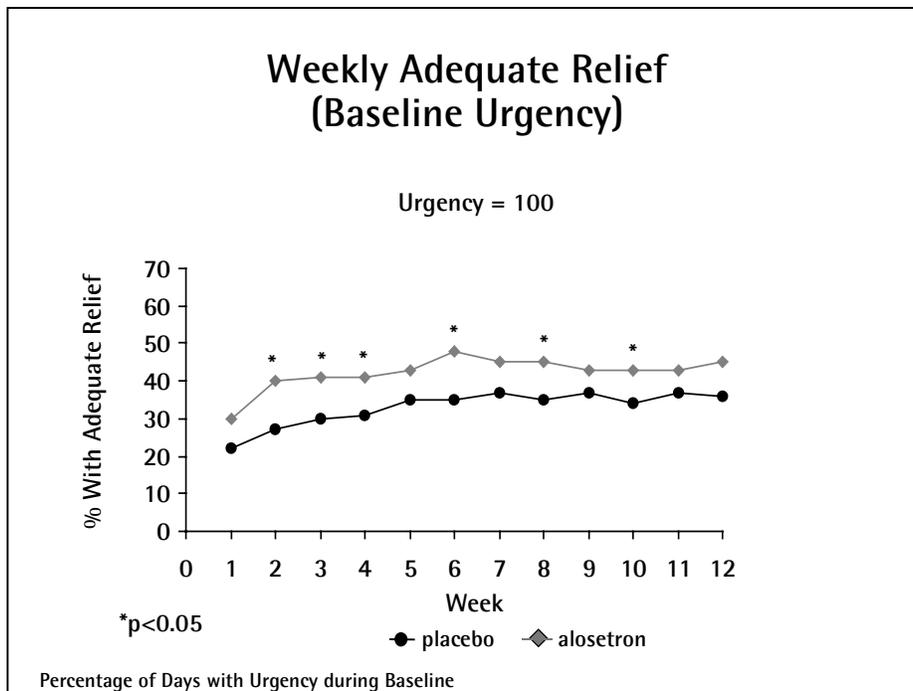


Figure 21 Weekly Relief of Pain in Patients Who Experienced Urgency on 100% of Days at Baseline

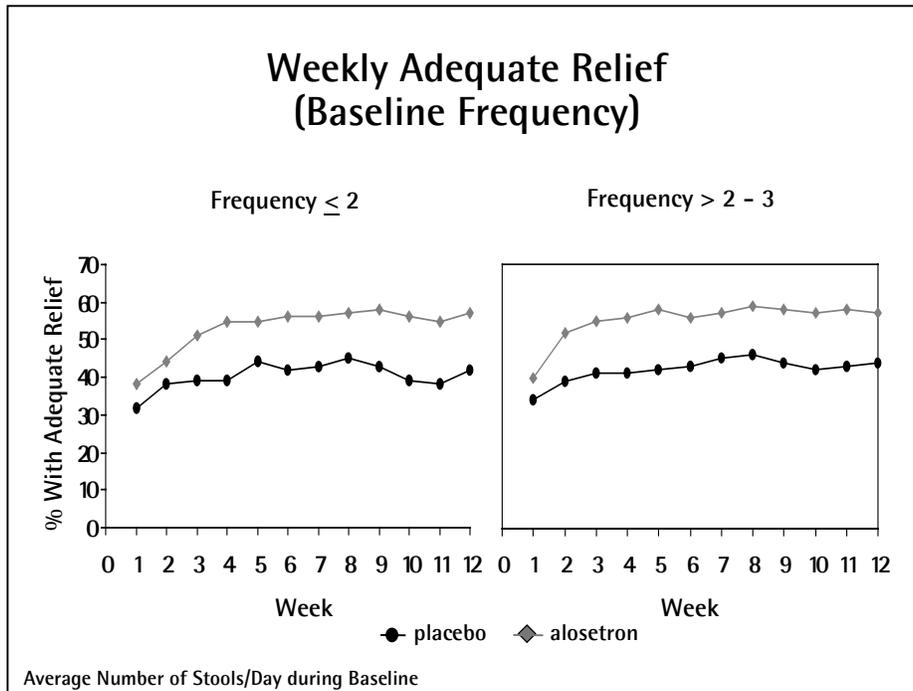


Figure 22 Weekly Relief of Pain In Patients Who Averaged 2 Or Fewer Stools/Day and Those Who Averaged More Than 2, But No More Than 3 Stools/Day at Baseline

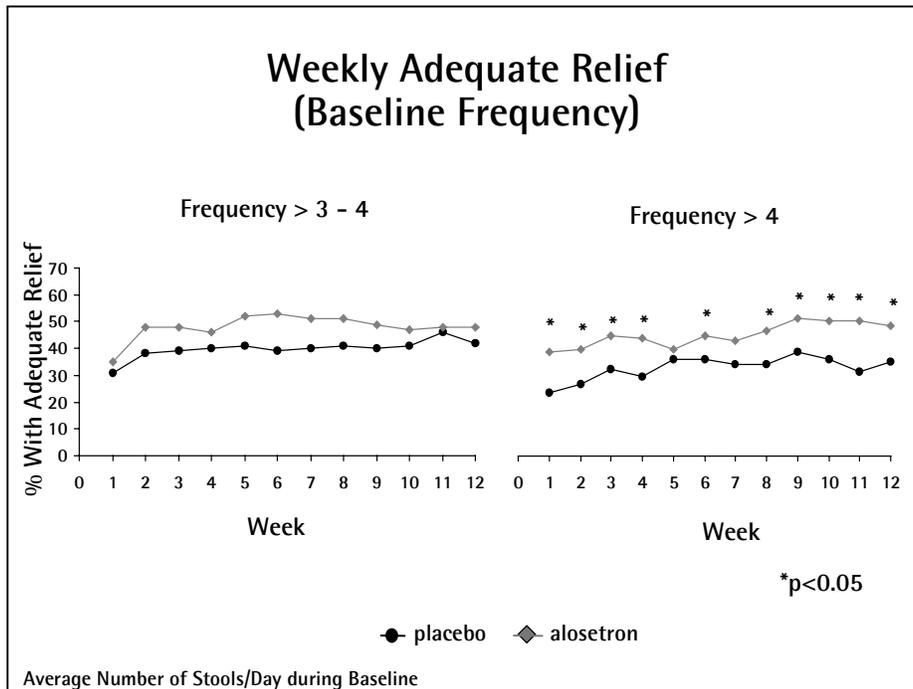


Figure 23 Weekly Relief of Pain in Patients Who Averaged More Than 3, But No More Than 4 Stools/Day and Those Who Averaged More Than 4 Stools/Day at Baseline

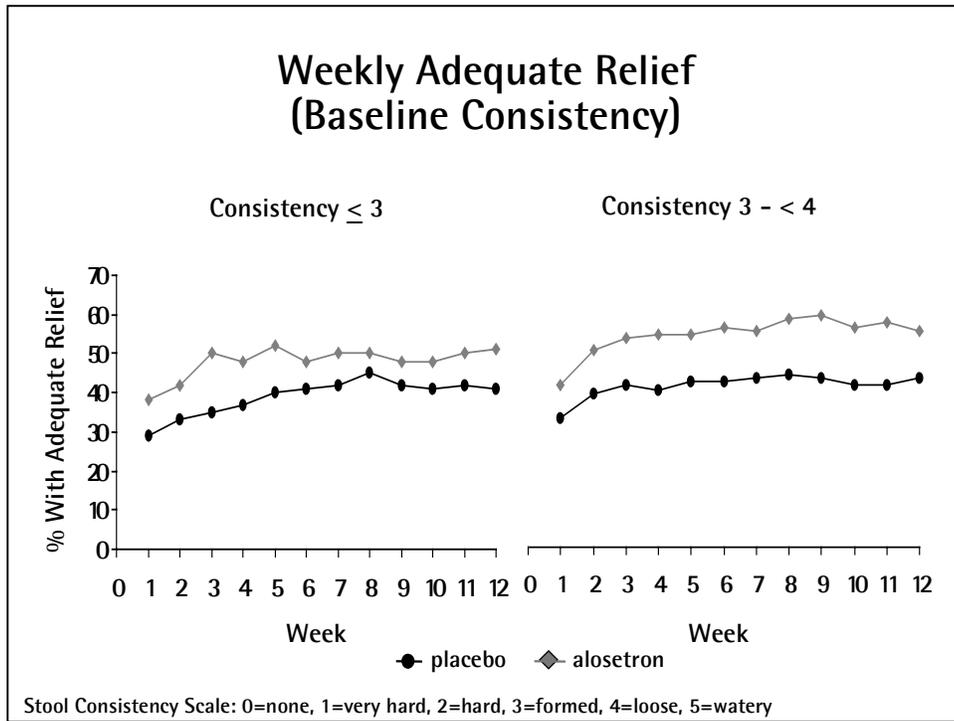


Figure 24 Weekly Relief of Pain in Patients Who Averaged Formed to Hard Stool and Those Who Averaged Between Formed and Loose Stool at Baseline

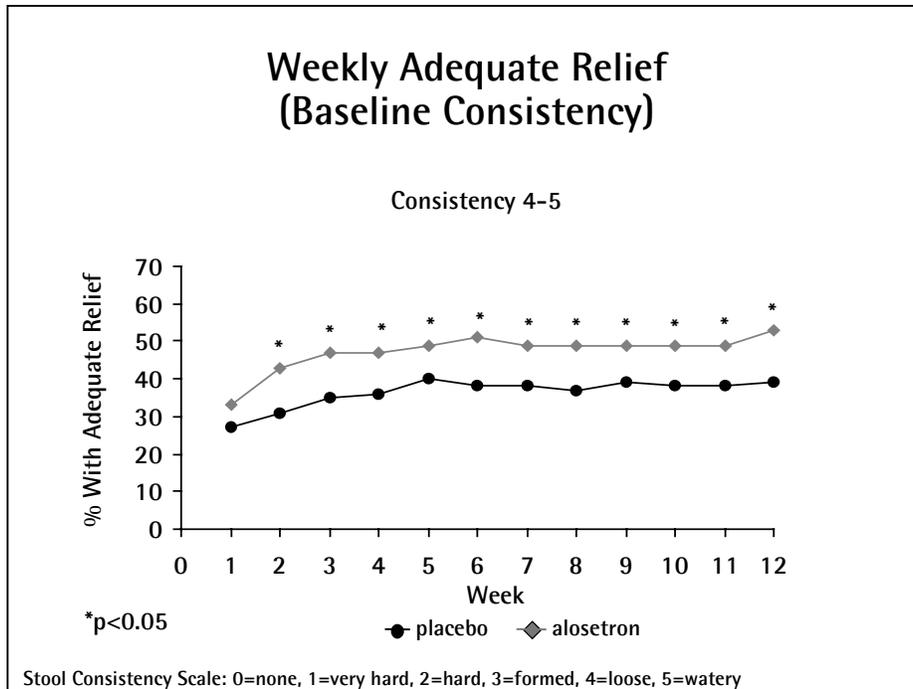


Figure 25 Weekly Relief of Pain in Patients Who Averaged Loose to Watery Stools at Baseline

Satisfactory Control of Bowel Urgency in Patients with Severe IBS Symptoms

Following approval of the original NDA, two large placebo-controlled trials were conducted in women with diarrhea-predominant IBS who reported the severe symptom of urgency on at least 50% of days during the two-week screening period prior to study entry (S3B30011 and S3B40031). Since urgency is one of the most debilitating symptoms of IBS, lack of satisfactory control of urgency on at least 50% days at baseline represented a more severely affected population than in the original trials. Although the protocol required lack of control of urgency on at least 50% of days, the patients enrolled in the trial, on average, had lack of control on approximately 80% of days. As illustrated in Figure 26, relative to placebo, significantly more of the alosetron-treated patients improved to satisfactory control of urgency on 75% or more days in the treatment period compared to placebo. Figure 27 illustrates a similar benefit for alosetron-treated patients over placebo in achieving satisfactory control of urgency on 85% or more of days in the treatment period.

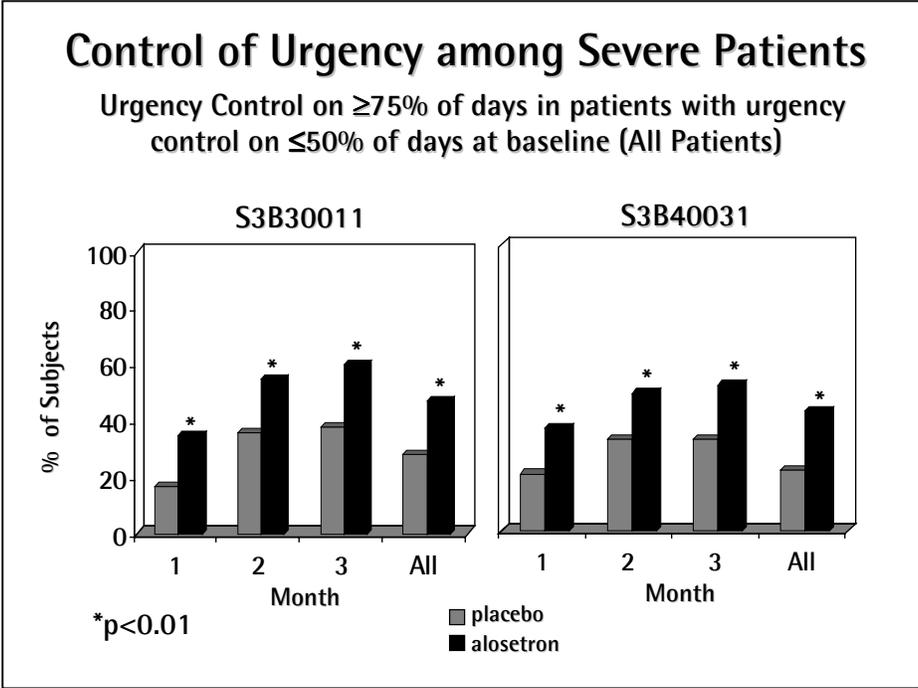


Figure 26: Percent of Patients with Urgency on $\geq 50\%$ of days at Baseline Who Improved to Urgency on $\leq 25\%$ of Days

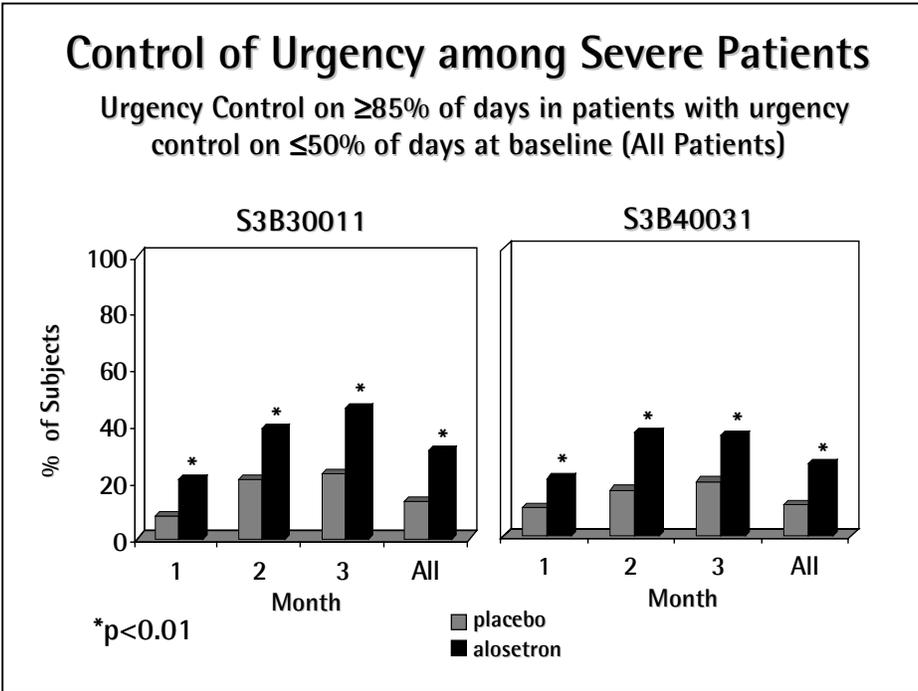


Figure 27. Percent of Patients with Urgency on $\geq 50\%$ of Days at Baseline Who Improved to Urgency on $\leq 15\%$ Days During Treatment

In response to an FDA request, this population has been further assessed to evaluate response to alosetron treatment in patients who reported lack of satisfactory control of urgency on at least 70% of days during screening. Figure 28 illustrates the percentage of these patients who improved to satisfactory control of urgency on 75% or more days during treatment and Figure 29 illustrates the percentage who improved to control of urgency on 85% or more of days during treatment. Of note is the similarity of results between those reporting lack of satisfactory control of urgency on at least 50% of days during screening to those who reported lack of control on at least 70% of days during screening. These results further support the clinical relevance of the benefits provided for patients with debilitating IBS symptoms.

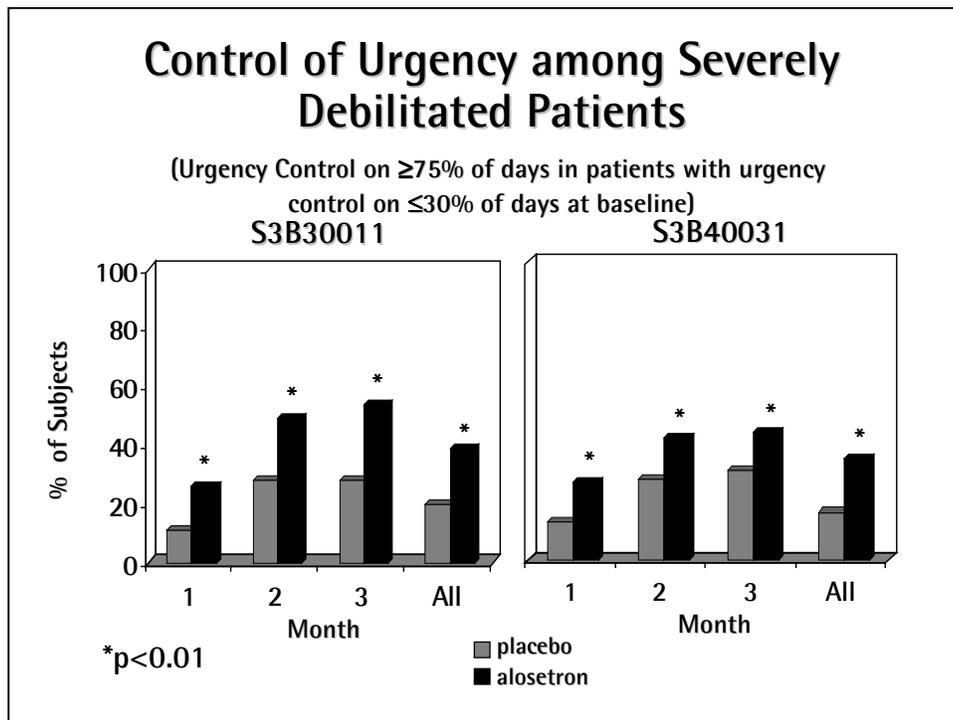


Figure 28: Percent of Patients with Urgency on $\geq 70\%$ of days at Baseline Who Improved to Urgency on $\leq 25\%$ of Days During Treatment

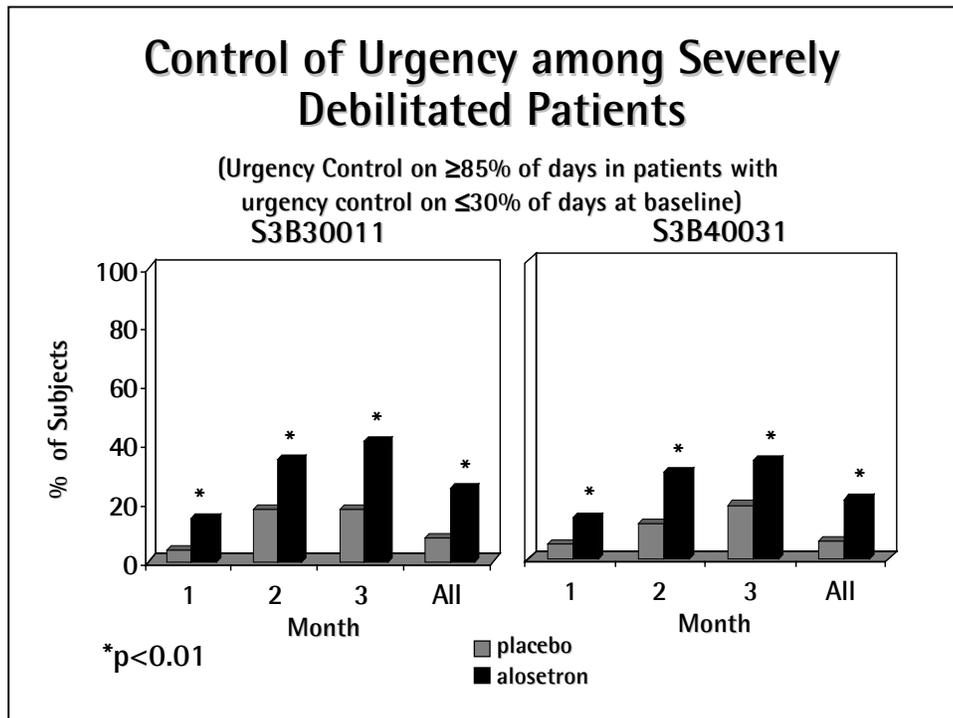


Figure 29: Percent of Patients with Urgency on $\geq 70\%$ of days at Baseline Who Improved to Urgency on $\leq 15\%$ of Days During Treatment

Change in Quality of Life Scores to None or Mild Symptoms

Additional evidence that alosetron provides benefit in patients with severe IBS symptoms was derived from an integrated analysis of responses among patients with severe QoL measures at baseline in the five placebo-controlled 12-week studies that utilized the IBSQoL questionnaire. Patients were included in the evaluation if they had responses at baseline classified as either 'often/most of the time/limited a lot/agree' or 'always/all the time/completely/strongly agree'. In these analyses, the proportions of severe patients at baseline who improved to responses indicating 'none' or 'mild' symptoms following treatment were compared between the alosetron and placebo treatment groups.

Results of these analyses showed that the proportion of severe patients at baseline who subsequently reported 'none' or 'mild' symptoms following treatment was significantly greater in alosetron-treated patients than placebo-treated patients for the following 15 IBS-specific QoL measures: feeling uncomfortable in social activities; avoiding social activities because no bathroom nearby; feeling embarrassed in social activities; feeling in the way of other's social activities; feeling angry about IBS; feeling less happy; feeling emotionally or

physically worn out by IBS; restricting moderate or vigorous activities; succeeding at work/main activity; getting less work/main activity done; avoiding work/main activity; affecting job/main activity performance; interfering with sexual activities. Figure 30 illustrates this improvement for items in the Social Activity Domain. Figure 31 illustrates improvement in the Activity Function Domain and Figure 32 in the Energy Scale.

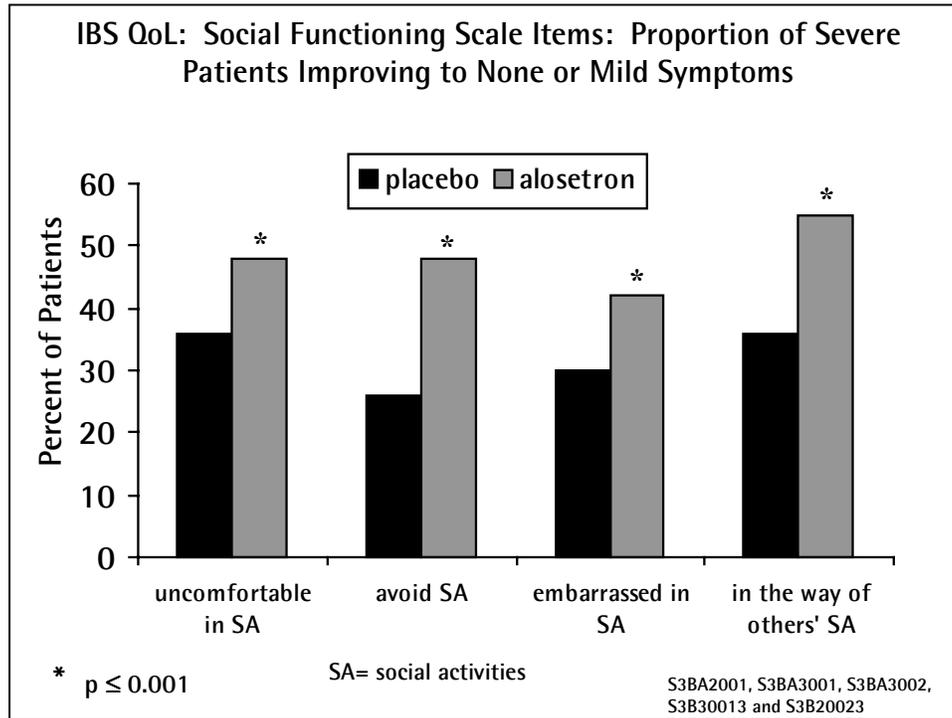


Figure 30: Improvement in Social Activity Domain for Subjects Severely Impacted at Baseline

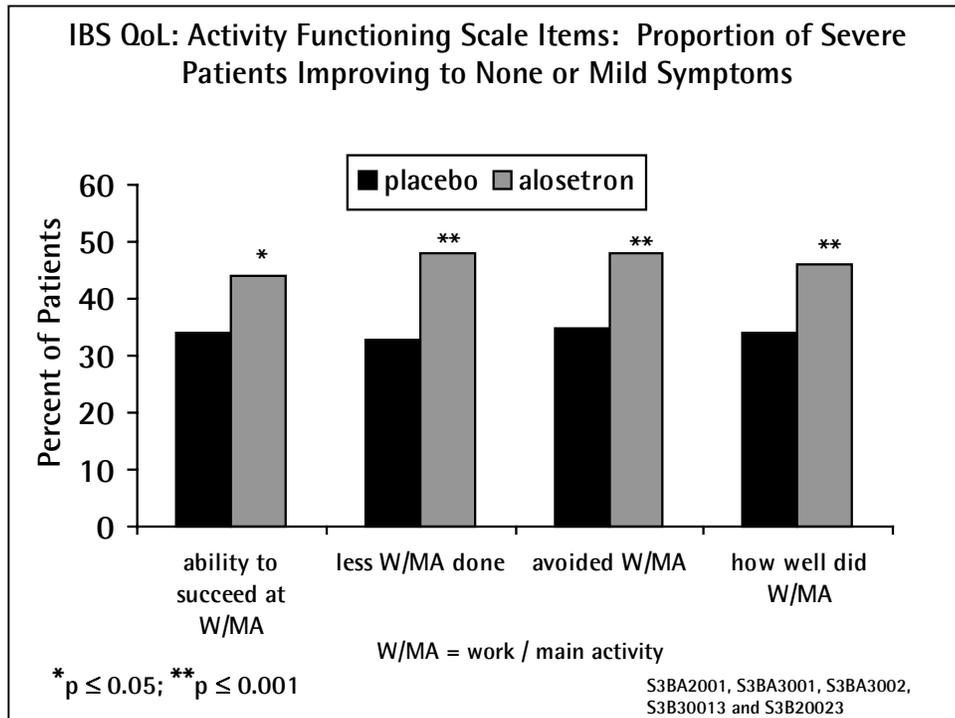


Figure 31: Improvement in Activity Function Domain for Subjects Severely Impacted at Baseline

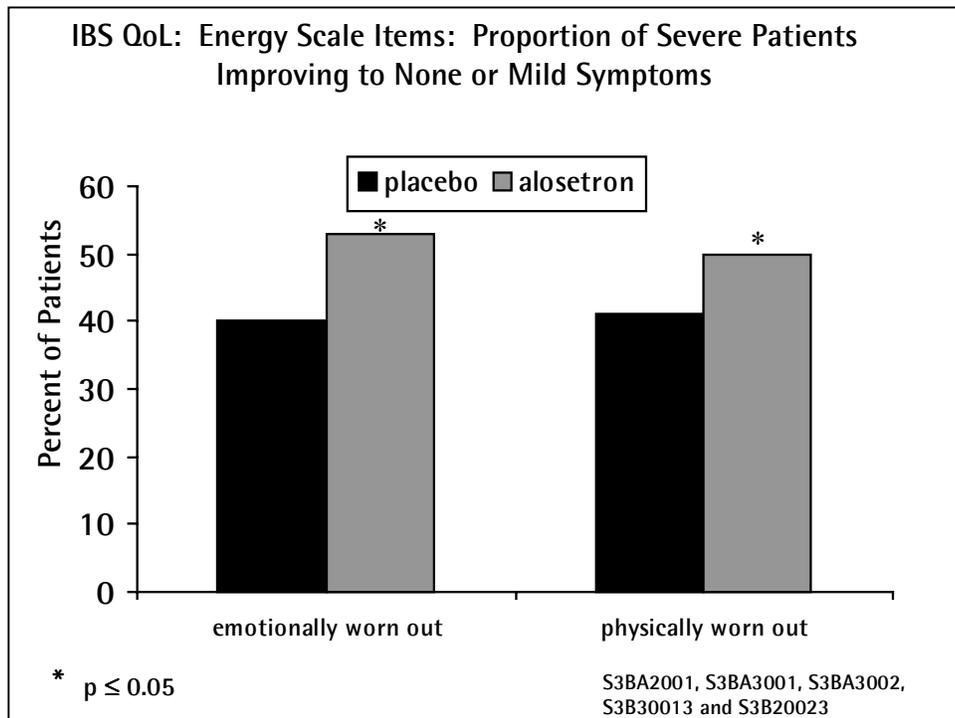


Figure 32: Improvement in the Energy Scale for Subjects Severely Impacted at Baseline

3.3.9 Efficacy in Men

In Western cultures, epidemiological data indicate that women suffer disproportionately more from IBS than do men. As a result, men were under-represented in the initial Phase II trials, which enrolled both genders, and the safety and effectiveness of alosetron was not established for men. As part of GSK's Phase IV commitment, a subsequent dose-ranging trial conducted exclusively in men suffering from diarrhea-predominant IBS (S3B20023) was completed. Results from this trial demonstrated that alosetron 1mg BID provided significantly greater adequate relief of IBS pain and discomfort than placebo in men with diarrhea-predominant IBS. Significant improvements were greatest during the last 6 weeks of a 12-Week Treatment Period. Alosetron also improved QoL and productivity end-points. Since GSK is presently not seeking to expand the indication to include men, these data are provided for information only and will not be further discussed in this Briefing Document.

3.3.10 Summary of Benefits

Repeat dose IBS clinical trials in North America and in Europe involving 10,805 alosetron-treated subjects have demonstrated a consistent and clinically meaningful beneficial effect of alosetron in women with diarrhea-predominant IBS. Trials have shown that alosetron improves the symptoms of pain and bowel dysfunction compared to placebo in subjects who are disabled by their symptoms (based on baseline symptom data). The benefits become apparent 1 to 4 weeks after initiating therapy and persist for as long as treatment is maintained. As shown in the year long study, tolerance to alosetron does not occur and symptoms rapidly return once treatment is stopped. Trials have also shown that alosetron confers benefits over European standard treatments and US traditional therapy. The overall effectiveness is further confirmed by the robust effect on the Global Improvement of IBS Symptoms endpoint (GIS). A therapeutic gain of up to 31% was achieved by alosetron compared to placebo when the overall impact of therapy was measured using the GIS and up to 40% when compared to traditional therapy.

The goal of any therapy is to decrease disease-related disability so as to improve well-being and daily functional status. Alosetron has achieved this. New data demonstrate the benefits of alosetron in patients with debilitating and/or severe IBS symptoms. Specifically, new findings include placebo-controlled trials in which alosetron provides significant clinical improvement in patients with substantial IBS-related disability (e.g. lack of control of bowel urgency on greater than 50% of days at baseline). In addition, alosetron has been shown to provide significant benefit on IBS related quality of life and productivity parameters.

In comparison to existing therapies, alosetron represents a significant improvement for the treatment of females with diarrhea-predominant IBS including those with severe baseline symptoms. Alosetron provides clinically meaningful efficacy in relieving the most bothersome IBS symptoms: pain, bowel urgency and diarrhea. Alosetron effectively treats the IBS symptom complex resulting in increased productivity both at home and at work.

4. SUMMARY OF SAFETY INFORMATION

4.1 Background: Understanding of Safety Data Prior to Product Withdrawal

This section of the Briefing Document discusses in detail, those adverse events (AEs) that received special attention during the NDA approval process and during the period of marketing, and based on what was known at the time the drug was withdrawn from the market.

4.1.1 Adverse Events of Special Interest at the Time of Approval

During the NDA review, there were three primary areas of focus identified by FDA with regard to safety. Accordingly, the following possible risks were the subject of deliberations during the FDA Gastrointestinal Drugs Advisory Committee on November 16, 1999:

- Constipation
- Ischemic Colitis
- Hepatic abnormalities

Constipation

Prior to the NDA approval, constipation was identified as the most frequently reported AE from clinical trials. Constipation was dose-related and reported by approximately 28% of patients treated with the recommended dose of 1mg BID in the completed Phase III trials of three months duration (S3B3001 and S3BA3002). This compared to 5% of patients who received placebo. Constipation was also the most frequently reported AE that resulted in premature withdrawal by patients treated with the drug in the two Phase III IBS trials (approximately 10%). Of the alosetron treated patients who became constipated, 65% reported mild to moderate severity and 75% had a single episode which was usually reported during the first month of treatment and had a median duration of six days. Data presented in the final report for a 12-month safety study (S3BA3003) submitted to FDA prior to NDA approval were generally consistent with the results from the two primary Phase III trials. In study S3BA3003, constipation was reported by 32% of patients in the alosetron 1mg BID treatment group versus 5% of patients who received placebo; constipation lead to premature withdrawal by 14% of alosetron treated patients.

At the time of approval, there had been three cases of constipation in alosetron treated patients who met the regulatory definition of a serious AE under 21 CFR 312.32(a) * and none in placebo treated patients.

Given the subjective nature of constipation, objective criteria were developed to identify cases that may possibly involve a complication due to constipation. Accordingly, for purposes of review of the clinical trials data, a working definition of complication of constipation was developed in an effort not to miss possible cases: an adverse event described or diagnosed as ileus, bowel obstruction, toxic megacolon, fecal impaction, or perforation reported as a serious adverse event (SAE), whether or not constipation was also reported.

There was one alosetron-treated and one placebo-treated patient with complications of constipation:

- Subject 02330 in the alosetron treated group, Study S3BB3002 (then ongoing trial in Europe) had a report of ileus. This patient was diagnosed with Crohn's disease and ileal stenosis at the time of the event ;
- Subject 06585 in the placebo treated group, Study S3BA3002 had a report of partial bowel obstruction.

There were no cases of constipation that resulted in permanent sequelae. At the time of approval, the product labeling carried a warning to advise prescribers of the frequency and nature of constipation reported in clinical trials.

* 21 CFR 312.32(a) defines *serious adverse drug experience* as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Ischemic Colitis

Ischemic colitis was the AE that received the greatest attention during the November 16, 1999 Advisory Committee discussion, and was also the focus of significant attention by the Agency during its safety review of the NDA. At the time of approval, approximately 3000 subjects had received alosetron in the clinical development program; 1903 patients from completed IBS Phase II or III trials and approximately 1250 patients in ongoing trials. Prior to approval there were a total of four reports of possible ischemic colitis in patients treated with alosetron versus no reports in patients treated with placebo. In these four cases, the onset of symptoms occurred between 2 days and 8 weeks after initiation of treatment with alosetron. All cases involved hospitalization and resolved without sequelae. In 3 of the 4 cases, constipation was not reported.

Each of the four cases of possible ischemic colitis were discussed in detail during the Advisory Committee presentation on November 16, 1999. The possibility of an infectious etiology was discussed as was the absence of data indicating a plausible mechanistic link between alosetron and bowel ischemia. Ultimately after considering additional clinical and immunohistochemical data the Agency concluded that no clear-cut evidence for a causal relationship between alosetron and ischemic colitis had been established but a direct or indirect contribution of alosetron could not be completely ruled out.

At the time of approval, the product labeling carried a warning that stated that ischemic colitis had been infrequently (defined as 1/100 to 1/1000) reported by patients in clinical trials and that the relationship with the drug was unknown.

Hepatic Abnormalities

FDA raised hepatic toxicity as a possible risk during its presentation at the Advisory Committee Meeting on November 16, 1999. The Agency's concern resulted from a single case of hepatitis. At the time of approval, a similar frequency for elevation (>2-fold) in LFTs was observed for alosetron- and placebo-treated groups. There were no SAE reports of hepatitis or elevated LFTs. The case of hepatitis described by FDA during its presentation on November 16, 1999 was described in the initial product labeling.

Other Events

In addition to the events described above, two deaths had been reported for alosetron-treated patients who participated in clinical trials prior to NDA approval; both deaths were due to cardiovascular disease, unrelated to alosetron treatment. Neither death involved serious gastrointestinal events or events which raised concern about the safety of alosetron. There

were no reports of serious gastrointestinal events that required surgical intervention or permanent sequelae.

4.1.2 Post-Marketing Adverse Events Leading to a Second Advisory Committee Meeting, Reassessment of Benefit-Risk Profile, and Design of a Risk Management Plan

Subsequent to approval of the NDA, additional reports of ischemic colitis were received from clinical trials and also from marketed product experience. In addition, rare (defined as occurring less than 1/1000) cases of complications of constipation were reported from clinical trials and also from marketed product experience; some of these cases included events requiring surgical intervention.

Prior to the Advisory Committee Meeting on June 27, 2000, the Agency and Sponsor agreed to the following assessment of the new safety information:

- A diagnosis of ischemic colitis in three cases reported post-approval from clinical trials. It was estimated that as of June 1, 2000, a total of 6852 female and male subjects had received alosetron in repeat dose studies.
- There had been a total of five cases derived from the voluntary, spontaneous reporting system with a diagnosis of ischemic colitis. It was estimated that as of June 1, 2000, a total of 130,000 prescriptions had been dispensed.
- Post-approval, there had been two new cases derived from the clinical trials database that involved hospitalization associated with complications of constipation. One case required surgical intervention (colectomy).
- There had been a total of four cases derived from the voluntary, spontaneous reporting system that involved hospitalization associated with constipation. Of these, two cases required surgical intervention (including one colectomy).

Both the sponsor and FDA agreed that the relative frequency and severity of cases of ischemic colitis reported post-approval were comparable to reports received prior to approval. However, subsequent to approval there had been post-approval reports of patients who had experienced complications of constipation with worse clinical outcomes than reports received prior to approval (surgery in three patients; permanent sequelae in one).

The new cases of ischemic colitis and complications of constipation resulted in a reassessment of the benefit-risk profile for alosetron. The new safety information along with a proposed risk management program was reviewed during a special Advisory Committee

meeting on June 27, 2000. In its briefing materials to a specially constituted committee (comprised of GI and Risk Management experts) FDA presented its position that:

- At the time of approval the relationship between ischemic colitis and alosetron was unknown. However, the Agency now believed that the additional reports of ischemic colitis supported a causal relationship with alosetron.
- The new reports of complications of constipation included cases with worse clinical outcomes than reports observed prior to approval. However, FDA acknowledged that some of these cases were probably related to inappropriate use of the drug by constipated patients.
- The Agency again raised the possibility of alosetron use being a risk factor for hepatic toxicity based on two spontaneously reported post-marketing cases.
- The FDA requested the Committee's input on how the benefit-risk profile for alosetron could be optimized and their assessment of the Risk Management Plan and labeling changes proposed by the sponsor.

During the meeting, three AEs of special interest were discussed: ischemic colitis, sequelae of constipation, and possible liver toxicity. The Committee generally accepted the proposed Risk Management Plan, intended to address the issues of ischemic colitis and complications of constipation. It was agreed that there was no signal for hepatic toxicity. In addition to other labeling changes proposed, the committee recommended that the sponsor change from a patient package insert to a Medication Guide that pharmacists would be legally obligated to provide to patients at the time of dispensing.

4.1.3 Adverse Events Leading to Product Withdrawal

Subsequent to the Advisory Committee meeting in June 2000, the sponsor pursued FDA approval of labeling changes including a Medication Guide. Labeling changes and the new Medication Guide were approved in August 2000. Physicians and pharmacists were informed of the documents and the description of the changes by the company via mail and the new labeling was posted on the company's and FDA's websites for alosetron. In addition, FDA highlighted the implementation of the Medication Guide in a press release. During the months following the Advisory Committee Meeting, and while the elements of the Risk Management Plan were in various stages of implementation, additional post-marketing reports of serious adverse events were received. Included in these reports were five cases with a fatal outcome.

During early November 2000, FDA communicated to the sponsor that it had reassessed the benefit-risk profile for the product as the result of the new serious adverse event reports from marketing experience. The Agency expressed significant concern regarding growing uncertainties about the nature and magnitude of possible risks as well as the ability of measures to reduce them adequately. Because of rapidly escalating concern about serious risks, there was insufficient time to allow further implementation of the elements of the Risk Management Plan or to consider new data from controlled trials. Accordingly, the FDA communicated a suggestion that the product be withdrawn. Following unsuccessful discussions with FDA, alosetron was withdrawn from the market on November 28, 2000.

Subsequent to product withdrawal, all active development activities were halted and data collection and statistical analysis activities were progressed. However, because the epidemiology studies to assess the risk factors for ischemic colitis could be applicable to other drug candidates for IBS, they were continued.

4.2 Overview of Currently Available Safety Data

When re-evaluating the benefit-risk profile of a drug, one must assess information from all available sources including data from clinical trials, observational studies, data from marketing surveillance (spontaneous adverse event reporting), and any new data from non-clinical studies. Controlled clinical trials and observational studies provide data that are most reliable. However, a limitation of clinical trial data is that conditions tend to be more controlled than real-world experience. Uncontrolled sources of surveillance, such as spontaneous AE reports, are useful, but also have significant limitations. Although safety signals of medical importance can arise from spontaneously reported cases, the data obtained are often factually uncertain, incomplete, and imprecise.

At the time alosetron was withdrawn from the market in the United States (US) a large, global clinical development program was ongoing. A Table of the Clinical Trials is provided as **Appendix I** to the Briefing Document. As noted above, following the withdrawal of alosetron, all studies were immediately brought to an orderly conclusion and final study reports planned. Studies that were discontinued prematurely were targeted for completion of abbreviated reports focusing only on a summary of safety data.

Final study reports for all clinical trials conducted by GlaxoSmithKline with alosetron have now been submitted to FDA along with an updated Integrated Summary of Safety. Included in the recent Supplemental Application are reports for 40 studies (22 in IBS) not previously

available in the original NDA. In addition, a summary of the spontaneous AE reports from marketing experience has been provided. There are no new results from non-clinical studies.

4.2.1 Extent of Exposure Clinical Trials

Evidence of the safety from clinical trials is derived from a total of 11,969 patients and volunteers who received alosetron in 93 clinical studies (24 conducted in IBS patients) conducted in the US and elsewhere. Data from 11,874 subjects in 86 studies were available for integrated analyses. Of these, 10,805 were IBS patients treated with alosetron; a total of 2935 subjects in the IBS studies received placebo.

Prior to approval, the alosetron safety database from clinical trials was derived from 53 completed studies, of which 5 were conducted in IBS patients. Nearly 3000 subjects received alosetron across all studies. Of these, 1903 patients were treated with alosetron (1552 women and 351 men) and 1044 received placebo in the IBS trials.

Among the 10,805 IBS patients who received alosetron, 86% (9316/10,805) received 1mg BID; of these, 54% received this dose for approximately 12 weeks. Longer exposure includes 807 patients who were treated with 1mg alosetron BID for 6 months or longer. A total of 525 patients received alosetron 1mg BID for 48 weeks or longer.

Dose	Females	Males	Total
< 0.1mg BID	77 (0.7%)	38 (0.4%)	115 (1.1%)
0.5mg BID	85(0.8%)	158(1.4%)	243 (2.2%)
1mg BID	8980 (83.1%)	336 (3.1%)	9316 (86.2%)
>1mg BID	758 (7.0%)	373 (3.5%)	1131 (10.5%)
Total Alosetron	9900 (91.6%)	905 (8.4%)	10,805 (100%)
Total Placebo	2697 (92%)	238 (8%)	2935 (100%)

Source: Table 2.1.1 ISS sNDA 21-107/S-005

Approximately 92% (9900/10,805) of the patients who received alosetron in IBS trials were female and approximately 8% (905/10,805) were male. A total of 9570 patients who received any dose of alosetron were <65 years of age (89% of all alosetron-treated patients), and 1235 patients were ≥65 years of age (11% of all patients exposed to alosetron). The majority (>90%) of the patients were caucasians.

4.2.2 Estimate of Market Exposure

Approximately 534,000 prescriptions for alosetron are estimated to have been dispensed (combined retail/mail order) from 13 March 2000 (product launch) through December 31, 2000 (*Sources*: Scott-Levin Source Prescription Audit and IMS National Prescription Audit Plus). Based on recently completed analyses of patient and prescription data, it is now estimated that approximately 275,000 individual patients were prescribed alosetron during this time period (*Source*: Scott-Levin Patient Parameters). Of the projected 275,000 patients receiving alosetron for the time period March 2000 to December 2000, approximately 95% of the patients were female and approximately 13% were 65 years of age or older (*Source*: Scott-Levin Physician Drug and Diagnosis Audit). Although the extent of off-label use is difficult to quantitate, adverse event reports and anecdotal information received by GSK have revealed that alosetron market experience included prescribing to male patients, patients with chronic diarrhea from non-IBS etiologies, patients with inflammatory bowel disease, and patients with constipation-predominant IBS.

As of February 18, 2002, GSK had received 3885 spontaneous AE reports (cases) involving alosetron. Each case was entered into the GSK safety database and was reported to FDA in accordance with regulatory requirements (21 CFR 314.80). Approximately 87% of all reports received by GSK were made by consumers. The vast majority of the spontaneous reports received followed announcement of the withdrawal of alosetron from the market and were related to requests for refunds or inquiries to obtain additional information about the withdrawal. In accordance with company policy, all telephone calls, written correspondence, and e-mails received by the company were reviewed for mention of possible AEs, and all with such a mention were treated as AE cases, regardless of the initial reason for the contact and regardless of whether the case was subsequently substantiated by a healthcare professional.

All market experience with alosetron was derived from the US. Outside of the US, marketing applications were filed in numerous countries. At the time of market withdrawal in the US, the majority of the applications were still under review. Although marketing applications were approved in several countries, marketing outside of the U.S. had not commenced in any country prior to product withdrawal in the US. Following the November 28, 2000 product withdrawal in the US, all efforts to initiate marketing in other countries were suspended.

4.3 Adverse Events of Special Interest

4.3.1 Constipation

In addition to its beneficial effect on abdominal pain, alosetron slows transit and increases the reabsorption of salt-water from the gut. This pharmacological effect, a class effect of 5-HT₃ receptor antagonists, is well recognized and dose-related. Accordingly, it was not unexpected that constipation was the most frequently reported adverse event both in clinical trials and during the post-marketing experience. Although serious AE reports involving complications of constipation resulting in sequelae were not noted prior to approval, infrequent reports of complications of constipation were received after market introduction, including cases involving hospitalization and/or surgery. Two cases from marketing experience resulted in a fatal outcome.

4.3.1.1 Constipation - Clinical Trials Experience

In clinical trials, constipation was not defined *a priori* and as such, adverse events of constipation reflect subjective changes in bowel frequency, stool consistency or patient reported symptoms of bowel discomfort associated with these changes. All reports of constipation were recorded as adverse events regardless of the number of bowel movements a subject had in a day or the stool consistency. In addition to a specific patient complaint of constipation, an adverse event of constipation was also recorded if the patient experienced the absence of stool for four consecutive days.

Reports of constipation were related to alosetron dose. Constipation was reported by 29% of subjects receiving alosetron 1mg BID in clinical trials. This adverse event occurred at substantially higher frequency in the alosetron-treated subjects compared to those receiving placebo (6%) and 11% of alosetron treated subjects withdrew from the trials because of constipation. The frequency of constipation was lower in IBS subjects treated with lower doses of alosetron; 11% in subjects receiving alosetron 0.5 mg BID. In approximately 75% of cases, constipation was reported: within the first two to three weeks following initiation of therapy; occurred once; was mild-to-moderate in severity; and lasted about one week. These results from the cumulative safety database are quite consistent with data available at the time of approval. Table 2 describes the incidence of constipation over time for the 0.5 and 1 mg BID dose groups from repeat-dose IBS studies. Table 3 displays the onset, severity, and duration of constipation across dose groups derived from the integrated database from IBS trials.

Table 2: Incidence of Constipation in Alosetron Repeat-Dose Studies in Patients with IBS by Study Duration

	% of Patients Reporting Adverse Event		
	Placebo (N=2935 ^a)	Alosetron 0.5mg BID (N=243 ^a)	Alosetron 1mg BID (N=9316 ^a)
Constipation			
Months 1-3	5	11	28
Month 1	3	10	24
Month 2	2	<1	6
Month 3	1	<1	4
Months 4-6	1	0	4
Months 7-9	1	b	3
Months 10-12	2	b	2

a N is given for the number of patients in the treatment group during Month 1; however, the calculation of %'s over time is based on the number of patients still in the study at each given time point.

b No patient exposures at this dose and duration.

Table 3: Reports of Constipation from Clinical Trials

Onset, Severity, and Duration of First Constipation in Alosetron Repeat-Dose Studies in Patients with IBS

	Placebo (N=2935: 238M/ 2697F)	Alosetron 0.1mg BID (N=115: 38M/ 77F)	Alosetron 0.5mg BID (N=243: 158M/ 85F)	Alosetron 1mg BID (N=9316: 336M/ 8980F)	Alosetron 2mg QD (N=472)	Alosetron 2mg BID (N=376: 184M/ 192F)	Alosetron 4mg BID (N=215: 161M/ 54F)	Alosetron 8mg BID (N=68: 28M/ 40F)	Mebeverine 135mg TID (N=390) ^b	Trimebutine 200mg TID (N=382) ^b
No. of Subject Reporting Constipation, % (% M/F)	6 (2/6)	3 (0/4)	11 (9/14)	29 (21/29)	11	16 (12/20)	20 (20/20)	29 (21/35)	3	7
Median Time to Onset, days	28 (24/28)	3 (0/3)	8 (8/8.5)	8 (10/8)	8	9 (5/13)	6 (6/6)	9 (5.5/11)	8	30
Severity, % (% M/F)										
Mild	30 (0/31)	0 (0/0)	33 (47/17)	24 (30/24)	7	15 (18/13)	39 (42/27)	5 (0/7)	18	48
Moderate	52 (60/52)	33 (0/33)	26 (33/17)	50 (51/50)	44	46 (50/44)	36 (33/45)	45 (50/43)	45	32
Severe	17 (40/17)	67 (0/67)	41 (20/67)	26 (19/26)	48	38 (32/41)	25 (24/27)	50 (50/50)	36	20
Duration, days (days M/F) Median	5 (11/5)	9 (0/9)	8.5 (4/13)	6 (6/6)	8	8 (7/8)	6 (4.5/10)	7 (6.5/7)	6	5

4.3.1.2 Serious Cases of Constipation and Complications of Constipation from Clinical Trials

This section summarizes reports of constipation that either met the regulatory definition of serious* or involved a complication. *It is important to note that for some cases involving a complication of constipation (as defined), constipation was not reported as a serious adverse event (SAE).*

A serious adverse event of constipation was reported by 10 subjects in repeat-dose IBS clinical trials; 9 on alosetron therapy (out of 10,805 subjects treated; 95% CI [4.1-17.1]) and 1 on mebeverine therapy (out of 390; 95% CI [0-5.6]). In 8 of the 9 alosetron cases, constipation resolved. However, one subject underwent a colectomy (subject 67694). Two of the 9 alosetron-treated subjects continued on study drug without interruption and completed the study with no further episodes of constipation. Two others temporarily interrupted study drug and resumed therapy without further reports of constipation. There were no serious adverse events of constipation reported in subjects treated with alosetron 0.5mg BID and there were no deaths associated with constipation in any study. The cases that listed constipation as an SAE are described in Table 4.

* 21 CFR 312.32(a) defines *serious adverse drug experience* as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Table 4: Constipation as an SAE in Completed Repeat-Dose IBS Studies

Study No.	Subject No. (Case No.)	Treatment Group/ Time to onset	Withdrawn from Study?	Outcome/ Duration
S3BA3002	07002 (A0062681A)	Alosetron 1mg bid/ 43 days	No	Resolved/ 6 days
S3BA3003	10417 (A0096576A)	Alosetron 1mg bid/ 337 days	No	Resolved/ 13 days
S3BB3001	00552 (B0060049A)	Mebeverine 135mg tid/ 5 days	Yes	Resolved/ 3 days
S3BB3002	02541 (B0060594A)	Alosetron 1mg bid/ 73 days	No	Resolved/ 4 days
S3B30017	174139 (B0088386A)	Alosetron 1mg bid/ 13 days	No	Resolved/ 20 days
S3B30020	67694 (A0119204A)	Alosetron 1mg bid/ 27 days	Yes	Colectomy/ 14 days
S3B30020	80655 (A0127276A)	Alosetron 1mg bid/ 128 days	Yes	Resolved/ 56 days
S3B30020	83206 (A0122409A)	Alosetron 1mg bid/ 71 days	Yes	Resolved/ 3 days
S3B30020	88034 (A0124327A)	Alosetron 1mg bid/ 41 days	Yes	Resolved/ 3 days
S3BB3002	03773 (B0068255A)	Alosetron 1mg bid/ 7 days	Yes	Resolved/ 7 days

A summary of the risk (incidence) and rate (incidence per unit of time) of constipation reported as an SAE for each month and cumulatively over 12 months is shown in Table 5 and in Figure 33. The results show that:

- The simple cumulative risk of constipation as an SAE among alosetron-treated IBS patients is 8.33 events per 10,000 patients (95% CI [3.8-15.8])
- The cumulative life table (exposure time-adjusted) risk increases from 0.03% at month 1 to 0.34% (~3.4 events per 1000 patients) at 12 months (95% CI [1.54-6.38]).
- During the first month of alosetron treatment the incidence rate of constipation as an SAE was 3.66 cases /1000 person-years (95% CI [0.76-10.7]), and by 12 months the incidence rate was ~3.2 cases/1000 person-years (95% CI [1.47-6.09]).

Table 5: Serious Constipation over Time in IBS Studies with Alosetron

Alosetron (N=10805)							
	No. of events	No. of subjects	No. subj. censored	Risk (%) ^a	Cumulative Risk (%)	Person-years (cumulative)	Incidence Rate (per 1000 person-years)
Month 1	3	10805	2146	0.0308	0.0308	819.367	3.661
Month 2	2	8657	1614	0.0255	0.0563	1501.014	3.331
Month 3	2	7042	3886	0.0392	0.0956	1988.951	3.519
Month 4	0	3151	729	0	0.0956	2219.178	3.154
Month 5	1	2421	417	0.0452	0.1407	2407.510	3.323
Month 6	0	2004	1280	0	0.1407	2522.247	3.172
Month 7	0	725	87	0	0.1407	2579.373	3.102
Month 8	0	638	15	0	0.1407	2632.861	3.039
Month 9	0	623	13	0	0.1407	2685.105	2.979
Month 10	0	610	10	0	0.1407	2736.288	2.924
Month 11	1	600	179	0.1959	0.3368	2784.124	3.233
Month 12	0	420	420	0	0.3368	2805.836	3.208
Placebo (N=2935)							
	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	2935	404	0	0	231.255	0
Month 2	0	2531	273	0	0	435.515	0
Month 3	0	2257	1461	0	0	591.989	0
Month 4	0	797	184	0	0	650.315	0
Month 5	0	612	93	0	0	698.882	0
Month 6	0	519	130	0	0	736.627	0
Month 7	0	389	10	0	0	769.189	0
Month 8	0	379	14	0	0	800.950	0
Month 9	0	365	6	0	0	831.690	0
Month 10	0	359	8	0	0	861.961	0
Month 11	0	351	191	0	0	888.846	0
Month 12	0	160	160	0	0	896.405	0
^a Life table estimate = No. of events / (No. of subjects - No. censored/2) x 100.							

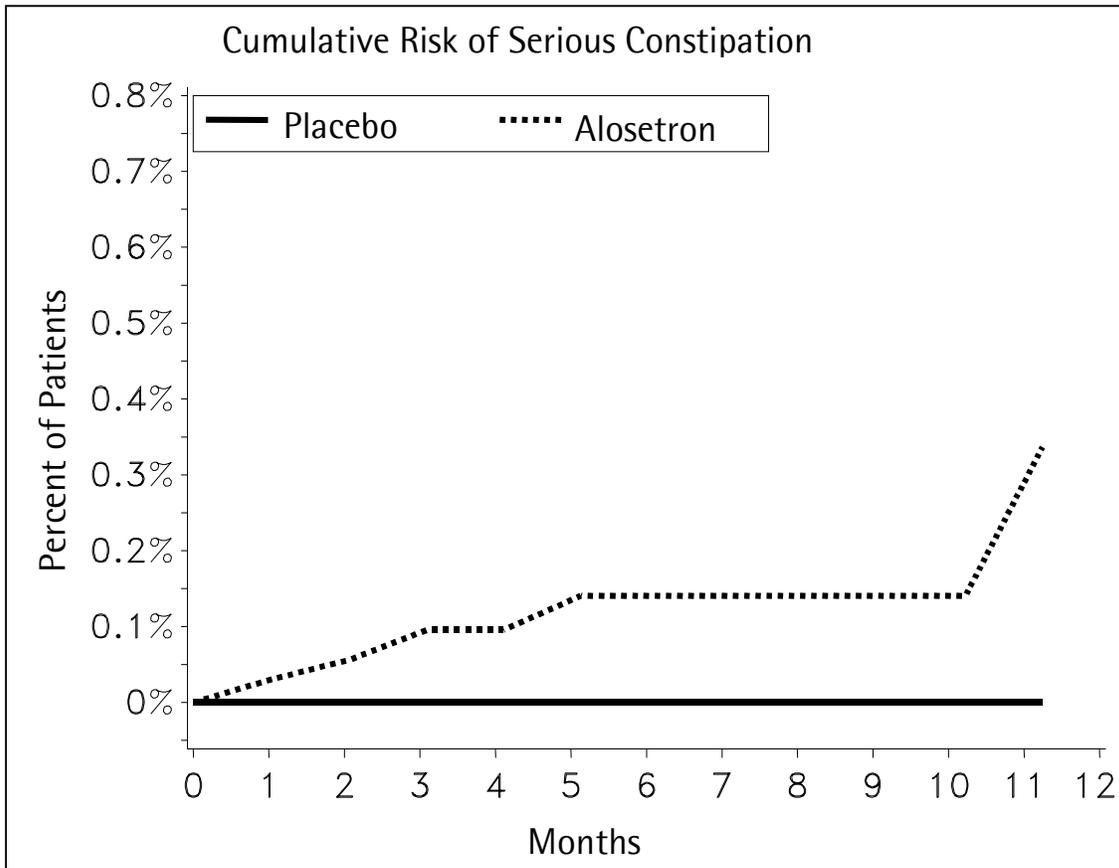


Figure 33. Cumulative Risk of Constipation

Given the subjective nature of constipation, and recognizing that it may not have been reported in all instances as a serious adverse event, for purposes of the alosetron clinical trials safety database, the term “complication of constipation” has been applied to reports involving ileus, bowel obstruction, toxic megacolon, fecal impaction (if the event meets the regulatory definition of serious), or perforation whether or not constipation was also reported.

In the IBS clinical trials, complications of constipation were reported or identified for 8 subjects treated with alosetron (out of 10,805 subjects treated; 95% CI [3.5-15.8]) and 3 patients treated with placebo (out of 2,935 subjects; 95% CI [0.6-8.8]). These cases are listed in Table 6. Subjects who experienced complications were hospitalized to treat events that included small bowel ileus, obstipation, obstruction, and impaction. Additional details on the cases, including co-morbidities and concomitant medications, are provided in **Attachment II**. Most cases had predisposing risks in terms of a prior history of constipation, concomitant illness, or the concomitant use of constipating medication. One patient, with a presentation suggestive of ongoing constipation, became obstipated following

exposure to alosetron and developed toxic megacolon. This necessitated a colectomy (subject 67694; also described in the section above). The remainder of the cases had no sequelae, and the patient’s symptoms resolved with discontinuation of alosetron therapy and supportive care. There were no complications of constipation reported in subjects treated with alosetron 0.5mg BID. In 4 of the 8 subjects treated with alosetron, and the 3 placebo-treated subjects, constipation was not reported as a serious adverse event according to the regulatory definition.

Table 6: Complications of Constipation in Completed Repeat-Dose IBS Studies

Study No.	Subject No. (Case No.)	Treatment Group/ Time to Onset	“Complications of Constipation”	Outcome/ Duration
S3BB3002	02330 (B0065267A)	Alosetron 1mg BID/ 10 days	Ileus	Resolved/ 14 days
S3B30020	65385 (A0128045A)	Alosetron 1mg BID/ 120 days	Partial small bowel obstruction	Resolved/ 11 days
S3B30020	67694 (A0119204A)	Alosetron 1mg BID/ 27 days	Obstruction Toxic megacolon	Colectomy/ 14 days
S3B30020	80655 (A0127276A)	Alosetron 1mg BID/ 120 days	Fecal impaction	Resolved/ 56 days
S3B30020	83206 (A0122409A)	Alosetron 1mg BID/ 71 days	Obstipation	Resolution/ 3 days
S3B30020	87373 (A0123385A)	Alosetron 1mg BID/ 91 days	Mild small bowel ileus	Resolved/ 4 days
S3B30025	176167 (B0087180A)	Alosetron 1mg BID/ 56 days	Bowel obstruction	Resolved/ 4 days
S3BB3002	03773 (B0068255A)	Alosetron 1mg BID/ 7 days	Fecal impaction	Resolved/ 7 days
S3BA3002	06585 (A0059467A)	Placebo/ 14 days	Partial bowel obstruction	Resolved/ 42 days
S3B30006	23647 (B0071141A)	Placebo/ 105 days	Ileus (adhesion)	Resolved/ 4 days
S3B30011	34911 (A0111425A)	Placebo/ 60 days	Ileus	Resolved/ 3 days

A summary of the risk (incidence) and rate (incidence per unit of time) of complications of constipation for each month and cumulatively over 12 months is shown in Table 7 and in Figure 34. The results show that:

- The simple cumulative risk of complications of constipation among alosetron-treated IBS patients is 7.4 events per 10,000 patients (95% CI [3.2-14.6]) compared with ~10

events per 10,000 placebo-treated patients (95% CI [2.1-29.9]), a relative risk (RR) of 0.72 (95%CI [0.17-4.2]).

- In alosetron-treated IBS patients, the cumulative life table (exposure time-adjusted) risk increases from 0.03% at month 1 to 0.155% (~1.6 events per 1000 patients; 95% CI [0.7-3.0]) at 12 months compared with a cumulative risk of 0.22% (2.2 events per 1000 patients; 95% CI [0.5-6.4]) in placebo-treated patients at 12 months.
- During the first month of alosetron treatment the incidence rate of complications of constipation was 3.7 cases /1000 person-years (95% CI [0.76-10.7]), and by 12 months the incidence rate was 2.9 cases/1000 person-years (95% CI [1.2-5.6]). In placebo-treated patients, the incidence rate during the first month and at 12 months was 4.3 (95% CI [0.1-24.1]) and 3.3 cases/1000 person-years (95% CI [0.7-9.8]), respectively. Hence, at 12 months the incidence density ratio (IDR) was 0.85 (95% CI [0.2-5.0]).

Table 7: Complications of Constipation over Time in IBS Studies with Alosetron							
Alosetron (N=10805)							
	No. of events	No. of subjects	No. subj. censored	Risk (%)^a	Cumulative Risk (%)	Person-years (cumulative)	Incidence Rate (per 1000 person-years)
Month 1	3	10805	2145	0.0308	0.0308	819.367	3.661
Month 2	1	8657	1614	0.0127	0.0436	1501.014	2.665
Month 3	2	7042	3889	0.0392	0.0828	1988.951	3.017
Month 4	2	3151	728	0.0718	0.1546	2219.178	3.605
Month 5	0	2421	417	0	0.1546	2407.510	3.323
Month 6	0	2004	1279	0	0.1546	2522.247	3.172
Month 7	0	725	87	0	0.1546	2579.373	3.102
Month 8	0	638	15	0	0.1546	2632.861	3.039
Month 9	0	623	13	0	0.1546	2685.105	2.979
Month 10	0	610	10	0	0.1546	2736.288	2.924
Month 11	0	600	179	0	0.1546	2784.124	2.873
Month 12	0	421	421	0	0.1546	2805.836	2.851
Placebo (N=2935)							
	No. of events	No. of subjects	No. subj. censored	Risk (%)^a	Cumulative Risk (%)	Person-years (cumulative)	Incidence Rate (per 1000 person-years)
Month 1	1	2935	403	0.0366	0.0366	231.255	4.324
Month 2	1	2531	273	0.0418	0.0784	435.515	4.592
Month 3	0	2257	1460	0	0.0784	591.989	3.378
Month 4	1	797	184	0.1418	0.2203	650.315	4.613
Month 5	0	612	93	0	0.2203	698.882	4.293
Month 6	0	519	130	0	0.2203	736.627	4.073
Month 7	0	389	10	0	0.2203	769.189	3.900
Month 8	0	379	14	0	0.2203	800.950	3.746
Month 9	0	365	6	0	0.2203	831.690	3.607
Month 10	0	359	8	0	0.2203	861.961	3.480
Month 11	0	351	191	0	0.2203	888.846	3.375
Month 12	0	160	160	0	0.2203	896.405	3.347

^a Life table estimate = No. of events / (No. of subjects - No. censored/2) x 100.

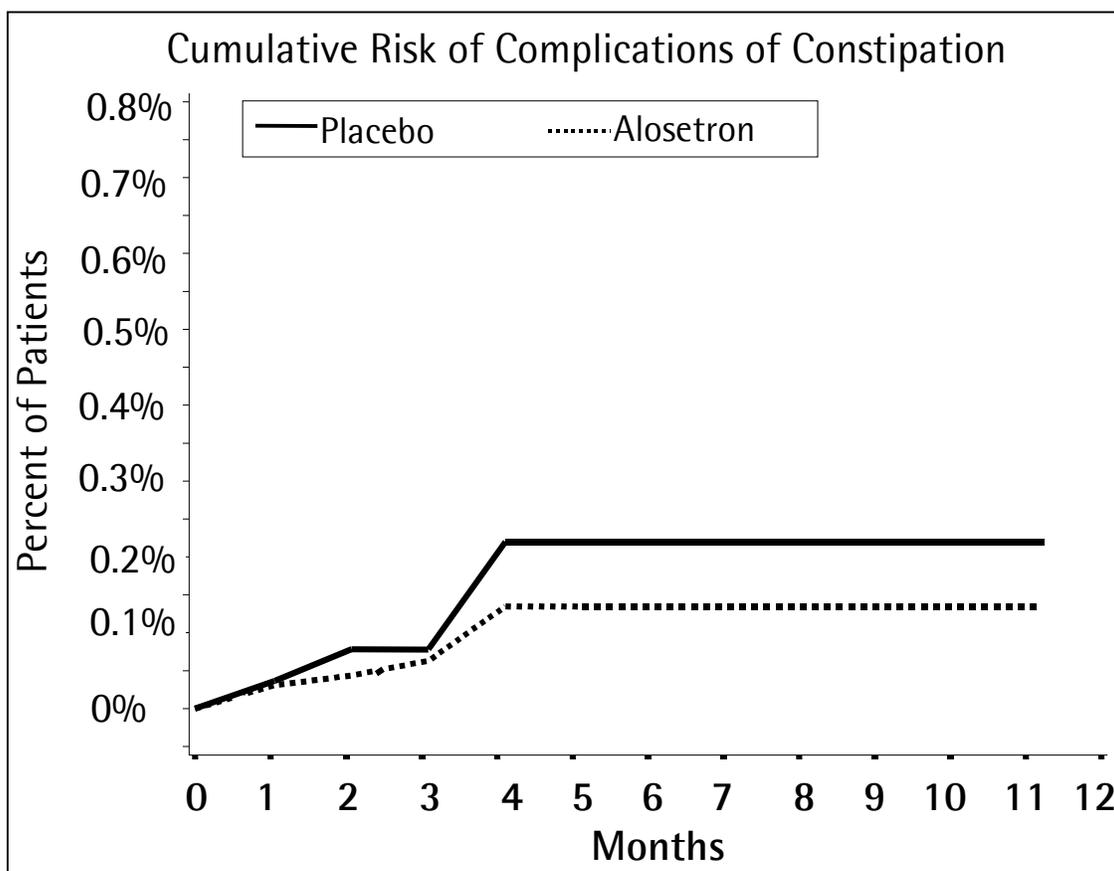


Figure 34. Cumulative Risk of Complications of Constipation

4.3.1.3 Serious Cases of Constipation and Complications of Constipation from Marketing Experience

Constipation was reported in 52% of the 3885 cases received from market experience. In 95% of these cases, constipation was a non-serious medical event.

During a review of the GSK spontaneous medical events database, cases of serious constipation initially received as of February 18, 2002 were identified using a multi-step search process. First, the GSK safety database was searched for all cases assessed as “serious” under the provisions of 21 CFR 314.80(a)*. From these serious cases, all cases

* 21 CFR 314.80(a) defines serious adverse drug experience as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

with a reported event of constipation or related term were identified, then individually reviewed to determine if constipation was the event that led to the assessment of “serious.” This last step was necessary because seriousness is coded at a case level, even though multiple terms are extracted and coded from the reporter’s narrative, many of which may not be serious under the provisions of 21 CFR 314.80(a). For example, the search using these terms may have revealed a case of a hip fracture leading to hospitalization and incidentally, the reporter mentioned that the patient had constipation in the hospital. In this example, the fracture was the event causing the case to be designated as “serious” and not the constipation, and this case would not be included in the diagnosis category of serious constipation.

Review of the spontaneous database revealed 100 cases of a serious adverse event of constipation. Of these, 58 were associated with complications of constipation and two had a fatal outcome. The 100 cases were reported primarily in female patients. Where reported, the time to onset of constipation was variable, ranging from 3 days to several months after initiating alosetron. However, symptoms developed within the first month of treatment in nearly two-thirds of the cases. Although in the majority of the cases, the symptoms of constipation resolved with discontinuation of treatment and supportive therapy, there were nine cases involving a perforated viscus and two patients experienced megacolon. Other patients suffered from intestinal obstruction or fecal impaction.

Table 8 lists the cases of serious constipation that described as complication of constipation. Intestinal perforation, toxic megacolon, intestinal obstruction (including ileus), and fecal impaction were considered complications of constipation. In Table 8 complications of constipation are listed in order of seriousness (highest to lowest). Each case is included only in the most serious complication category applicable to that case.

Table 8 – Cases Involving Complications of Constipation

Complication	Number of Cases	Case ID Numbers
Perforation of the intestine	9	^a A0122865A, ^a A0128810A, A0129291A, A0133164A, A0133209A, A0136562A, A0141150A, A0153402A, A0153403A
Toxic Megacolon	2	A0127417A, A0134176A
Intestinal Obstruction, including <i>Ileus</i>	30	A0117392A, ^a A0117431A, A0125873A, A0125896A, A0127032A, A0127144A, A0130764A, ^a A0130853A, A0131674A, A0131970A, A0133097A, A0133143A, A0133173A, A0133365A, A0134876A, A0134937A, A0135987A, A0136357A, A0138204A, A0138395A, A0139265A, A0139795A, A0141627A, A0145819A, A0145828A, A0145836A, A0154760A, A0158450A, A0158474A, A0359589A
Fecal Impaction	17	A0123178A, A0125375A, A0126653A, A0126710A, A0127066A, A0131872A, A0131878A, A0133033A, A0133184A, A0133339A, A0133946A, A0133950A, A0134395A, A0136355A, A0153405A, A0153406A, , A0154756A
Any of the Above Complications	58	
None of the Above Complications	42	A0118883A, A0125847A, ^a A0126318A, A0126729A, A0126751A, A0126993A, A0127138A, A0127326A, , A0128319A, A0131891A, A0131969A, A0133035A, A0133142A, A0133327A, A0133446A, A0133457A, A0133814A, A0134064A, A0134070A, A0134539A, A0135362A, A0135822A, A0136390A, A0136570A, A0137469A, A0137584A, A0137761A, A0141612A, A0144484A, A0145827A, A0145829A, A0145834A, A0146835A, A0145838A, A0153401A, A0153404A, A0154776A, A0158451A, A0158458A, A0158471A, A0169543A, A0359586A
Total	100	

^a These 7 cases (A0117431A, A0122865A, A0126318A, A0127417A, A0128810A, A0130853A, A0136562A) also had colonic ischemia secondary to complications of constipation.

Fifty-eight cases described a complication of constipation. Although details are limited in some of these cases, many patients experiencing complications of constipation had comorbidities such as diverticulitis, inflammatory bowel disease, a history of constipation or were using constipating medications in addition to alosetron. Age was reported in 53 of 58 patients with complications of constipation (median age 50 years; range 20 to 82 years).

Supersedes page 70 in Volume 1 of the Briefing Document for LOTRONEX® (alosetron hydrochloride) Tablets

Table 9 lists the cases of serious constipation with **severe outcomes**, defined as death, intestinal surgery, anorectal surgery, hospitalization, emergency room visit, and disimpaction. In this table, outcomes are listed in order of severity (highest to lowest). Each case is included only in the most severe outcome category applicable to that case.

Table 9: Cases of Serious Constipation with Severe Outcomes

Outcome	Number of Cases	Case ID Numbers
Death	2	A0129291A, A0130853A
Intestinal Surgery	15	A0118883A, A0122865A, A0127417A, A0128810A, A0133164A, A0133173A, A0133209A, A0133457A, A0136562A, A0137469A, A0137584A, A0139795A
Anorectal Surgery	7	A0133814A, A0134064A, A0134539A, A0135822A, A0136390A, A0141612A, A0359586A
Hospitalization	54	A0117392A, A0117431A, A0123178A, A0125873A, A0126318A, A0126653A, A0126751A, A0127032A, A0127138A, A0127144A, A0127326A, A0128319A, A0130764A, A0131674A, A0131872A, A0131891A, A0131970A, A0133035A, A0133142A, A0133143A, A0133327A, A0133339A, A0133365A, A0133950A, A0134070A, A0134176A, A0134395A, A0134876A, A0134937A, A0135362A, A0135987A, A0136357A, A0136570A, A0137761A, A0138204A, A0138395A, A0139265A, A0141627A, A0145819A, A0145827A, A0145828A, A0145829A, A0145834A, A0145836A, A0145838A, A0153404A, A0154760A, A0158450A, A0158451A, A0158458A, A0158471A, A0158474A, A0169543A, A0359589A,
ER Visit	10	A0125375A, A0127066A, A0131878A, A0133097A, A0133184A, A0146835A, A0153401A, A0153405A, A0153406A, A0154756A
Disimpaction	3	A0126710A, A0131969A, A0136355A
Any Severe Outcome	91	
Outcomes other than those listed above	9	A0125847A, A0125896A, A0126729A, A0126993A, A0133033A, A0133446A, A0133946A, A0144484A, A0154776A,
Total	100	

Ninety-one cases of serious constipation described severe outcomes, most commonly, hospitalization (54 cases) and intestinal surgery (15 cases). Two patients with serious constipation died.

- The first patient (A0129291A), an 82-year-old woman prescribed alosetron for diarrhea-predominant IBS, was hospitalized for constipation and died following surgery for a ruptured diverticulum. This patient was concomitantly receiving hydrocodone and belladonna and reported a 5-day history of constipation.
- The second patient (A0130853A) was a 62-year-old woman in a nursing home for Alzheimer's disease receiving alosetron for treatment of chronic diarrhea. She underwent surgery to correct Ogilvie's syndrome and was not resuscitated after she developed adult respiratory distress syndrome.

Taking together the information provided in Tables 8 and 9, 94 of the 100 cases of serious constipation described a complication of constipation and/or a severe outcome.

4.3.1.4. Possible Risk Factors for Constipation and Complications of Constipation

Understanding the context of infrequent or rare safety events is fundamental to assessing the magnitude of risk. When reports of ischemic colitis and complications of constipation were first reported it was recognized that a better understanding of the incidence, natural history, and risk factors for these gastrointestinal events were needed. GSK initiated epidemiologic studies to assess the epidemiology of colon ischemia, complications of constipation requiring hospitalization and bowel surgery. These studies represent the first population-based research of the incidence and risk factors for these gastrointestinal outcomes and provide background information on the occurrence of these events in patients with and without IBS.

In the Phase IV study of over 5 million UHC members (EPI-40060), in a period of time prior to the availability of alosetron, data indicated that the incidence of complications of constipation requiring hospitalization was higher for women than for men, and increased with age. IBS was associated with a substantial elevation in risk for complications of constipation, ranging from a 2.8 to 4.4-fold elevation in risk compared to non-IBS patients. Data from the case control study in the same setting indicate that patients using drugs to treat diarrhea or have constipation as a side effect were at increased risk for complications of constipation.

The UHC study also examined the incidence of bowel surgery. The incidence of bowel surgery was higher in women than in men. The incidence varied by age, with the older age

group at an increased risk. Patients with IBS were at substantially increased risk for bowel surgery compared to patients without IBS.

Within the UHC study, GSK also studied the incidence of complications of constipation requiring hospitalization and bowel surgery in patients receiving alosetron. The study was originally designed to include 10,000 alosetron-treated patients but was truncated due to the withdrawal of alosetron. Within UHC, GSK studied 3,631 patients treated with alosetron and 2,480 patients were not treated with alosetron. In the cohort studied, data based on ICD-9 codes indicate that there were no differences between the two groups in the incidence of complications of constipation requiring hospitalization or bowel surgery.

One other ongoing epidemiologic study (EPI-40110) was initiated to study the incidence of complications of constipation in the General Practice Research Database. This work is in progress and may provide additional information on the incidence and risk factors for complications of constipation.

These studies are summarized in **Attachment I** to this section.

4.3.1.5 Strategies to Reduce Risks Associated with Constipation

Appropriate selection of patients, counseling with regard to benefits-risks associated with alosetron, and careful monitoring are the fundamentals for safe use. The development of severe constipation is largely avoidable if the drug is used as directed. Complications of constipation may be mitigated with appropriate patient selection, careful monitoring and discontinuation of the drug if signs of constipation occur. Therefore, with appropriate education from their physicians about possible risks and actions to be taken if symptoms arise, it is expected that patients will not confuse the benefits of alosetron with constipation. The proposed Risk Management Plan includes a patient-physician agreement document that is intended to ensure that patients have received the critical information about benefits-risks that are also described in the Medication Guide.

There is not a single, generally recognized definition for constipation. Constipation is patient-defined and is typically associated with a change in bowel habits (decreased frequency) and/or stool consistency (harder stools). These symptoms may appear alone or together with abdominal bloating or pain. Straining, hard or lumpy stools, and/or the absence of bowel movements are all characteristics of constipation and readily recognized as such by patients. Indeed, surveys of subjects identified increased stool frequency and loose stool consistency among the most bothersome symptoms associated with IBS, indicating that patients are particularly cognizant of these characteristics of their bowel habits. Regardless,

prescribers will need to reinforce instructions for self-monitoring and ensure appropriate follow-up while patients are on alosetron. Should constipation occur, stopping alosetron therapy and if necessary, instituting conservative measures including laxatives, should resolve constipation in the great majority of patients before any serious problems might occur.

Appropriate diagnosis and selection of patients is critical since certain conditions may increase risks associated with treatment with alosetron. Standards of care dictate that patients with a history of constipation or anatomical abnormalities, which could interfere with colon peristalsis or bowel evacuation, should avoid constipating drugs such as alosetron. Alosetron is contraindicated for patients with a history of chronic or severe constipation, patients who have had a previous complication from constipation, history of intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforation, and/or adhesions, a history of ischemic colitis, Crohn's disease or ulcerative colitis, and patients who have active diverticulitis. Patients taking other constipating medications may be at greater risk for complications of constipation, therefore prescribing alosetron in these patients should occur only if the benefits clearly outweigh the risks.

Confused or demented patients unable to sense the status of their bowels will be less able to recognize early symptoms and should not be treated with alosetron. Also, patients who are unaware of risks associated with constipation following treatment with alosetron because of an inability to communicate should not be treated with alosetron. Routine medical practice recognizes that elderly or generally debilitated patients are at greater risk of any medical complication including constipation and therefore should be treated with greater care and attention.

Constipation associated with alosetron has been shown to be a dose-related adverse event. Following continuous doses of 1 mg BID in clinical trials, 11% of patients withdrew due to constipation versus 4% of those treated with 0.5 mg BID, and 0.9% treated with placebo. Further, while there were nine cases classified as serious in the 1 mg BID treatment group, there were no reports from clinical trials in the patients treated at a daily dose 1 mg (0.5 mg BID). Anecdotal information suggests that lower doses or alternative regimens can provide benefits with reduced risks. Subsequent to market introduction and following the product withdrawal, many patients have informed GSK that they were able to achieve benefit at doses lower than recommended in the product labeling without experiencing constipation. Because some patients are more sensitive to the possible constipating effects of the drug, proposed changes to the product labeling include initiating therapy with a trial dose of 1mg daily. Only if the patient adequately tolerates this initial starting dose and does not receive adequate relief of symptoms after 4 weeks, should the 1mg BID dose be instituted. This

upward titration of dose is expected to decrease the incidence of constipation or severity of constipation in those patients who may be particularly sensitive to it.

In summary, serious constipation is believed to be a largely avoidable risk and severe outcomes can be minimized if appropriate patients are selected, they are adequately informed, and appropriately monitored. Should constipation occur it is quickly reversible with appropriate action. Unfortunately, it is impossible to realize a goal that no patient treated with alosetron will ever experience a constipation-related SAE. As shown by case control studies in a population not exposed to alosetron, bowel perforation can also occur spontaneously and can occur secondary to diverticulitis, inflammatory bowel disease or indeed in association with constipation in the absence of alosetron treatment.

4.3.2 Overview of Ischemic Colitis and Mesenteric Ischemia

The term “ischemic colitis” is often used generically to describe all aspects of colon ischemia. However, it is clinically appropriate to distinguish colon ischemia (which includes ischemic colitis) from mesenteric ischemia because these conditions differ in their clinical presentation and outcomes. As described by Greenwald and Brandt, until the 1950s, the only well recognized form of colonic ischemia was gangrene.¹⁴ Colonic ischemia, however, now is recognized to exist as a spectrum of injury including reversible colonopathy (submucosal or intramural hemorrhage; transient colitis) and irreversible disease. In the majority of cases, ischemic colitis involves inflammatory changes to focal segments (typically the watershed area) of the colon and typically presents with mild-to-moderate abdominal pain, diarrhea, and hematochezia. In most instances, ischemic colitis is a self-limiting and reversible condition that can be managed conservatively.

The risk factors for colonic ischemia have not been well elucidated. Most cases of colonic ischemia do not have a recognizable cause, but in most instances of spontaneously occurring colonic ischemia the event is primary. The true incidence of colonic ischemia is believed to be underestimated because many patients have mild or transient disease and therefore do not seek medical help. Although historically, ischemic colitis has been associated with only the elderly, in recent years an increasing number of young people have been identified with colon ischemia associated with distance running, various medications or coagulopathies.¹³

Ischemic colitis is sometimes erroneously considered to be analogous to acute mesenteric ischemia. In contrast to colon ischemia, mesenteric ischemia, occlusion, or infarction typically has a severe clinical presentation that results from interruption of blood flow to a significant length of small bowel and often, proximal colon. These conditions are associated with significant morbidity (e.g., surgical resection of infarcted bowel) and mortality¹³.

Tissue ischemia can also occur in circumstances where blood to a segment of bowel is interrupted or becomes insufficient for secondary reasons. Thus, with diverticulitis, bowel

perforation or ulceration, an inflammatory mass is present and together with associated edema may cause tissue ischemia secondary to the pathological process. Microscopic examination would be expected to reveal changes consistent with ischemia. Likewise, thinning of a severely dilated wall of colon as seen in Ogilvie's syndrome or in toxic megacolon may also be associated with a secondary interruption of blood flow resulting in ischemic changes.

Within this section, overviews of reports of ischemic colitis are provided separately for cases originating from clinical trials ([Section 4.3.2.1](#)) and marketing experience ([Section 4.3.2.3](#)). A listing of summary findings is provided below:

Clinical Trials

- Ischemic colitis was an infrequent but important adverse event reported by 17 out of 11,874 subjects receiving alosetron (1 in 698 patients) compared to 1 out of 3500 subjects receiving placebo; RR=5.0 (95% CI [0.8-210]).
- The incidence rate of ischemic colitis at one year was 5.9 cases per 1000 person-years (95% CI [3.4-9.4]) among alosetron-treated subjects, versus 1.1 cases per 1000 person-years (95% CI [0-6]) for placebo-treated subjects, IDR=5.44 (95% CI [0.9-229]).
- The association with alosetron treatment was greatest during the first month of treatment.
- No clear or consistent risk factors were identified and there were no clinical prodromes.
- There is no evidence that subjects reporting either constipation or the use of estrogens were at higher risk.
- All events were self-limiting, most resolving promptly on discontinuation of therapy with 40% being treated as outpatients.
- Many of these subjects had confounding medical findings.
- There were no deaths and no patients experienced permanent sequelae associated with primary colon ischemia.
- The frequency and the nature of reports for cases of ischemic colitis in patients treated with alosetron in clinical trials is comparable to that at the time of approval (4/~3000 [1 in 750] at the time of approval versus 17/11,874 [1 in 698]).

Spontaneously Reported Adverse Events from Marketing Experience

- Review of the post marketing safety database revealed 80 cases of suspected or demonstrated ischemic colitis.
- Where data are available, the median time to onset of symptoms was 2 weeks after initiation of alosetron therapy (mean, 35 days; range, 12 hours to 6 months). Considering all 80 cases of suspected or demonstrated ischemic colitis, 52 patients (65%) presented

with rectal bleeding or blood in stool, and 45 (56%) presented with abdominal pain *and* rectal bleeding or blood in stool, signs and symptoms that are distinct from those of IBS. Presenting signs and symptoms were not reported in all cases.

- Concurrent constipation was reported in 20 (25%) of cases. The use of hormone replacement therapy or oral contraceptives was reported in 19 (24%) of cases.
- Most cases of ischemic colitis were self-limiting and resolved with supportive care and discontinuation of alosetron.
- Considering all 80 cases, hospitalization was reported in 48 cases (60%). Six patients, three of whom were known to be elderly, underwent intestinal surgery. Of the 58 cases with probable or possible ischemic colitis, hospitalization was reported in 39 cases (67%), and three patients underwent intestinal surgery.
- No deaths were reported among the 80 cases of suspected or demonstrated ischemic colitis.

Although there were no cases from clinical trials, a total of 12 cases from marketing experience include events consistent with or possibly consistent with mesenteric ischemia, occlusion, or infarction. Three of these cases involved a fatal outcome. Nine of these cases are heavily confounded by the patient's prior medical conditions, and three contain limited medical documentation. Summary information about these cases is also presented in this section. A description of these cases follows the discussion of ischemic colitis cases.

GSK initiated epidemiologic work to study the incidence and risk factors for colonic ischemia. Interim data (**Attachment I**) from this study suggest that:

- The incidence of colonic ischemia is increased 3-4 -fold in patients after a diagnosis of IBS compared to patients without IBS.
- Use of drugs that reduce bowel motility as a primary effect or as a side effect were identified as a risk factor by case-control analyses.

Within the UHC study, GSK also examined the incidence of colon ischemia in patients receiving alosetron. The study was originally designed to include 10,000 alosetron patients but was truncated due to the withdrawal of alosetron. In this study we evaluated 3,631 patients treated with alosetron and 2,480 patients who were not treated with alosetron. No cases of colon ischemia occurred in either of the two cohorts. Nonetheless, an estimate for the incidence of colonic ischemia in alosetron users can be obtained from the upper bound of the exact confidence interval of the one-sample Poisson rate parameter based on no cases having been observed in 1,617 patient years of data, which is 2.28 cases per 1,000 patient years.

4.3.2.1 Reports of Colonic Ischemia from Clinical Trials

All clinical trials have now been completed or terminated and the safety data summarized as part of the supplemental NDA. Although the number of subjects and patients treated with alosetron in clinical trials has increased substantially from 2756 (1903 IBS patients) at the time of approval to 11,874 (10,805 IBS patients) now, the relative frequency of reports of ischemic colitis has remained generally consistent:

- Approval February 9, 2000: 4/~3000 total patients (1/750)
- June 27, 2000 Benefit-Risk reassessment: 7/6852 ((1/979) based on completed trials and estimated exposures from ongoing trials)
- December 7, 2001 ISS: 16/11,874 (1/742) based on completed studies; no studies ongoing)
- March 7, 2002 following case adjudication with FDA: 17/11,874 (1/698)

There have been a total of 17 cases in alosetron-treated patients identified as possible ischemic colitis from clinical trials; 14 were reported as ischemic colitis and three others classified as possible or probable ischemic colitis based on subsequent evaluation. **Attachment III** summarizes the available clinical data for the 18 ischemic colitis cases. (17 alosetron, 1 placebo). As was the case at the time of approval and during the June 2000 assessment of safety, reports of ischemic colitis have occurred with disproportionate frequency for alosetron-treated patients when compared to those who received placebo. This disparity remains even when one accounts for the large difference between those who received drug (11,874) versus placebo (3,500).

In addition to the 17 cases described above, the integrated safety database, includes a total of 13 other alosetron-treated patients for whom colitis was reported as an AE. Other causes of colitis were reported in eight of these patients: collagenous (n=1), lymphocytic (n=1), microscopic (n=1), sigmoiditis/coloproctitis (n=1), secondary to constipation (n=2), and non-specific (n=2). The etiology was not specified or found on subsequent evaluation in the 5 remaining patients.

It is generally accepted in medical practice that a diagnosis of ischemic colitis is only confirmed after positive endoscopic and histologic findings. The 17 cases of ischemic colitis have been classified as possible or probable ischemic colitis on the basis that a diagnosis is supported by: clinical evidence and endoscopic and/or biopsy findings that were suggestive of, but not necessarily consistent with a diagnosis of ischemic colitis. The 17 cases include:

- The original four cases discussed prior to approval (**Subjects: 2829, 7195, 15687, and 34069**),
- The three additional cases agreed with FDA prior to the June 27, 2000 Advisory Committee Meeting (**Subjects: 78134, 72823, and 72824**),
- A total of ten new cases of patients treated with alosetron (**Subjects: 40398, 63223, 66556, 69433, 71843, 77574, 80357, 82125, 86746, 182603**); 5 of the 10 new cases were derived from a large, open-label study (S3B30020).

All 17 patients underwent endoscopic examination. Sixteen of the 17 subjects had biopsies performed and reviewed by the local pathologist. Of these, 13 had biopsy interpretations reported as either diagnostic of, consistent with, or suggestive of ischemic colitis. Three of the 17 subjects did not have the typical clinical, endoscopic and/or histologic findings of ischemic colitis. **Subject 80357** (study S3B30020) presented with constipation and abdominal pain but no rectal bleeding. In addition, colonoscopy showed sigmoid diverticulae with ulcerations which were felt could be due to ischemic colitis or diverticulitis. Biopsies were not obtained. The male **Subject 40398** (study S3B20023) had an episode of bloody diarrhea which was evaluated 56 days after the event, 10 days after conclusion of the study. Colonoscopy revealed a small rectal polyp and hemorrhoids and was otherwise normal. Biopsies of the transverse colon were normal but the rectosigmoid colon showed “focal fibrosis, consistent with a history of ischemic colitis and focal mild active colitis.” **Subject 49203** (study S3B30012) presented with constipation, straining with bowel movements and blood in her stool. The patient did not report abdominal pain. The findings on colonoscopy and biopsy were reported as “non-specific colitis and/or ischemic colitis”.

One placebo-treated subject who presented with bloody diarrhea was subsequently evaluated and categorized as possible ischemic colitis since her clinical presentation and sigmoidoscopic findings were consistent with the diagnosis (**Subject 8245**; study S3BA3003). The histologic findings of “lamina propria congestion and edema, not diagnostic of ischemia” did not confirm the diagnosis.

Twelve of the 17 patients reported a medical event that met the regulatory definition of serious and 16/17 withdrew from the study. In general, the clinical presentation was acute and without any prodrome. Most subjects had sudden onset of mild to moderate lower abdominal pain followed within 24 hours by rectal bleeding or bloody diarrhea. In some cases, non-bloody diarrhea preceded the bloody diarrhea. The subjects’ ages ranged from 20 to 75 years. Sixteen of the subjects were female. All subjects were receiving alosetron 1mg BID, except for one subject who received 2 mg BID and the male subject who received 0.5mg BID. There were no specific concomitant medications identified as a predisposing factor in these subjects, nor was there any particular comorbid condition identified. Subjects were

specifically evaluated to determine whether constipation or hormone/estrogen use may have predisposed patients to ischemic colitis. Twenty-five percent of the subjects reported complaints of constipation and 60% had concomitant use of hormones/estrogens. This frequency of constipation and use of hormones/estrogens was similar to the general alosetron-treated population in the clinical trial program.

Of the 17 patients, nine patients were evaluated for evidence of a hypercoagulable state. Seven had normal thrombosis or coagulation panels, and one had a history of a pulmonary embolus, one had a low protein C level and subsequently developed a DVT (deep vein thrombosis). In a study evaluating the effects of co-administration of alosetron with oral contraceptives, alosetron had no effect on thrombosis variables (Study S3B10948; completed since original NDA approval).

Although there was a wide range of time to onset of symptoms of ischemic colitis, from 2 to 162 days, eleven cases occurred during the first month of treatment and the incidence did not increase with increasing duration of alosetron therapy. All events were self-limiting. Approximately 40% of the alosetron treated subjects were managed as outpatients. For hospitalized subjects, periods of hospitalization were of short duration (1 to 7 days). All subjects were treated conservatively. Alosetron treatment was discontinued in all subjects except for **Subject 40398** (study S3B20023) who continued alosetron until the completion of the study without recurrence of the episode of ischemic colitis.

With one possible exception, all of the events for the 17 subjects resolved without sequelae. The reported sequelae in **Subject 15687** (study S3BA3001), one of the four original cases, is based on a repeat colon exam approximately two months after discontinuing alosetron administration which revealed mild non-specific erythema of unknown clinical significance. Biopsy results were found to be essentially normal.

4.3.2.2 Onset, Risk, and Incidence Rate Of Ischemic Colitis Summary of All Studies Evaluating Alosetron

Most of the cases of ischemic colitis (11/17) occurred during the first month of treatment:

- The simple cumulative risk of ischemic colitis among alosetron-treated patients is 14.3 events per 10,000 patients (95% CI [8.3-22.9]), which is 1 event in 698 patients compared with 2.86 events per 10,000 placebo-treated patients (95% CI [0.07-15.9]), which is 1 event in 3500 patients, RR=5.0 (95% CI [0.8-210]).

- In alosetron-treated patients, the life table (exposure time adjusted) risk varies over time and is highest during the first month. The cumulative life table risk increases over time to 0.30% (3 in 1000 patients; 95% CI [1.7-4.8]) at 12 months compared with a cumulative risk of 0.28% (2.8 events per 1000 patients; 95% CI [0-15.6]) in placebo-treated patients at 12 months.
- During the first month of alosetron treatment the incidence rate of ischemic colitis was 12.9 cases /1000 person-years (95% CI [6.42-23.0]), and by 12 months the incidence rate was 5.9 cases/1000 person-years (95% CI [3.4-9.4]). In placebo-treated patients, the incidence rate during the first month and at 12 months was 0 (95% CI [0-14.9]) and 1.1 cases/1000 person-years (95% CI [0-6]), respectively. Hence, at twelve months the IDR=5.44 (95% CI [0.9-229]).

Table 10 summarizes the risk (incidence) and rate (incidence per unit of time) of ischemic colitis for each month and cumulatively over 12 months. Figures 35 and 36 provide an estimate of time to onset and cumulative risk of ischemic colitis, respectively.

**TABLE 10 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	11	11874	3061	0.1063	0.1063	854.751	12.869
Month 2	1	8802	1538	0.0124	0.1189	1549.110	7.746
Month 3	2	7263	4043	0.0382	0.1570	2053.494	6.818
Month 4	2	3218	736	0.0702	0.2272	2288.976	6.990
Month 5	0	2480	452	0	0.2272	2481.201	6.448
Month 6	1	2028	1298	0.0725	0.2998	2597.201	6.546
Month 7	0	729	91	0	0.2998	2654.554	6.404
Month 8	0	638	15	0	0.2998	2708.127	6.277
Month 9	0	623	13	0	0.2998	2760.456	6.158
Month 10	0	610	10	0	0.2998	2811.725	6.046
Month 11	0	600	179	0	0.2998	2859.640	5.945
Month 12	0	421	421	0	0.2998	2881.465	5.900
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.

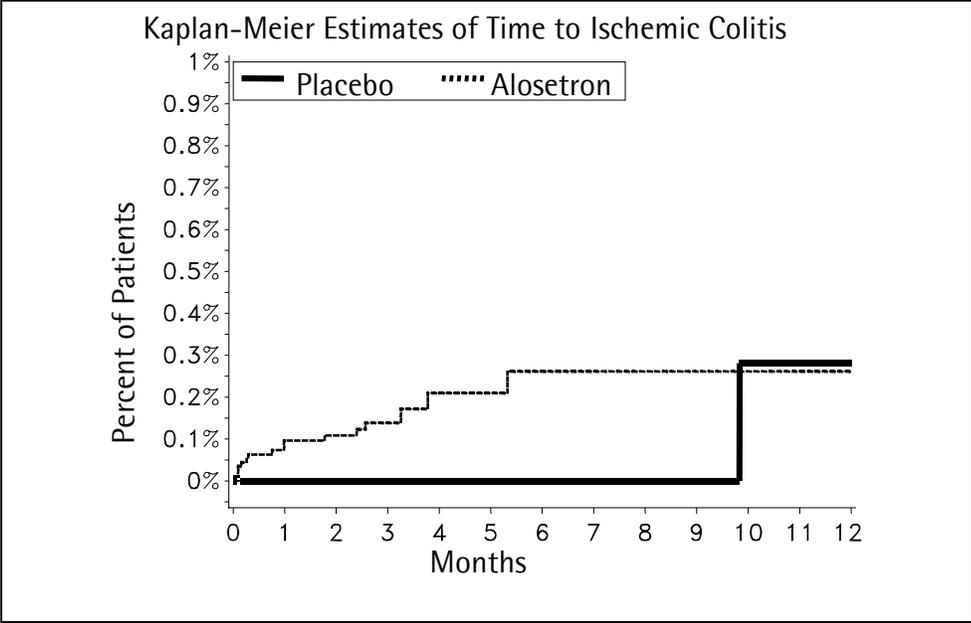


Figure 35 Estimate of Time to Onset

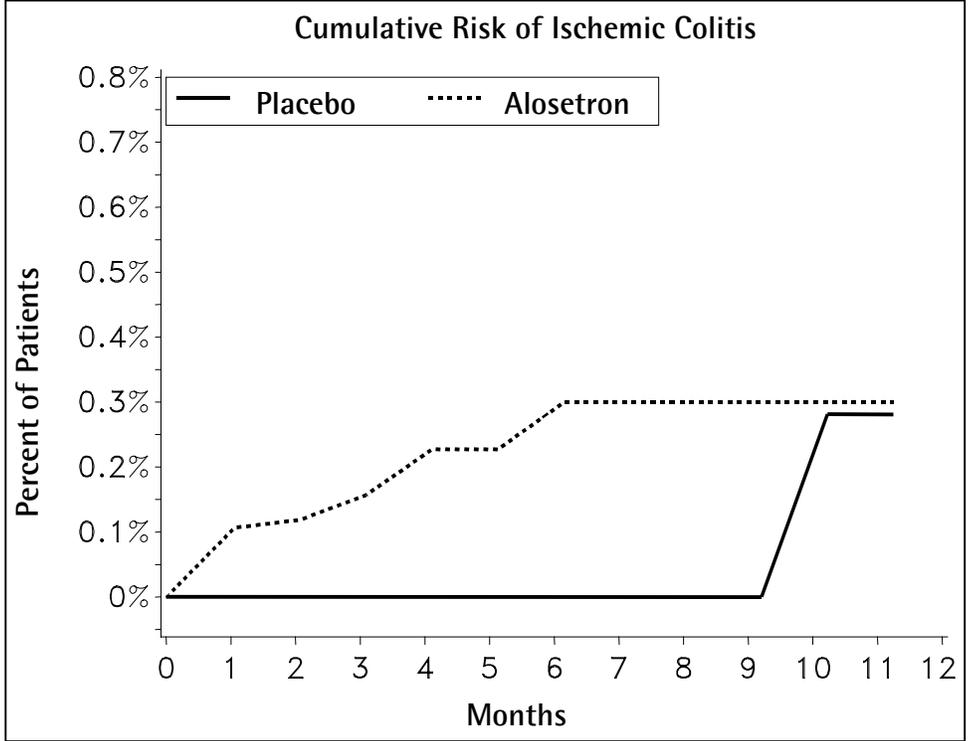


Figure 36 Cumulative Risk of Ischemic Colitis

4.3.2.3 Reports of Ischemic Colitis from Marketed Experience

The spontaneous adverse events database revealed 80 reported cases of ischemic colitis classified as probable, possible or insufficient evidence to support a diagnosis. Because spontaneous AE cases are often incomplete and are heterogeneous with respect to the type of information reported, each case of suspected ischemic colitis was classified by GSK to characterize the medical information available to support the diagnosis. The categories described below were adopted following discussions with FDA:

- **Insufficient evidence to support the diagnosis.**
- **Possible ischemic colitis** - The diagnosis is supported primarily by clinical evidence. Some cases include radiographic and/or endoscopic findings that were compatible with, but not diagnostic of, ischemic colitis.
- **Probable ischemic colitis** - The diagnosis is supported by clinical evidence PLUS endoscopic and/or biopsy findings. In some cases with good documentation of biopsy and/or endoscopy findings, but poor documentation of clinical evidence, the clinical evidence was assumed.

Of the 80 cases, 44 were classified as probable and 14 as possible cases based on available medical documentation. For 22 cases there was insufficient evidence to support the diagnosis. All but one of the 58 probable or possible cases involved women and 23% involved patients who were 65 years of age or older. Onset of symptoms was reported as occurring from 12 hours to 6 months after initiating therapy, and the clinical presentation typically included hematochezia with or without abdominal pain. Most cases of ischemic colitis were self-limiting and resolved with supportive care and discontinuation of alosetron. Of the 58 cases with probable or possible ischemic colitis, hospitalization was reported in 39 cases (67%), and three patients underwent intestinal surgery. No deaths were reported among the 80 cases of suspected or demonstrated ischemic colitis. In Table 11, a summary of the characteristics of all cases (n=80) is contrasted with a summary of the subset of those cases classified as possible or probable ischemic colitis (n=58).

Table 11 - Characteristics of Cases of Ischemic Colitis from Marketing Experience

All Cases (n=80)	Cases Classified as Possible or Probable Ischemic Colitis (n=58)
<p>Seventy-five patients were female and 2 patients were male. Gender was not reported in 3 cases.</p>	<p>Fifty-seven patients were female and 1 was male.</p>
<p>Where exact age was reported (66 cases), the median age was 55 years (range, 25 to 81 years). Where exact or approximate age was reported (68 cases), 18 patients (26%) were ≥ 65 years of age.</p>	<p>Where exact age was reported (56 cases), the median age was 55 years (range, 25 to 80 years). Where exact or approximate age was reported (57 cases), 13 patients (23%) were ≥ 65 years of age.</p>
<p>Where time to onset of symptoms of ischemic colitis was reported (50 cases), the median time to onset was 2 weeks and the mean time to onset was 35 days after initiation of alosetron therapy (range, 12 hours to 6 months).</p>	<p>Where time to onset of symptoms of ischemic colitis was reported (45 cases), the median time to onset was 2 weeks and the mean time to onset was 32 days after initiation of alosetron therapy (range, 12 hours to 6 months).</p>
<p>In most cases, patients presented with signs and symptoms that are distinct from those associated with IBS: 52 (65%) presented with rectal bleeding or blood in stool, and 45 (56%) presented with abdominal pain and rectal bleeding or blood in stool. Presenting signs and symptoms were not reported in all cases.</p>	<p>In most cases, patients presented with signs and symptoms that are distinct from those associated with IBS: 46 (79%) presented with rectal bleeding or blood in stool, and 39 (67%) presented with abdominal pain and rectal bleeding or blood in stool. Presenting signs and symptoms were not reported in all cases.</p>
<p>Concurrent constipation was reported in 20 (25%) of the cases.</p>	<p>Concurrent constipation was reported in 14 (24%) of the cases.</p>
<p>The use of hormone replacement therapy or oral contraceptives was reported in 19 (24%) of the cases.</p>	<p>The use of hormone replacement therapy or oral contraceptives was reported in 18 (31%) of the cases.</p>

Table 12, summarizes the outcomes for all cases (n=80) and for the subset of cases classified as possible or probable or ischemic colitis (n=58).

Table 12 – Outcomes for Cases of Ischemic Colitis from Marketing Experience

All Cases (n=80)	Cases Classified as Possible or Probable Ischemic Colitis (n=58)
<p>Patient outcomes were described as resolved or improved in 50 cases, unresolved in 4 cases, and unknown in 26 cases. Where sufficient detail was provided, most cases of ischemic colitis appear to have been self-limiting, resolving following discontinuation of alosetron and supportive care.</p>	<p>Patient outcomes were described as resolved or improved in 45 cases, unresolved in 4 cases, and unknown in 9 cases. Where sufficient detail was provided, most cases of ischemic colitis appear to have been self-limiting, resolving following discontinuation of alosetron and supportive care.</p>
<p>No deaths were reported.</p>	<p>No deaths were reported.</p>
<p>Hospitalization was reported in 48 cases (60%). Some cases contained insufficient information to determine if the patient was hospitalized.</p>	<p>Hospitalization was reported in 39 cases (67%). Some cases contained insufficient information to determine if the patient was hospitalized.</p>
<p>Transfusion of blood products was reported in 1 case (A0133951A). This case is described below under the description of cases with intestinal surgery.</p>	<p>Transfusion of blood products was reported in 1 case (A0133951A). This case is described below under the description of cases with intestinal surgery.</p>
<p>Intestinal surgery was reported in 6 cases, including one report of unspecified surgery</p>	<p>Intestinal surgery was reported in 3 cases.</p>

Six cases included a report of intestinal surgery. Brief summaries of these cases are provided below:

- A0121632A (probable ischemic colitis):** A physician reported that a 69-year-old female developed ischemic colitis 5 days after initiating alosetron for the treatment of diarrhea-predominant IBS. Alosetron was discontinued. The patient was hospitalized and discharged after 5 days. Diarrhea subsequently returned (post-prandial only) with no further abdominal pain. One month after discontinuation of alosetron, the patient was noted to be dehydrated from diarrhea. Prednisone was

begun with a presumptive diagnosis of inflammatory bowel disease, as skin lesions were found. One week later, diarrhea was much improved. Approximately 5 weeks later, 10 weeks after discontinuing alosetron, the patient was hospitalized with bowel obstruction and underwent right colectomy. Surgical findings were stenosis in mid-transverse colon, several regions of ulceration distinct from the stricture including near cecum, and adhesions from small bowel to mid-transverse colon. Histology of the surgical specimen was compatible with ischemic colitis. Outcome was reported as “improved.”

- **A0132292A (probable ischemic colitis):** A physician reported that a female in her seventies received alosetron for treatment of diarrhea thought to be due to IBS. The patient was taken to the emergency room with “distended bowel” after taking alosetron for 7 days. Concurrent medication included Lomotil. Colonoscopy revealed ischemic colitis and a partial bowel resection was performed. Outcome was reported as “resolved.”
- **A0133951A (probable ischemic colitis):** A 65-year-old female with anemia, antral gastritis, esophageal ulcerations and peripheral vascular disease (s/p angioplasty of the right leg with stent placement) received alosetron for treatment of IBS. After approximately 6 months of alosetron use she developed abdominal pain and experienced gastrointestinal blood loss. Colonoscopy revealed ischemic cecum with necrotic mucosa. She underwent an exploratory laparotomy with right hemicolectomy and a pathologic diagnosis of severe ischemic colitis was confirmed. The patient did well post-operatively.
- **A0154774A, A158460A, A173943A (insufficient evidence):** These cases are attorney reports describing female patients who developed ischemic colitis. According to the reports, three underwent colon resection and one underwent an unspecified surgical procedure. No additional records are available.

In addition to the cases reported as ischemic colitis, a number of cases involved reports of bleeding per rectum. Further review of cases with a temporal relationship to abdominal pain identified possible etiologies in most including constipation-related hemorrhoid bleeding and anal fissure, diverticulitis and the use of NSAIDs. In the remaining cases there was insufficient evidence to suggest a diagnosis.

4.3.2.4 Mesenteric Ischemia, Occlusion, or Infarction

The GSK database contains 12 spontaneous case reports that mention events consistent or possibly consistent with mesenteric ischemia, occlusion, or infarction. (There were no

Supersedes page 87 in Volume 1 of the Briefing Document for LOTRONEX® (alosetron hydrochloride) Tablets

reports of mesenteric ischemia, occlusion, or infarction in the clinical studies with alosetron.) In three cases the reports do not contain sufficient evidence to support the diagnoses of mesenteric ischemia and/or mesenteric infarction. Nine cases are heavily confounded by the patients' medical conditions.

- All patients were female.
- The median patient age was 52 years (range, 33 to 92 years). Four patients were ≥ 65 years of age.
- The time to onset of presenting symptoms was variable, ranging from 4 hours after a single dose of alosetron to three months after discontinuation of therapy.
- Three cases describe a fatal outcome. All three cases were heavily confounded by predisposing factors.
- Hospitalization was reported in 11 cases and one case resulted in a visit to the emergency room.
- Intestinal surgery was reported in nine cases. Eight of the nine cases were heavily confounded with predisposing factors such as pre-existing intestinal vascular insufficiency, hypercoagulable state, and thrombotic disease. The ninth case was difficult to evaluate due to insufficient information.

Summaries of these cases are described below:

A0123214A: A physician reported that a 59-year-old female with a history of multiple gastrointestinal complaints, including abdominal cramping, post-prandial urgency, and chronic constipation, was seen by a gastroenterologist several times over a period of approximately 8 to 9 months. IBS was diagnosed after multiple radiologic and endoscopic studies were negative. In March 2000, she was hospitalized with worsening post-prandial abdominal pain, loose stools, intermittent vomiting, and a 25-lb. weight loss. During this hospitalization, Librax was prescribed for the treatment of her IBS symptoms. Two weeks later, she was re-hospitalized with abdominal pain, nausea, vomiting, hematochezia, and hypertension (BP>200/110). Subsequently, the patient developed fever and leukocytosis and was treated empirically with antibiotics. Alosetron was commenced on the second hospital day for treatment of IBS symptoms. The patient was discharged with continuing diarrhea and cramping. One week later, the patient was re-hospitalized with "constant" abdominal pain, profound watery diarrhea, nausea, vomiting, rectal bleeding, and additional weight loss. Angiography performed on the fourth hospital day revealed complete occlusion of the superior mesenteric and celiac arteries, as well as numerous small collateral vessels to a small celiac artery. Exploratory laparotomy was performed; the findings included (1) severe ischemia of the entire GI tract, with early necrosis of the small bowel and colon, and (2) complete occlusion of the

celiac and superior mesenteric arteries, with severe atherosclerotic plaque. No clots were identified. Two bypass grafts were placed and mild improvement of small bowel perfusion was noted intra-operatively. Re-exploration at 24 hours revealed occlusion of both grafts and total infarction and necrosis of the small bowel and most of the colon. The patient expired shortly thereafter.

- **A0125536A:** A physician reported that an obese 33-year-old female (weight >300 lbs) with a history of hypercoagulable state (Factor V Leiden) and deep vein thrombosis received approximately 2 days of treatment with alosetron. She discontinued treatment due to either increased pain or lack of efficacy (reporter not sure). Approximately 2 days later, she developed abdominal pain and was hospitalized. Surgery (jejunal resection) was performed and she was found to have mesenteric vein thrombosis.
- **A0129910A:** A physician reported that a 55-year-old female received alosetron for a chronic diarrheal symptoms. Past medical history was notable for migraines treated with sumatriptan. After 4 weeks of treatment, alosetron was discontinued due to symptoms of constipation and RLQ pain and was not restarted. Colonoscopy was performed 2 weeks after discontinuation of alosetron to evaluate ongoing post-prandial RLQ pain. She was diagnosed with segmental colitis in which a 6-7 cm segment of the ascending colon was noted to have linear ulcerations. Biopsy showed acute inflammatory exudate, and the reporting gastroenterologist diagnosed ischemic colitis. In the ensuing months (off alosetron), a diagnosis of inflammatory bowel disease was made, and the patient was treated with high dose corticosteroids and antibiotics. Approximately 9 months after discontinuation of alosetron, the patient underwent exploratory laparotomy for RLQ pain, and a hemicolectomy was performed due to right colon necrosis. The patient was discharged after 13 days, and continued to improve after surgery.
- **A0133921A:** A physician reported that a 46-year-old female with a history of severe coronary artery disease (3 previous myocardial infarctions) and receiving multiple medications (including metoprolol and warfarin) received alosetron for 5 days for treatment of diarrhea and stomach flu (no history of IBS) with no sequelae. Approximately 2 weeks after discontinuing alosetron, she had gastrointestinal bleeding. Warfarin was temporarily discontinued after her PT and PTT were found to be significantly elevated. Colonoscopy performed at this time showed no evidence of ischemic colitis. Approximately 1 week later (3 weeks after discontinuing alosetron), she experienced hemodynamic instability and abdominal pain. Exploratory laparotomy revealed small bowel necrosis, presumably from a superior mesenteric vein occlusion. The patient underwent surgery (jejunal resection). The patient expired approximately 8 months after surgery.

- **A0134744A:** A consumer reported that approximately 3 weeks after elective repair of a thoracic aortic aneurysm, his 72-year-old wife developed a “blood clot in her colon” and underwent surgery. A physician confirmed that the patient underwent hemicolectomy for an ischemic and infected colon. According to the consumer, alosetron had been taken for approximately 1 month and was discontinued prior to the aortic surgery.
- **A0141438A:** A physician reported that a 63-year-old diabetic female with ongoing tobacco use and extensive vascular disease (including renal artery stenosis and superior mesenteric artery disease treated with angioplasty) took alosetron for several weeks for abdominal symptoms that were believed to represent a flare-up of long-standing IBS. Her symptoms continued and subsequent work-up led to a diagnosis of mesenteric ischemia. The patient underwent superior mesenteric artery bypass surgery and recovered.
- **A0142306A:** A physician reported that a 69-year-old female with multiple risk factors for acute occlusive mesenteric ischemia, including myeloproliferative disease and protein C and protein S deficiencies, received alosetron for approximately 4 weeks. The patient underwent surgery for small bowel necrosis several weeks after discontinuing alosetron treatment. The patient was diagnosed with widespread venous thrombosis at the time of bowel necrosis. Doppler studies showed thromboses in the femoral, popliteal, peroneal, and posterior tibial veins as well as the superior mesenteric vein.
- **A0120076A:** A physician reported that a 76-year-old female with a history of intermittent porphyria and intermittent atrial fibrillation developed increased stool frequency, abdominal pain, fever, agitation, and disorientation 7 weeks after starting alosetron. An ECG showed marked ST segment elevation which normalized several hours later and the patient’s WBC count was elevated. A presumptive diagnosis of acute mesenteric ischemia or mesenteric artery thrombosis was made. No diagnostic testing was performed. The patient was treated empirically with low molecular weight heparin. Three days later, colonoscopy and abdominal CT scan were negative for ischemia. The patient recovered with no sequelae.
- **A0123884A:** A physician reported that a 64-year-old female presented to the emergency room with abdominal pain and a normal WBC count. The reporter made a clinical assessment that “all symptoms were consistent with mesenteric infarction,” but no additional information or diagnostic evaluations were reported.
- **A0153528A:** A physician reported that a 45 year-old female received a single dose of alosetron on January 3, 2000 (note: alosetron was not marketed until March 2000). Four hours later she was hospitalized for severe abdominal pain, which led to exploratory surgery. Superior mesenteric vein thrombosis was diagnosed. The reporter stated that the patient’s entire small bowel was infarcted and that the region from the proximal

jejunum to the distal ileum was resected. She underwent surgical re-exploration ten months later for “wash out.”

- **A0154770A:** A 42-year-old female with a prior history of angiodysplasias and ischemic colitis since 1997, including chronic ischemic ulcer at the splenic flexure since 1999, received 6 weeks of alosetron therapy with "good results." She discontinued therapy at the time of market withdrawal. Approximately 2.5 months after discontinuing use of alosetron, she developed a recurrence of ischemic colitis in the transverse and sigmoid colon. A prophylactic hemicolectomy was performed approximately one month later. Ischemic changes were not seen on the surgical specimen and were thus believed to have resolved.
- **A0359773A:** An attorney reported that a 92-year-old female with long standing IBS, peripheral vascular disease (s/p femoral-popliteal bypass), and Ogilvie's syndrome, died after using alosetron for three months. Medical records indicate that she suddenly collapsed in a chair after experiencing a sudden onset of upper body pain. A head CT showed acute parietal infarction, and in her physical examination abdominal distention was noted. The death certificate listed intestinal infarction as the cause of death. No information was provided to support this diagnosis.

4.3.2.5 Strategies to Reduce Risks Associated with Colonic Ischemia

Ischemic colitis is an infrequent but clinically significant adverse event that has been reported in clinical trials following treatment with alosetron. Ischemic colitis has also been reported in patients treated with marketed product. Because risk factors are not known, ischemic colitis must be considered an idiosyncratic risk. The goal of the risk management strategy for this event is to minimize the occurrence of severe outcomes. All of the cases of ischemic colitis from clinical trials and the great majority of cases reported from marketing experience involving colonic ischemia were self limiting and resolved with supportive care. Risk for patients who may develop ischemic colitis may be mitigated by appropriate and prompt action on the part of patients and physicians at the first sign of ischemic colitis.

As part of the Risk Management Program, prescribers will need to counsel all patients on the possible risk of ischemic colitis, reinforce instructions for self-monitoring and ensure appropriate follow-up while patients are treated with alosetron. Should any symptoms of ischemic colitis develop such as rectal bleeding, bloody diarrhea, or new or worsening abdominal pain, alosetron should be discontinued immediately and the patient evaluated promptly. Passage of blood per rectum or mixed with stool is not consistent with IBS symptoms and always warrants investigation. Although IBS patients often have hemorrhoids

or other anorectal abnormalities that may result in the presence of blood in the stool, this is usually easily distinguished from ischemic colitis on clinical grounds.

Appropriate diagnosis and selection of patients is critical since certain conditions may increase risks associated with ischemic colitis. It is prudent to exclude patients that may be at greater risk for colonic ischemia until more is known about this condition and its relationship with IBS. Therefore, in addition to the contraindications previously described, patients with a prior history of ischemic colitis or impaired intestinal circulation should not take alosetron.

The literature suggests that in some patients ischemic colitis may become chronic or significant enough to cause lasting consequences. Even with stringent vigilance to exclude patients who might be at increased risk and with aggressive management of early symptoms, it should be recognized that additional cases of ischemic colitis will likely be reported in patients prescribed alosetron, and in some instances, these may develop serious complications. This possible risk must be weighed against the possible benefits by the patient and physician.

4.4 Surgeries and Transfusions Associated with Serious GI Events

A total of 25 spontaneous cases that include reports of intestinal surgery *not* associated with adverse events of special interest (i.e., ischemic colitis; mesenteric ischemia, occlusion or infarction; complications of constipation) were also reported. These included spontaneous perforation, perforation secondary to diverticular disease or infectious colitis, inflammatory bowel disease, anorectal surgery not related to constipation and lysis of adhesions. [In one case of colonic perforation (A0120067A), additional information was received from FDA after February 18, 2002 but arrived too late to permit a full assessment for purposes of this Briefing Document.] There were 11 cases in which blood transfusions were administered to patients who had serious AEs. In most instances upper GI bleeding, thrombocytopenia, peri-operative complications, colonic polyps and use of anticoagulant therapy precipitated the need for blood products. Often these patients were elderly and in all cases the role of alosetron is extremely doubtful.

4.5 Deaths

4.5.1 Clinical Trials

There were a total of 5 treatment-emergent deaths in subjects treated with alosetron in clinical trials versus 4 in subjects in other treatment groups (2 placebo, 1 trimebutine, 1 traditional IBS therapy). Four of the five treatment-emergent deaths in alosetron treated subjects were due to cardiovascular disease (2 were identified prior to approval). No patients

in clinical trials had a fatal outcome following a report of ischemic colitis or complication of constipation (there were no reports of mesenteric ischemia). Death occurred for unknown reasons in one patient and all the deaths were judged unrelated to the treatment with alosetron.

4.5.2 Marketing Experience

The database from marketing experience includes 19 spontaneous case reports involving patients who were treated with alosetron and subsequently experienced medical events with a fatal outcome. Five of the 19 deaths were related to cardiovascular events (**A0130992A**, **A0131324A**, **A0137166A**, **A0147038A**, **A0158454A**). Three other deaths were not specifically gastrointestinal related; one case involved multidrug overdose (**A0154966A**), one case involved sepsis (Staphylococcus) seven months after the patient discontinued alosetron (**A0158455A**); one case involved death from an unknown cause (**A0158461A**).

The 11 remaining deaths were related to gastrointestinal events. The median age of these patients was 67 years (range, 46 to 92 years), with eight patients being ≥ 65 years of age. These cases are briefly described below:

- Two deaths were in patients with acute mesenteric syndromes (**A0123214A**, **A0133921A**). In both of these cases, there are significant confounding factors in the patients' medical histories. A third death occurred in a 92 year-old subject who had extensive vascular disease (**A0359773A**). The death certificate listed intestinal infarction as the cause of death; however there were no data provided to support the diagnosis. These three cases are discussed in under Section 4.3.2.4 of the Briefing Document.
- Two deaths were in elderly patients with complications of constipation (**A0129291A**, **A0130853A**). These patients are discussed in Section 4.3.1.3 of the Briefing Document.
- Two deaths occurred in 70-year-old patients with complications of colonic perforation that were thought to be due to ruptured sigmoid diverticula (**A0126868A**, **A0133203A**). Constipation was not reported in either of these cases.
- Case **A0154772A** is a report from an attorney of an 83-year-old patient with a history of stroke, dementia, malnutrition, and gastric outlet obstruction due to peptic ulcer disease. The patient developed hypotension and abdominal distension five days after the placement of a gastrostomy feeding tube. Radiographic findings were compatible with an ileus or small bowel obstruction. The patient expired before surgery could be performed.

Three deaths appear to have resulted from underlying gastrointestinal conditions:

- One case involved a 79-year-old female with chronic anorexia associated with severe malnutrition and chronic diarrhea (A0142561A). These symptoms persisted on alosetron therapy. She continued to lose weight and died from multi-organ failure and dehydration from her underlying condition.
- A second patient died from complications of upper gastrointestinal bleeding that was thought to be due to underlying vascular disease (A0127461A). Alendronate, a drug associated with esophageal ulceration, was identified as a co-suspect drug in this case.
- The third case (A143731A) involves a 63 year-old female with a history of bowel obstruction, adhesions, radiation enteritis, and stage 4 cirrhosis. She developed bowel obstruction due to adhesions and subsequently died from complications of cirrhosis.

4.6 Risks Associated with Alternative Therapies

Alosetron is the only FDA approved therapy that has been proven effective in large adequate and well-controlled trials to treat the multiple symptoms of IBS. There is no ‘gold standard’ therapy against which to compare alosetron. Conventional or traditional therapy is ill-defined and consists of a variety of approaches ranging from dietary changes and behavioral modification to OTC and prescription medications. These medications are often used in combination and on a trial and error basis. The following drug classes form part of the pharmaco-therapeutic options for IBS and as described above; each is associated with a degree of risk. Most of these medications have been available for many years and very few have been approved for use in IBS. Many are available over-the-counter. Although side effects are often anticipated, they typically are not reported nor recorded and so the magnitude of the risks to individuals and to the public health is unknown.

Treatment of abdominal cramping and pain is frequently tried with antispasmodics and anticholinergics. The effectiveness of these agents has not been demonstrated in adequate and well-controlled trials and they lose their effectiveness with chronic use. Further, dose-dependent side effects including xerostomia, mydriasis, urinary retention, constipation, dizziness and blurred vision are common. Other drugs used to treat pain include NSAIDS but these are recognized to be associated with significant gastrointestinal morbidity.¹⁵ The gastrointestinal safety of the Cox-2 inhibitors has yet to be demonstrated and recently concerns have been voiced around potential cardiovascular side effects¹⁶. Although effective at treating pain, the prescription of opioid-based medications is severely restricted because of

the significant risks of side effects ranging from paralysis of the gastrointestinal tract to alterations in mood and habit-forming tendencies. Chronic use of antidiarrhea medications carry risks of constipation, obstipation, impaction and perforation as well as long term bowel atony. Anxiolytics have minimal effect on pain and, although they may be useful for short-term use in acute anxiety episodes, the risks associated with CNS depression, drug abuse, dependence and overdose makes them poor candidates for the chronic care of IBS. Tricyclic antidepressant therapy is typically initiated at a lower dose than that used for treating depression. Nevertheless, this class of drugs carries significant risks, that include arrhythmias and myocardial infarction, CNS depression, anticholinergic side effects and a notable risk of overdose. Selective serotonin re-uptake inhibitors (SSRIs) are generally associated with fewer side effects, but are also recognized as being less effective, possibly due to the increase in anxiety, agitation, insomnia and diarrhea reported by patients.

5. SUMMARY OF BENEFIT-RISK PROFILE FOR ALOSETRON

IBS is a functional gastrointestinal disease since, as yet, no biochemical or anatomical abnormalities have been identified to explain the syndrome. Evidence is growing that enhanced perception of visceral events through dysregulation of the enteric nervous system plays an important role in IBS symptom development.^{4,17} Serotonin, a major neurotransmitter in the gastrointestinal tract is released by mucosal cells and enteric neurons in response to a variety of stimuli and is thought to be instrumental in the bowel dysregulation seen in IBS. Alosetron is believed to exert its beneficial effect by modulating the impact of serotonin on afferent nociceptive pathways and intrinsic motor function.^{4,18}

Traditionally, a disease remains poorly understood by physicians and patients alike until the pathophysiological mechanism of the disease is elucidated, becomes widely accepted, and diagnostic markers are identified. To some extent this applies to IBS. The absence of a clearly defined mechanism of action and the fact that IBS seemingly does not shorten life expectancy should in no way minimize the seriousness of the disease and trivialize its debilitating impact on individuals. IBS negatively affects quality of life to an extent similar to that seen with major depression and chronic renal failure. The unmet medical need represented by IBS is very significant given that 5-10% of women suffers from diarrhea-predominant IBS and that many are not satisfactorily treated with available therapies.

Adequate and well controlled studies comparing alosetron to placebo in short term and long term studies have demonstrated a remarkable degree of consistency of beneficial effects on the multiple symptoms of diarrhea-predominant IBS in women. From 50-70% of diarrhea-predominant IBS women treated with alosetron, responded to therapy with therapeutic gains ranging from 15-30% over placebo. Patients debilitated by IBS expressed a notable

improvement in their overall symptoms on multiple quality of life domains and on measures of productivity. The effectiveness of alosetron has now been substantiated by data from more than 10,000 IBS subjects exposed to alosetron in clinical trials. The responder rates and therapeutic gains compare favorably with efficacy evaluations of many medications commonly used to treat other illnesses. This is supported by the many patients who were prescribed alosetron and, after evaluating the risks and benefits according to their personal values, demanded that GSK and FDA collaborate to reconsider the availability of alosetron. This is real-life testament of the positive impact this medication has had for many IBS sufferers.

Constipation was reported in 29% of alosetron-treated patients who received the recommended dose of 1 mg BID in the clinical trial population and was also the most frequently reported adverse event resulting in withdrawal (11%). It was also the most frequently reported adverse event in the spontaneous (post-marketing) database. Based on these data, constipation is the dominant risk associated with alosetron use. How serious a health hazard constipation represents is very difficult to quantify. Definitions of constipation are vague and the sensation is very subjective. Many of the spontaneous complaints of constipation were made by consumers subsequent to the decision to withdraw alosetron. Reports also came from patients motivated to call GSK to request refunds for unused medications further complicating the ability to draw conclusions. Most episodes of constipation occurred early in therapy, occurred once, were mild-to-moderate in intensity, and resolved within a week without other intervention. Some patients developed complications of constipation that necessitated hospitalization, disimpaction procedures, and surgeries with fatal outcomes occurring in two cases. Under the controlled conditions of clinical trials, the risk of developing a complication of constipation is rare (<0.1%) and not treatment-related. Epidemiological data indicate that patients with IBS have a higher risk of developing complications of constipation. In addition, most of the reported serious complications of constipation came from patients treated in clinical practice for which detailed case information was often insufficient or lacking. Where information was present, the cases were invariably medically complex and confounded by morbidity and the use of concomitant polypharmacy.

There is no evidence that alosetron behaves unlike other constipating drugs of the opiate, anti-cholinergic or calcium antagonist class. Contemporary data on the risks associated with these drugs is lacking because the risks are generally appreciated and adverse events are generally not reported. The epidemiological data suggest that drugs used to treat diarrhea or have constipation as a side effect carry significantly higher risk of developing complications of constipation. Therefore, it is reasonable to conclude that an IBS patient taking medication to treat diarrhea or bowel urgency will face a similar spectrum of risks regardless of the

therapy selected. However, it is also clear that attention to patient selection, education, dose and monitoring may prevent these complications. Hence, patients who are constipated or have a history of constipation or who are prone to constipation because of anatomical or other abnormalities should not take alosetron. Likewise, it is prudent to avoid the concomitant use of constipating medication with alosetron and it is important to withdraw therapy at the first sign or symptom of constipation. It is also prudent to treat elderly patients with increased care since advancing age is associated with a decline in the ability to cope with medical complications. The risk of developing constipation with alosetron may be decreased by initiating therapy at a lower dose (1mg QD) and advancing the dose (up to 1mg BID) after 4 weeks only if it is well tolerated and if symptoms persist.

In summary, complications of constipation represent the dominant possible safety risk. For the vast majority of patients, constipation can be detected early and will resolve with cessation of therapy and supportive care including laxatives as needed. Patients receiving alosetron will receive education through the Risk Management Program that patients receiving other constipating medications do not receive. Developing complications of constipation, however, represents a serious, albeit, rare potential risk. IBS, patient-specific factors and medications may play a contributory role. The risk associated with constipation can be minimized through the Risk Management Plan.

Ischemic colitis represents the next dominant possible safety risk. Patients diagnosed with IBS may be at greater risk of developing ischemic colitis than non-IBS patients. It is unknown whether hematochezia developed in some patients with colonic ischemia misdiagnosed as IBS. The risk of developing ischemic colitis in the clinical trial population exposed to alosetron exceeded that in the placebo population. A mechanism linking alosetron to ischemic colitis has not been elucidated. No other risk factors were identified including constipation or use of estrogen or NSAIDs. The nature of an association between alosetron and the episodes of ischemic colitis remains unknown. The diagnosis of IBS appears to be an independent risk factor for the occurrence of acute colonic ischemia. Drugs used to treat diarrhea or that induce constipation are also associated with colonic ischemia by an unknown mechanism of action.

The typical ischemic insult in ischemic colitis is transient and has resolved by the time signs and symptoms become apparent. As a result, episodes typically are self-limiting and resolve without sequela. This was the presentation for all of the ischemic colitis cases reported in the clinical trials and in the vast majority of cases from the spontaneous database (where outcome was reported). Nonetheless, prudence dictates that alosetron should be contraindicated in certain patients since they could be at increased risk of developing colonic ischemia or complications from ischemia. These include patients with a history of ischemic

colitis, or impaired intestinal circulation. Crohn's disease, ulcerative colitis and diverticulitis symptoms may overlap with IBS. The impact of alosetron on pain, urgency and diarrhea in these patients is not known. Conceivably, since serious complications associated with constipation or ischemic colitis could occur, alosetron should not be used in these patients. Hematochezia is not a sign of IBS, and in addition, since new or worsening abdominal pain could be a heralding symptom for an ischemic episode, patients presenting in this way should immediately stop taking alosetron and seek medical assistance.

The typical ischemic insult in ischemic colitis is transient and has resolved by the time signs and symptoms become apparent. As a result, episodes typically are self-limiting and resolve without sequela. This was the presentation for all of the ischemic colitis cases reported in the clinical trials and most of the cases from the spontaneous database.

6. CONCLUSIONS

It is now recognized that diarrhea-predominant IBS is a debilitating illness affecting a large number of patients. The emerging epidemiological data suggests that IBS is associated with the serious gastrointestinal co-morbidities of complications of constipation, colonic ischemia, and bowel surgery. Conventional therapy has failed to satisfy the significant unmet medical need of IBS. Patients and physicians have had to depend on treatment approaches with unproven benefits and in some instances with significant safety risks. The new efficacy data presented in the Supplemental Application, combined with the data described in the original NDA, provides clinically meaningful evidence that alosetron is efficacious in ameliorating individual debilitating symptoms, global symptoms, and important functional outcomes in women with moderate and severe diarrhea-predominant IBS. As with all medications, alosetron has been associated with harmful effects. The most notable has been constipation, which in rare instances has resulted in serious complications and death. Constipation typically occurred early in therapy and in almost all instances resolved when therapy was stopped and supportive care provided. Titrating the dose could decrease the incidence of constipation. However, the most important intervention to minimize the risk of developing complications of constipation is proper patient selection, education, and monitoring. Ischemic colitis may represent an idiosyncratic and unpredictable risk that occurs infrequently. Like constipation it tended to occur early in the treatment course and almost all events were self-limiting resolving without sequelae. Careful selection of patients, education and monitoring are prudent measures that can be instituted through the Risk Management Plan to mitigate the risks.

Alosetron provides clinically meaningful benefits, but is associated with infrequent or rare risks of serious harmful effects. Implementing the Risk Management Plan can keep these

risks at a minimum. Only knowledgeable physicians will select the patients who lack therapeutic alternatives and for whom benefits of therapy outweigh risks. Physicians will educate their patients and both will attest that benefits and risks are understood and accepted. In addition, enhanced labeling, including a revised package insert and the mandated distribution of a Medication Guide with each prescription, together with a decreased pill count in unit-of-use dispensing, will facilitate communication and follow-up. Additional communication initiatives will educate prescribers and patients alike to allow them to make an informed decision on how to better manage IBS. New clinical and epidemiology studies and the prompt review of spontaneous safety reports will better define and further improve the management of these risks. In conclusion, the clinically meaningful new data support a favorable benefit-risk assessment of alosetron to allow market reintroduction for women with diarrhea-predominant IBS who have failed conventional therapy.

Attachment I: Epidemiology Studies

EPIDEMIOLOGY STUDIES

As part of its Phase IV commitments, GlaxoSmithKline initiated epidemiologic studies in different populations designed to describe the epidemiology of colonic ischemia (ischemic colitis; IC), complications of constipation requiring hospitalization and bowel surgery in a period of time before the availability of alosetron. In addition, GSK studied the utilization of LOTRONEX and the incidence of colon ischemia, complications of constipation requiring hospitalization and bowel surgery in the UnitedHealthcare Research Database. These studies are the first population-based research of the incidence and risk factors for these gastrointestinal outcomes.

Data from these studies have been provided to the FDA. A listing of the epidemiologic studies is provided below:

- **EPI-40060 Phase I.** The Occurrence of Colonic Ischemia, Complications of Constipation, and Non-Specific Colitis in Relation to Irritable Bowel Syndrome in the UnitedHealthcare Research Database. Outcomes studied: Colonic ischemia, complications of constipation requiring hospitalization, non-specific colitis.
- **EPI-40060 Phase II.** The Occurrence of Colonic Ischemia, Complications of Constipation and Bowel Surgery in Relation to Irritable Bowel Syndrome in the UnitedHealthcare Research Database. Outcomes studied: Colonic ischemia, complications of constipation requiring hospitalization and bowel surgery.
- **EPI-40060.** Predictors of Colonic Ischemia: A Case-Control Study. Outcome studied: Colonic Ischemia
- **EPI-40060.** Predictors of Complications of Constipation Requiring Hospitalization: A Case-Control Study. Outcomes studied: Complications of constipation requiring hospitalization.
- **EPI-40060.** Utilization Patterns of LOTRONEX Users
- **EPI-40060.** The Occurrence of Colonic Ischemia, Complications of Constipation and Bowel Surgery in Relation to LOTRONEX Use
- **EPI-40063.** A Descriptive Study of Ischemic Colitis in the General Practice Research Database: A Feasibility Study. Outcome studied: Ischemic colitis.
- **EPI-40109 Part A.** Retrospective Cohort Study of Vascular Insufficiency of the Intestine and Ischemic Colitis in the General Practice Research Database (GPRD). Outcomes studied: Vascular insufficiency of the intestine and ischemic colitis.
- **EPI-40109 Part B.** Nested Case-Control Study of Ischemic Colitis in the General Practice Research Database (GPRD). Outcome studied: Ischemic colitis.

- **EPI-40107**. Incidence, Outcomes, and Risk Factors for Ischemic Colitis in Olmsted County, Minnesota, 1976-1998. Outcome studied: Ischemic colitis.
- **EPI-40110**. An Epidemiological Study of the Association between Drug Use, Constipation and Other Clinical Risk Factors and the Risk of Developing Fecal Impaction, Intestinal Obstruction, Intestinal Perforation, Ileus or Megacolon in the General Practice Research Database (GPRD). Outcome studied: Complications of constipation.
- **A Retrospective Review of Ischemic Colitis Diagnosed in Gastroenterology and Internal Medicine Practices (GSK Document Number RM2000/00426/00)**.

Methods Overview

GSK conducted studies in the UnitedHealthcare Research Database, the General Practice Research Database and in Olmsted County, Minnesota. Study designs included retrospective cohort studies to evaluate the incidence of disease and nested case control studies to evaluate risk factors. The studies utilized, as a starting point, automated databases and used ICD-9 (US), HICDA (US/Mayo) or Oxford Medical Information Systems (OXMIS) (UK) codes to identify diagnoses of interest.

In Phase I of EPI-40060 GSK utilized ICD-9 codes in the claims data to identify cases of IBS, colon ischemia and complications of constipation. In Phase II of this study the investigators corrected for several potential artifacts in the risk estimates observed in Phase I. In Phase II, definitional algorithms for IBS, colonic ischemia, and complications of constipation were developed using medical records in conjunction with claims. Through abstraction and cross validation, investigators identified the constellation of diagnoses, procedures and drugs in the claims that most accurately identified patients with each of these conditions. Next, the revised definitions were applied to the entire study population in order to refine the data presented in Phase I. In Phase II, the investigators also categorized the time interval between the IBS diagnosis and the outcomes into four intervals to provide more detail about the temporal relationships between IBS and the outcomes of interest. Patients with diagnoses such as ulcerative colitis and Crohn's disease were analyzed separately in Phase II.

In study EPI-40107 of ischemic colitis, the Mayo Medical Center (MMC) diagnostic classification system was used to identify cases of ischemic colitis. This classification system is based on HICDA codes which are a hospital-based modification of ICD-9 codes. Cases were identified by a specific HICDA code for ischemic colitis. Chart abstraction is in progress for this study.

In the UK database studies of ischemic colitis, vascular insufficiency of the intestine and complications of constipation (EPI-40063, EPI-400109, EPI 40110) GSK examined

ischemic colitis utilizing a specific OXMIS code. In addition, GSK examined the codes included under vascular insufficiency of the intestine and codes that were specific for complications of constipation.

In all of the studies, computerized data have been supplemented with additional chart abstraction, review by gastroenterology consultants and, in EPI-40060, definitional algorithms. Not all studies have been completed; the following summary provides findings available to date.

GSK also conducted a retrospective chart review (Glaxo Wellcome Document Number RM2000/00426/00) in 14 US-based Gastroenterology and Internal Medicine practices to determine the occurrence of a diagnosis of IC and to evaluate the signs, symptoms, patient characteristics, diagnostic procedures and clinical course of IC in these settings. The final study report for this study was previously submitted to NDA 21,107 on October 23, 2000.

Results: Epidemiology of Colon Ischemia, Complications of Constipation and Bowel Surgery

A summary of the epidemiologic studies and data available to date is provided below.

EPI-40060 Phase I: The Occurrence of Colonic Ischemia, Complications of Constipation and Non-Specific Colitis in Relation to Irritable Bowel Syndrome in the UnitedHealthcare Research Database. (Report submitted July 2001)

Objective: The objective of this study was to calculate the age and gender specific incidence rates of colonic ischemia, complications of constipation requiring hospitalization and non-specific colitis among people with and without IBS in a time period before the introduction of LOTRONEX. Phase I relied solely on claims data.

Study Population: The population was comprised of over 5 million members of the UnitedHealthcare managed care organization between January of 1995 and December 1999. All study subjects were required to have at least six months of continuous enrollment. As there is no unique ICD-9 code for ischemic colitis, the code for vascular insufficiency of the intestine was used to capture cases of colonic ischemia.

Key Results:

Colonic Ischemia: The incidence increased with female gender and age. After adjusting for the confounding effects of age, gender and calendar year, an IBS visit in the previous six months was the strongest predictor of this outcome, accounting for an 8-fold increase

in risk. Among those hospitalized, the incidence increased with female gender and age. After adjusting for the confounding effects of age, gender and calendar year, an IBS visit in the previous six months was the strongest predictor accounting for a 7-fold increase in risk for this outcome.

Complication of constipation requiring hospitalization: The incidence of complications of constipation increased with female gender and age. After adjusting for the confounding effects of age, gender, and calendar year, an IBS visit in the previous six months was the strongest predictor of complications of constipation, accounting for about a 7-fold increase in risk.

Non-specific colitis: The incidence of this event was the highest among all the outcomes studied. The incidence varied by age, with the younger age group at an increased risk. After adjusting for the confounding effects of age, gender, and calendar year, an IBS visit in the previous six months was the strongest predictor in this outcome, accounting for approximately a 7-fold increase in risk.

Conclusions: In this study of over 5 million UnitedHealthcare members, a prior visit for IBS was associated with a statistically significant elevation of 7-8 fold for colonic ischemia, complications of constipation and non-specific colitis. These data rely solely on the claims data from the UHC Research Database.

EPI-40060 Phase II: The Occurrence of Colonic Ischemia, Complications of Constipation and Bowel Surgery in Relation to Irritable Bowel Syndrome in the UnitedHealthcare Research Database. (Report submitted in the sNDA; Revised Report submitted February 2002)

Objective: The objective of this study was to calculate the age and gender specific incidence rates of colonic ischemia, complications of constipation requiring hospitalization and bowel surgery among people with and without IBS using claims-based algorithms in a time period before the introduction of LOTRONEX.

Study Population: The population was comprised of over 5 million members of the UnitedHealthcare managed care organization between January of 1995 and December 1999. All study subjects were required to have at least six months of continuous enrollment. Case definitions for colonic ischemia and complications of constipation were defined for claims data by identifying subjects who carried these diagnoses, abstracting a sample of medical records, and comparing the claims patterns to the results of the abstraction.

Key Results:

Colonic ischemia: The incidence rate of colonic ischemia increased with age. There was a 3-4 -fold increase in risk for colonic ischemia among patients with IBS relative to those in the non-IBS group.

Complications of constipation requiring hospitalization: The incidence increased with female gender and age. The risk associated with IBS ranged from a 2.8 – 4.4 - fold increased risk of complications of constipation among the IBS group compared to the non-IBS group.

Bowel Surgery: The incidence of bowel surgery was higher in females except those patients excluded from analyses due to other conditions. The incidence varied by age, with the older age group at an increased risk. The risk associated with IBS ranged from 2.5-5.0- fold risk increase in risk compared to the non-IBS group.

Conclusions: This study expanded on Phase I and corrected for several potential artifacts in the risk estimates observed in Phase I. A diagnosis of IBS was associated with substantial elevations in risk for each of the outcomes evaluated.

EPI-40060. Predictors of Colonic Ischemia: A Case-Control Study. Outcome studied: Colonic Ischemia (Report submitted to the sNDA; Revised Report submitted February 2002)

Objective: Using a large medical claims database, GSK conducted retrospective case control study with the objective of identifying the demographic, clinical, and health care utilization predictors of colonic ischemia.

Study Population: The source population was the fundamentally the same as EPI-40060 Phases I and II.

Key Results: The risk for colonic ischemia increased with age. A preceding diagnosis of IBS marks a risk of colonic ischemia approximately 2.75-fold above that of persons who have not received this diagnosis in the past. Use of drugs to treat diarrhea and drugs with constipation as a side effect were associated with a diagnosis of colonic ischemia. Non-specific colitis heralds an increased risk, although it was prevalent in only two percent of the cases. A visit to a gastroenterologist in the 6 months prior to the outcome is associated with increased risk.

Conclusions: Clinically evident colonic ischemia arises preferentially in patients with prior abdominal symptoms and attendant medical care. IBS is the most prominent among these and a preceding diagnosis of IBS conferred a significant risk of colonic ischemia compared to those without IBS. Drugs that reduce bowel motility, whether as a primary effect or as a side effect are associated with the outcome.

EPI-40060. Predictors of Complications of Constipation Requiring Hospitalization: A Case Control Study. Outcome studied: Complications of constipation requiring hospitalization. (Report submitted in the sNDA; Revised Report submitted February 2002)

Objective: Using a large medical claims database, GSK conducted a retrospective case control study with the objective of identifying the demographic, clinical, and health care utilization predictors of complications of constipation requiring hospitalization.

Study Population: The source population was the fundamentally the same as Phases I and II.

Key Results: Patients with a first hospitalization for complications of constipation were almost 2.8 times more likely to have had a prior diagnosis of IBS than controls. Cases were almost seven times more likely to have a diagnosis that disqualified them from the study. A diagnosis of diverticular disease was also moderately associated with the outcome. The use of drugs that induce constipation had been used by 25 percent of cases. Patients who had used these drugs were 4.7 times more likely to have complications of constipation.

Conclusions: The predictors of complications of constipation appear to be, in large part, predictors of complication itself. Several gastrointestinal diagnoses, including IBS, were associated with substantially increased risk. The use of drugs that cause constipation was prevalent and may account for a significant fraction of the complications of constipation requiring hospitalization.

EPI-40063: A Descriptive Study of Ischemic Colitis in the General Practice Research Database: A Feasibility Study (Report submitted in the sNDA)

Objective: The objective of this pilot study was to obtain population-based estimates of IC and to assess the association between IBS with IC in females in the GPRD. GSK also sought to determine the extent to which cases of IC might be missed in the study of a specific code for IC. This pilot study was conducted by GSK.

Study Population: The study population consisted of female patients in the GPRD between 1990-1997 with a recorded diagnosis of IC in their medical history. A specific code for ischemic colitis is available in the GPRD and was utilized to identify cases.

Results: A total of 128 female patients had a diagnosis of IC during the study period. The majority of cases (76%) were aged 70 or older. The incidence rate of IC among females of all ages was 1.3 per 100,000 person-years and there was a positive relationship with age, reaching an incidence rate of 10.2 per 100,000 person-years in patients aged 80+.

Of the 128 patients with an IC diagnosis, 11 female patients had a diagnosis of IC and IBS; 7 of these patients had the IC diagnosis following the IBS diagnosis. The age-specific IC incidence rates in the IBS cohort were approximately twice that of those in the total female population and showed a ten-fold increase in patients aged 80 and over. A review of cases coded with less specific codes did not uncover additional cases of IC. The data suggest that records of abdominal pain, rectal bleeding and non-specific colitis in the absence of a diagnosis of IC do not provide a sufficient basis to suspect an IC event. The results suggest that patients in the GPRD who have records of these events but who do not have a recorded diagnosis of IC are unlikely to have had an ischemic colitis event.

Conclusions: The occurrence of IC increased with increasing age and was higher in patients following an IBS diagnosis. The number of cases with IBS however, was small. GPRD records of abdominal pain and rectal bleeding and non-specific colitis in the absence of an IC diagnosis do not provide a sufficient basis to suspect a possible IC event.

EPI-40109 Part A: Retrospective Cohort Study of Vascular Insufficiency of the Intestine and Ischemic Colitis in the General Practice Research Database (GPRD). (Report submitted in the sNDA)

Objective: The objective of this study was to calculate the incidence of ischemic colitis and vascular insufficiency of the intestine in males and females in the GPRD. This study was conducted by the Boston Collaborative Drug Surveillance Program and expanded on the pilot study initiated by GSK (EPI-40063).

Study Population: The study population was comprised of patients over the age of 35 in the GPRD between 1988 to 1998. Patients had at least two years of recorded information in the computerized database for this study.

Results: Preliminary data indicate that the rate of IC among patients over age 35 was 2.0 per 100,000 (95% CI 1.7-2.5). The total rate for vascular insufficiency of the intestine for all ages was 5.0 per 100,000 (95% 4.3-5.6).

EPI-40109 Part B: Nested Case Control Study of Ischemic Colitis in the General Practice Research Database (GPRD). (Report Submitted in the sNDA)

Objective: The objective of this study was to study the risk factors for ischemic colitis in the GPRD. This case control study was nested within the retrospective cohort described above. The study was conducted by the Boston Collaborative Drug Surveillance Program.

Study Population: The study population was comprised of cases of ischemic colitis who had at least two years of recorded information in the computer prior to the diagnosis of ischemic colitis and their matched controls in the GPRD between 1988 to 1998.

Results: The data suggest that history of cardiovascular disease, NSAID use, gastrointestinal disease, history of abdominal surgery, and current smoking were risk factors for IC in both males and females. Among women use of HRT was as a possible risk factor for IC. These data suggest that patients having any of these risk factors are at around a two-fold increased risk for developing IC.

Conclusions: These preliminary data suggest that history of cardiovascular disease, NSAID use, history of abdominal surgery, history of gastrointestinal disease and current smoking are possible risk factors for IC. Among women, use of HRT was a possible risk factor for IC. These data suggest that patients having of these risk factors are at approximately a two-fold increased risk for developing IC. Chart abstraction is in progress for this study.

EPI-40107: Incidence, Outcomes, and Risk Factors for Ischemic Colitis in Olmsted County, Minnesota, 1976-1998. (Report submitted in the sNDA)

Objective: The objective of the first phase of the study is estimate the incidence and describe the clinical characteristics of cases of ischemic colitis in Olmsted County, Minnesota. The objective of the second phase of the study is to evaluate the risk factors for ischemic colitis.

Study Population: The project utilizes the resources of the Rochester Epidemiology Project, a medical record linked diagnostic index. The Mayo Medical Center (MMC) diagnostic classification system is based on HICDA codes which are a hospital-based modification of ICD-9 codes.

Results: A total of 152 cases with the HICDA code for ischemic colitis have been identified. To date, 133 records have been reviewed; 88% (117) were determined to be definite or probable cases of ischemic colitis. Sixty-three percent of the cases were female. The median age at diagnosis is 72; 12 cases were diagnosed at the age of 50 or younger. Using a number of assumptions a very rough estimate and probably minimal estimate of the incidence of IC is 6.2 cases per 100,000 person years.

Conclusions: This is the first study of ischemic colitis in Olmsted County, Minnesota. A very crude estimate of the incidence of IC based on the data available to date is 6.2 cases per 100,000 person-years which is comparable to the incidence of Crohn's disease in Olmsted County. Chart abstraction for this study is underway.

A Retrospective Review of Ischemic Colitis Diagnosed in Gastroenterology and Internal Medicine Practices (GSK Document Number RM2000/00426/00). (Report submitted Oct 2000).

Objectives: The objectives of this study were to describe the occurrence of a diagnosis of IC in a population seeking healthcare in Gastroenterology and Internal Medicine settings and to evaluate symptoms, signs, patient characteristics, diagnostic procedures and clinical courses for IC.

Study Population: The records of 584,944 patients were electronically searched; 1006 patient records were manually reviewed. Patient records must have been coded with one of the ICD-9 codes usually used by the sites for IC and have final documentation of a final diagnosis of IC in the chart within the studied time periods.

Results: A total of 854 ischemic colitis events in 815 patients were identified. More of the IC patients were female and there was a wide age range (18-98, median 69). Nearly 90% of patients were 50 years old or greater. The symptoms and signs of IC were compatible with those described in the literature. Greater than 99% of the patients had a diagnostic procedure performed to confirm the diagnosis of IC. Colonoscopy and flexible sigmoidoscopy were most commonly performed. Tissue biopsy supported the diagnosis of IC in the majority of events. The majority of events resolved without sequelae. IBS was present in the history of seven percent of patients; thirteen percent of

the IBS patients experienced IC events that were preceded by constipation. In the majority of IBS patients, the IC was self-limiting and resolved without sequelae.

Conclusions: In the 14 practices studied, the diagnosis of ischemic colitis was made by colonoscopy and flexible sigmoidoscopy; not just by clinical signs and symptoms. The majority of cases of ischemic colitis in IBS patients were self-limiting and resolved without sequelae.

EPI-40110: An Epidemiologic Study of the Association between Drug Use, Constipation and Other Clinical Risk Factors and the Risk of Developing Fecal Impaction, Intestinal Obstruction, Intestinal Perforation, Ileus or Megacolon in the General Practice Research Database (GPRD). (Report submitted in the sNDA)

Objective: To assess incidence rates of fecal impaction, intestinal obstruction, intestinal perforation, ileus or megacolon in the general population and to explore the association between exposure to various drugs, a history of constipation and other risk factors and the risk of developing a first-time diagnosis of one of these various gastrointestinal outcomes.

Study Population: This was a population-based observational study in the GPRD. Within the general population in patients 18-80 years of age GSK identified all patients with a first time diagnosis of the outcomes of interest. GSK conducted a cohort analysis to assess incidence rates of the outcomes and a case control analysis to study the relationship of exposure to selected medications, constipation and other clinical risk factors and the risk of developing one of these outcomes.

Results: Preliminary data indicate that among 1 million patients there were 595 cases with a first-time diagnosis of an outcome of interest. The highest incidence rate was observed for intestinal obstruction (IR 1.74 [95%CI 1.58-1.92]/10,000 person-years), the lowest for megacolon (IR 0.02 [95% CI 0.01-0.04]/10,000 person-years. In the case control analyses, current exposure to anticholinergic, antipsychotic or antidepressive drugs with associated with an increased risk for developing most of the outcomes. A history of constipation was associated with an increased risk of fecal impaction, intestinal obstruction or ileus. Various intestinal diseases were strongly associated with the risk of developing fecal impaction, intestinal obstruction or intestinal perforation.

Conclusions: In this observational study, preliminary data indicate that various medications, constipation and a history of some gastrointestinal or cardiovascular diagnoses were associated with a substantially increased risk of developing the gastrointestinal outcomes of interest. Some of the risk factors may overlap to some

degree and therefore residual confounding may limit the precision of the estimates. However, this study may help to define the role of clinical risk factors in the etiology of the gastrointestinal outcomes of interest and to identify patients who are at particularly high risk for developing such outcomes. Chart abstraction is ongoing in this study.

EPI-40060: Utilization Patterns of LOTRONEX (Report submitted in the sNDA)

GlaxoSmithKline undertook a study of utilization patterns using the UnitedHealthcare database. This studied patients receiving LOTRONEX between March and December 2000.

Objectives: The objectives of this study were the following:

1. Characterize the demographics of LOTRONEX users by age, gender and geographic location
2. Characterize the medical history based on medical service claims in the six months prior to receiving LOTRONEX with a focus on GI conditions
3. Characterize the frequency of visits to gastroenterologists in the six month period before the first use of LOTRONEX
4. Characterize the prescription drug dispensings in the six month period before the first LOTRONEX dispensing

Study Population: GSK identified all LOTRONEX users in 23 health plans from 18 states between March 2000 and November 2000 in the UHC Research Database. Among these patients, GSK further identified patients who had six months of continuous eligibility in the health plan. These patients were considered eligible for the study.

Key Results by Objective:

Objective 1: GSK identified 2,823 eligible patients. Eighty-six percent were female and the majority of patients were between the ages of 31-60 with a median age of 45 years. LOTRONEX was most frequently prescribed by gastroenterologists and family practitioners.

Objective 2: Forty-nine percent of the female LOTRONEX users and 39% of the male LOTRONEX users had a diagnosis of irritable colon in the six months prior to the dispensing of LOTRONEX. The most commonly performed GI related outpatient procedure in the six months prior to receiving LOTRONEX were fecal occult blood tests and colonoscopy.

Objective 3: Thirty-eight percent of female patients and 31% of males were seen by a gastroenterologist in the 3 month period immediately prior to the initiation of LOTRONEX. Over 90% of female patients and over 80% of male patients were seen at least once by a health care provider in the three months prior to the initiation of LOTRONEX.

Objective 4: Five out of the top fifteen drug dispensings in the six-month period prior to the initiation of LOTRONEX were for treatment of the symptoms related to the gastrointestinal system. In the six months prior to the initiation of LOTRONEX, 38% of females and 28% of males filled a prescription for a drug that may induce constipation as a side effect of the drug.

Conclusion: This study describes and characterizes the healthcare utilization and medical history of 2,823 patients dispensed LOTRONEX between March and November 2000. The data are based on medical claims in the six months prior to the initiation of LOTRONEX with a special focus on gastrointestinal conditions. This is the first study to describe the use of LOTRONEX in the post-marketing setting.

EPI-40060 The Occurrence of Colonic Ischemia, Serious Complications of Constipation and Bowel Surgery in Relation to LOTRONEX Use (Report submitted in March 2002)

Objectives: The objectives of this study were to determine the incidence of colonic ischemia, complications of constipation requiring hospitalization and bowel surgery among person who used LOTRONEX from March – December 2000. These outcomes were measured in a demographically similar cohort of patients with IBS but no use of LOTRONEX. The originally planned study was to include 10,000 LOTRONEX users and a like number of comparison subjects. With the withdrawl of LOTRONEX, the cohort sizes were reduced.

Study Population: Members of UHC in 25 health plans during the period September 1, 1999 to December 31, 2000. Two cohorts were identified 1) LOTRONEX users and 2) patients with an IBS diagnosis that were not dispensed LOTRONEX.

Results: The cohort sizes were limited to 3,631 LOTRONEX users and 2,480 comparison subjects. No cases of colonic ischemia were identified among LOTRONEX users or among comparison subjects with any LOTRONEX use. The incidence rate for complications of constipation among LOTRONEX users did not differ significantly from

that of IBS patients with no LOTRONEX use. There were no significant differences in the incidence rates of bowel surgery between the two cohorts.

Conclusions: Within the statistical limitations resulting from the small sample size, LOTRONEX users did not appear to differ from IBS patients not using LOTRONEX in the incidence of complications of constipation or bowel surgery. No cases of colon ischemia occurred in either cohort. Nonetheless an estimate for the incidence of colonic ischemia in LOTRONEX users can be obtained from the upper bound of the exact confidence interval for the one-sample Poisson rate parameter based on no cases having been observed in 1,617 patient years of data, which is 2.28 cases per 1,000 patient years.

Attachment II: Complications of Constipation

**Clinical Summary Information for Cases Involving Complications of Constipation
(Part 1)**

Study #	Subject #	Case ID ^a	Age	Sex	Weight (kg)	Dose (mg)	Regimen	Time to Onset (days)	Duration (days)	Chief Complaint	Complication
S3BB3002	2330	B0065267A	45	F	51	1	BID	10	14	Recurrent lower abdominal pain	Ileal stenosis Ileus
S3BB3002	3773	B0068255A	54	F	66.5	1	BID	7	7	Abdominal pain Constipation	Fecal impaction
S3BA3002	6585	A0059467A	31	F	65.5	Placebo	BID	14	42	Severe diarrhea Vomiting Abdominal pain	Partial bowel obstruction
S3B30006	23647	B0071141A	71	F	58	Placebo	BID	105	4	Abdominal pain Vomiting	Ileus
S3B30011	34911	A0111425A	67	F	94.5	Placebo	BID	60	3	Severe lower abdominal cramps Nausea Chills	Ileus
S3B30020	65385	A0128045A	77	F	55.1	1	BID	120	11	Nausea, Vomiting Abdominal cramps Bloating Constipation	Partial small bowel obstruction
S3B30020	67694	A0119204A	56	F	58.7	1	BID	27	14	Severe abdominal cramping Peri-umbilical abdominal pain which progressed to the lower	Obstruction Secondary ischemic colitis Toxic megacolon

**Clinical Summary Information for Cases Involving Complications of Constipation
(Part 1)**

Study #	Subject #	Case ID ^a	Age	Sex	Weight (kg)	Dose (mg)	Regimen	Time to Onset (days)	Duration (days)	Chief Complaint	Complication
										abdominal quadrants Nausea Vomiting	
S3B30020	80655	A0127276A	26	F	185.7	1	BID	120	56	Cramping lower abdominal pain	Colitis Fecal impaction
S3B30020	83206	A0122409A	48	F	unk	1	BID	71	3	Left-sided abdominal pain	Obstipation
S3B30020	87373	A0123385A	67	F	112.1	1	BID	91	4	Abdominal pain Vomiting, Dehydration Diarrhea	Small bowel ileus
S3B30025	176167	B0087180A	56	F	62.3	1	BID	56	4	Flu-like symptoms Vomiting Nausea Abdominal cramps Shaking	Bowel obstruction

^a Case ID number is available only if the case met the regulatory criteria for a serious adverse experience.

**Clinical Summary Information for Cases Involving Complications of Constipation
(Part 2)**

Study #	Subject #	Case ID^a	Concomitant Medications	Co-morbid Conditions	Radiological Examinations	Treatment	Outcome
S3BB3002	2330	B0065267A	None	Crohn's disease diagnosed at time of event by laparotomy 4 yr hx of abd pain	Abdominal sonography suggested Crohn's disease and suspected stenosis in the terminal ileus	Unknown	Resolved
S3BB3002	3773	B0068255A	None	Hx of hospitalization for constipation and disimpaction	None recorded	Metamizole Enema Manual disimpaction	Resolved
S3BA3002	6585	A0059467A	TRIPHASIL	endometrioma	CT scan – non-conclusive, possible adhesions. Small bowel follow-through - partial small bowel obstruction.	Unknown	Resolved
S3B30006	23647	B0071141A	hydroxyzine lspaghula	Adhesions close to the terminal ileum diagnosed by laparotomy	X-ray – subileus Barium meal showed no passage through the terminal ileum	Unknown	Resolved

**Clinical Summary Information for Cases Involving Complications of Constipation
(Part 2)**

Study #	Subject #	Case ID^a	Concomitant Medications	Co-morbid Conditions	Radiological Examinations	Treatment	Outcome
S3B30011	34911	A0111425A	multivitamin fluoxetine aspirin	Diverticulosis	Abd x-ray – “small colon paralyzed”	IV antibiotic	Resolved
S3B30020	65385	A0128045A	calcium paroxetine	Coronary artery disease Diverticular disease Hemorrhoids	KUB showed increase stool in rectum and rectosigmoid; air fluid levels in the small bowel, but no evidence of significant obstruction Abd film showed partial small bowel obstruction	Clear liquid diet Enemas	Resolved
S3B30020	67694	A0119204A	tolterodine PREMPRO trazodone citalopram tramadol LOTREL rofecoxib	Hypertension Hx of: Peptic ulcer disease Abdominal surgery	CT scan – nonspecific transmural thickening of a loop of small bowel as well as left colon	Total colectomy with Brook ileostomy	Resolved after complicated post-surgical course

**Clinical Summary Information for Cases Involving Complications of Constipation
(Part 2)**

Study #	Subject #	Case ID ^a	Concomitant Medications	Co-morbid Conditions	Radiological Examinations	Treatment	Outcome
S3B30020	80655	A0127276A	ortho-tricyclen LOTREL docusate sennosides	Hypertension Morbid obesity	Barium enema - 13 x 5 cm mass in mid descending colon probably feces that had been in the colon for several months	Colonoscopic removal of large hard fecal mass	Resolved f/u colon'y revealed small polyps in the rectum and cecum in addition to previously noted arterio- venous mal- formation
S3B30020	83206	A0122409A	Vicoden Percocet Vicoprofen	Personality disorder Somatization disorder	CT Scan – normal except colon full of stool	Enema x 2 Golytely Miralax	Resolved
S3B30020	87373	A0123385A	conjugated estrogens quinapril salmeterol loperamide fexofenadine verapamil doxazosin nisoldipin omperazole atorvastatin citalopram albuterol	Acute gastro- enteritis Hypertension Hiatal hernia Polyps	Abdominal series showed mild small bowel ileus and mild hepatomegaly	IV fluids Interruption of alosetron therapy	Resolved restarted study drug after event resolved and reported no further problems
S3B30025	176167	B0087180A	conjugated estrogen	Unknown	Abd x-ray revealed severe intestinal distention and subocclusion	IV fluids pethidine codeine dicyclomine dimenhydrinate	Resolved

^a Case ID number is available only if the case met the regulatory criteria for a serious adverse experience.

Attachment III: Ischemic Colitis

**Clinical Summary Information for Cases of Ischemic Colitis
(Part 1)**

Study #	Subject #	Case ID ^a	Age (yrs)	Sex	Weight (kg)	Dose (mg)	Regimen	Time to Onset (days)	Duration (days)
S3BA2001	2829	A0045146A	33	F	75.5	2	BID	2	75
S3BA3002	7195	A0063673A	48	F	88.2	1	BID	21	9
S3BA3003	8245	Non-serious	26	F	59.1	PLC	BID	299	11
S3BA3001	15687	A0070339A	41	F	79.0	1	BID	54	60
S3B30013	32451	A0128636A	54	F	84.5	1	BID	3	12
S3B30011	34069	A0104382A	61	F	62.3	1	BID	8	7
S3B20023	40398	Non-serious	41	M	97.3	0.5	BID	97	53
S3B30012	49203	Non-serious	31	F	130	1	BID	27	67
S3B30020	63223	A0118885A	55	F	72.7	1	BID	77	7
S3B30020	66556	A0130093A	75	F	88.6	1	BID	150	7
S3B30020	69433	Non-serious	37	F	54.5	1	BID	112	5
S3B30020	71843	Non-serious	37	F	100.9	1	BID	77	3
S3B30020	72823	A0119211A	64	F	66.3	1	BID	1	6
S3B30020	72824	A0119203A	57	F	63.2	1	BID	4	7
S3B30020	78134	A0117919A	20	F	60.9	1	BID	3	4
S3B30020	80357	A0125056A	51	F	82.7	1	BID	21	21
S3B30020	82125	A0124705A	61	F	81.6	1	BID	7	14
S3B30031	182603	Non-serious	64	F	75.0	1	BID	30	31

a Case ID number is available only if the case met the regulatory criteria for a serious adverse experience.

**Clinical Summary Information for Cases of Ischemic Colitis
(Part 2)**

Study #	Subject #	Case ID ^a	Pre-Tx Exam	Diagnosis Clinical/ Colon/ Biopsy	Segment of Bowel	Chief Complaint	Concomitant Medications	Co-morbid Conditions
S3BA2001	2829	A0045146A	colon 1994	clinical, colonoscopy and biopsy	40–80 cm	Cramping abdominal pain Diarrhea Hemoccult positive stool	Estradiol patch Famotidine TUMS	Smoker Hx of: Cholecystectomy Hysterectomy
S3B3002	7195	A0063673A	colon 1996	clinical, colonoscopy and biopsy	30-60 cm	Severe abdominal cramping Rectal bleeding Nausea Vomiting	Captopril Nifedipine Indapamide Potassium Fluoxetine	Hypertension Depression Hx of: PUD Pulmonary emboli Cushing's disease
S3BA3003	8245	Non-serious	colon 1995	flexible sigmoidoscopy and biopsy	Not reported	Abdominal pain Bloody diarrhea	ORTHO-NOVUM Fexofenadine	Not recorded
S3BA3001	15687	A0070339A	colon 1994	clinical, colonoscopy and biopsy	Midtransverse to proximal sigmoid colon	Abdominal pain Rectal bleeding	NSAID 3-4 gms/day Fluoxetine	Not recorded
S3B30013	32451	A0128636A	colon 2000	clinical, flexible sigmoidoscopy, and biopsy	Sigmoid colon	Abdominal discomfort and cramping, rectal bleeding, bloody diarrhea, nausea and vomiting	Aspirin multivitamin	Diverticulosis Hemorrhoids

**Clinical Summary Information for Cases of Ischemic Colitis
(Part 2)**

Study #	Subject #	Case ID ^a	Pre-Tx Exam	Diagnosis Clinical/ Colon/ Biopsy	Segment of Bowel	Chief Complaint	Concomitant Medications	Co-morbid Conditions
S3B30011	34069	A0104382A	colon 1998	clinical, colonoscopy and biopsy	Descending to mid-transverse colon	Severe abdominal pain	Amitriptyline Raloxifene Multivitamin	Osteoarthritis Anemia Restless leg syndrome
S3B20023	40398	Non-serious	colon 1999	biopsy	Mucosa appeared normal; biopsies obtained from transverse and rectosigmoid colon	Rectal bleeding	Atorvastatin Acetaminophen	Hyperlipidemia Colon polyps Hemorrhoids
S3B30012	49203	Non-serious	none	colonoscopy, biopsy	unknown	constipation with bleeding on straining	Vitamin E Hydrochloro-thiazide metoprolol lisinopril omeprazole ibuprofen Phazyme alprazolam lansoprazole	Obesity Hypertension Anxiety GERD

**Clinical Summary Information for Cases of Ischemic Colitis
(Part 2)**

Study #	Subject #	Case ID ^a	Pre-Tx Exam	Diagnosis Clinical/ Colon/ Biopsy	Segment of Bowel	Chief Complaint	Concomitant Medications	Co-morbid Conditions
S3B30020	63223	A0118885A	flex sig 1998	clinical and flexible sigmoidoscopy	Distal descending colon to proximal sigmoid colon	Severe, crampy, lower abdominal pain with rectal bleeding and diarrhea	Premarin Loperamide	Hx of: Depression Fundoplication Lactose intolerance Hysterectomy Microscopic colitis
S3B30020	66556	A0130093A	colon 2000	clinical, colonoscopy and biopsy	Proximal sigmoid with most severe changes mid-descending and distal descending colon	Severe lower abdominal pain Nausea Vomiting Rectal bleeding Fever Chills Bloody diarrhea	Ramipril Verapamil Alprazolam Ibuprofen Alendronate Fiorinal Multivitamin Acetaminophen Psyllium husk	Hx of: Diverticulosis Internal hemorrhoids
S3B30020	69433	Non-serious	sig- mido- scopy 1998	clinical, colonoscopy and biopsy	Left colon	Crampy abdominal pain Bloody diarrhea	Alprazolam Minocycline	Asthmatic bronchitis Ovarian cyst Arthritis Depression Anxiety

**Clinical Summary Information for Cases of Ischemic Colitis
(Part 2)**

Study #	Subject #	Case ID ^a	Pre-Tx Exam	Diagnosis Clinical/ Colon/ Biopsy	Segment of Bowel	Chief Complaint	Concomitant Medications	Co-morbid Conditions
S3B30020	71843	Non-serious	colon 1996	clinical, colonoscopy and biopsy	Splenic flexure and mid-descending colon	Abdominal cramping Bloody diarrhea	Paroxetine Loperamide	Anxiety
S3B30020	72823	A0119211A	colon 1998	clinical, colonoscopy and biopsy	Proximal to the splenic flexure	constipation followed by cramping abdominal pain and bloody diarrhea	Estradiol Prasterone Thyroxine Zolpidem Lansoprazole Alprazolam	Gastric reflux Diverticulosis Hypothyroidism Hx of smoking
S3B30020	72824	A0119203A	colon 2000	clinical colonoscopy and biopsy	Descending and sigmoid colon	Abdominal cramps Diarrhea Rectal bleeding	Lansoprazole Atenolol Premarin Clonazepam	Severe reflux Family hx of colon cancer
S3B30020	78134	A0117919A	flex sig 1997	clinical, colonoscopy and biopsy	Splenic flexure and descending colon	Nausea Vomiting Severe Abdominal pain Rectal bleeding	NOREDETTE	Smoker (1/2 pack/day) Hx of kidney stones
S3B30020	80357	A0125056A	colon 1999	clinical and colonoscopy	Sigmoid colon	Abdominal pain Constipation	Famotidine Hyoscyamine Progesterone DONNATOL Alprazolam ESGIC	Hx of diverticulosis

**Clinical Summary Information for Cases of Ischemic Colitis
(Part 2)**

Study #	Subject #	Case ID ^a	Pre-Tx Exam	Diagnosis Clinical/ Colon/ Biopsy	Segment of Bowel	Chief Complaint	Concomitant Medications	Co-morbid Conditions
S3B30020	82125	A0124705A	flex sig 1998	clinical, colonoscopy and biopsy	Descending and distal transverse colon	Abdominal cramping Bloody diarrhea Nausea Vomiting	PREMARIN Benazepril	Hypertension Hx of diarrhea with NSAID use
S3B30031	182603	Non-serious	colon 2000	clinical, colonoscopy and biopsy	Splenic flexure	Left lower quadrant pain Recurrent rectal bleeding	Ibuprofen Chlordiazepoxide Nitro spray	Angina Smoker Osteoarthritis

a Case ID number is available only if the case met the regulatory criteria for a serious adverse experience.

**Clinical Summary Information for Cases of Ischemic Colitis
(Part 3)**

Study #	Subject #	Case ID ^a	Labs	Radiological Examinations	Endoscopic Examinations	Histological Findings
S3BA2001	2829	A0045146A	stool negative for: salmonella, shigella, <i>E. coli</i> 0157 campylobacter, <i>C. difficile</i> ova & parasite	KUB – questionable thickening within descending colon Abd CT scan – minimal thickening of the colon at the splenic flexure	Colonoscopy - mucosal erythema, edema, and scattered erosions at 40- 80cm. A 2 nd colon performed 2 days later revealed submucosal hemorrhage and edema at 30-60cm	Local path - 1st-not consistent with diagnostic features of ischemic-mediated mucosal damage. 2nd-no definitive evidence of active colitis or ischemic mediated mucosal damage External path – no evidence of ischemic colitis
S3B3002	7195	A0063673A	WBC: 17,500 Stool culture negative for: <i>C. difficile</i> salmonella shigella campylobacter <i>E. coli</i> 0157	None reported	Colonoscopy - mucosal sloughing, ulceration, and inflammation from 30-60 cm	Local path- consistent with ischemic colitis External path – suggestive of infectious etiology <i>E. coli</i> O157 positive
S3BA3003	8245	Non-serious	None reported	None reported	Flexible sigmoidoscopy- possible ischemic colitis	lamina propria congestion and edema, not diagnostic of ischemia
S3BA3001	15687	A0070339A	WBC: 10,300 Hgb: 11.2 Hct: 33 LFT: normal	Abnormal X-ray – mild ileus, mild distension of colon, no dilated small bowel loops	Colonoscopy - severe segmental colitis from midtransverse to proximal sigmoid colon with multiple shallow irregular ulceration skip areas consistent with ischemic colitis or Crohn's disease	Local path - most consistent with ischemic colitis; necrosis that was superficial and inflammatory; destruction of superficial crypts with normal architecture of the deeper crypts; no granulomas External path – infectious colitis most likely

**Clinical Summary Information for Cases of Ischemic Colitis
(Part 3)**

Study #	Subject #	Case ID ^a	Labs	Radiological Examinations	Endoscopic Examinations	Histological Findings
S3B30013	32451	A0128636A	None reported	None reported	Flexible sigmoidoscopy – sigmoid diverticulosis, focal patchy areas of inflammation. No frank ulceration or tumor. Overall, fairly mild in appearance and is nonspecific	Focal ischemic changes
S3B30011	34069	A0104382A	WBC: 19,700 Hgb: 15.5 Stool culture negative for: ova and parasite <i>C. difficile</i> Protein C deficiency	CT-“mural thickening” of “entire transverse and descending colon, as well as the distal ascending colon at the hepatic flexure”	Colonoscopy – midtransverse and descending colon patchy areas of erythema/edema	ischemic colitis
S3B20023	40398	Non-serious	None reported	None reported	Colonoscopy -performed 56 days after event was normal	focal fibrosis, consistent with a hx of ischemic colitis and focal mild active colitis
S3B30012	49203	Non-serious	None reported	None reported	Colonoscopy – Non-specific colitis and/or ischemic colitis	Non-specific colitis and/or ischemic colitis
S3B30020	63223	A0118885A	stool culture neg for salmonella shigella campylobacter <i>E. coli</i> 0157 thrombosis panel normal	Abdominal X-ray – normal	Flexible sigmoidoscopy – ulceration, inflammation in proximal sigmoid colon	Local path - no features of ischemia External path – non-specific, perhaps early ischemic injury, but not diagnostic <i>E. coli</i> O157 - neg

**Clinical Summary Information for Cases of Ischemic Colitis
(Part 3)**

Study #	Subject #	Case ID ^a	Labs	Radiological Examinations	Endoscopic Examinations	Histological Findings
S3B30020	66556	A0130093A	Thrombosis panel normal	None reported	Colonoscopy - extensive edema, multiple areas of ulceration with exudate/hemorrhagic appearance and few spots of bluish discoloration	mucosa with ischemic changes including submucosal hemorrhage and acute and chronic inflammation
S3B30020	69433	Non-serious	Stool culture negative for: Salmonella Shigella Staphylococcus Yeast <i>E. coli</i> 0157 Coagulation panel normal	None reported	Colonoscopy - patchy areas of submucosal punctate hemorrhage, superficial ulceration in the left colon	Possible ischemia
S3B30020	71843	Non-serious	WBC: 10,300 Hgb: 14.8 Hct: 43.2	None reported	Colonoscopy -segmental colitis with patchy erythema, erosions, and edema of the splenic flexure and mid-descending colon	nonspecific mild abnormalities suggestive of ischemic colitis; very mild and focal acute inflammation with focal superficial erosion and minimal focal glandular attenuation
S3B30020	72823	A0119211A	thrombosis panel normal	None reported	Flexible sigmoidoscopy – large amount of blood visible in the sigmoid colon (could not complete exam due to pain) Colonoscopy - ischemic colitis proximal to the splenic flexure and scattered nonspecific colitis	Local path -ulcerated and inflamed colorectal mucosa suggestive of ischemic changes, however, the histological features were not absolutely specific for ischemic colitis External path – suggestive of ischemic pattern of injury

**Clinical Summary Information for Cases of Ischemic Colitis
(Part 3)**

Study #	Subject #	Case ID ^a	Labs	Radiological Examinations	Endoscopic Examinations	Histological Findings
S3B30020	72824	A0119203A	stool culture neg for: salmonella shigella campylobacter <i>C. difficile</i> ova & parasite thrombosis panel normal	None reported	Colonoscopy -non-specific colitis in the descending and sigmoid colon	Local path - Inflammation and degenerative changes consistent with ischemic colitis External path – compatible with ischemic pattern of injury
S3B30020	78134	A0117919A	stool culture neg for: salmonella, shigella, campylo- bacter <i>E. coli</i> 0157	Abdominal X-ray – normal	Colonoscopy - erythema with loss of vasculature and a few shallow ulcerations in the descending colon and splenic flexure	atrophic colonic mucosa with mild acute and chronic inflammation and fibrosis of the lamina propria consistent with ischemic colitis
S3B30020	80357	A0125056A	Serum chemistry – normal	None reported	Colonoscopy - multiple diverticula present in the sigmoid colon, evidence of edema, erythema, and ulcerations in the sigmoid colon consistent with diverticulitis or ischemic colitis	not done
S3B30020	82125	A0124705A	stool negative for: salmonella, shigella, campylo-bacter ova & parasite coagulation panel normal	CT-moderate thickening of the proximal two-thirds of the descending colon extending to above the splenic flexure, ascending colon	Colonoscopy - severe ulcerations, erythema, and friable tissue of descending and distal transverse colon consistent with ischemic colitis	fibrinopurulent exudate, epithelial debris, coagulative necrosis, and bacteria colonization; histological features most consistent with pseudomembranous colitis, however ischemic colitis was not ruled out

**Clinical Summary Information for Cases of Ischemic Colitis
(Part 3)**

Study #	Subject #	Case ID^a	Labs	Radiological Examinations	Endoscopic Examinations	Histological Findings
S3B30031	182603	Non-serious	stool culture negative for: salmonella, shigella, campylobacter, <i>E. coli</i> 0157 Coagulation panel normal	Abdominal x-ray unchanged from 1996	Colonoscopy - patchy colitis of an acute nature with a dusky appearance in various areas in the bowel and acute hemorrhagic appearance at the 45-60cm level; classic appearance in the water shed zone for acute ischemic colitis	acute ischemic colitis

a Case ID number is available only if the case met the regulatory criteria for a serious adverse experience.

**Clinical Summary Information for Cases of Ischemic Colitis
(Part 4)**

Study #	Subject #	Case ID ^a	Hospitalized; Duration (days)	F/U	Evidence of Hypercoagulable state
S3BA2001	2829	A0045146A	Y (5)	2.5 months later, pt. reported all symptoms had resolved after initiation of treatment with acidophillus tablets	Not evaluated
S3B30020	7195	A0063673A	Y (1)	Unknown	Hx of pulmonary embolus following pelvic fracture
S3BA3003	8245	Non-serious	N	Unknown	Not evaluated
S3BA3001	15687	A0070339A	Y (3)	2 months later, colonoscopy normal	Not evaluated
S3B30013	32451	A0128636A	N	unknown	Not evaluated
S3B30011	34069	A0104382A	Y (7)	Unknown	Low Protein C level; R calf DVT, 8 days after hospital discharge
S3B20023	40398	Non-serious	N	Unknown	Not evaluated
S3B30012	49203	Non-serious	N	unknown	Not evaluated
S3B30020	63223	A0118885A	Y (3)	Unknown	Thrombosis panel normal
S3B30020	66556	A0130093A	Y	Unknown	Thrombosis panel normal
S3B30020	69433	Non-serious	N	Unknown	
S3B30020	71843	Non-serious	N	Unknown	Thrombosis panel normal
S3B30020	72823	A0119211A	N	Unknown	Thrombosis panel normal
S3B30020	72824	A0119203A	N	Unknown	Thrombosis panel normal
S3B30020	78134	A0117919A	Y (3)	Unknown	Not evaluated
S3B30020	80357	A0125056A	Y	Unknown	Not evaluated
S3B30020	82125	A0124705A	Y (3)	Unknown	Coagulation panel normal
S3B30031	182603	Non-serious	N	Unknown	Coagulation panel normal

a Case ID number is available only if the case met the regulatory criteria for a serious adverse experience.

III. RISK MANAGEMENT PLAN

In this section GSK describes the framework for a proposed Risk Management Plan (RMP) for LOTRONEX®(alosetron hydrochloride) Tablets that is intended to provide the benefits of the drug to appropriate and informed patients while risks are appropriately managed; striking a balance between the need to mitigate the risk of infrequent but serious adverse events and the need to make the drug available without placing extraordinary burdens on patients and prescribers.

The RMP is a comprehensive program consisting of several interrelated elements:

- Revisions to the product labeling and Medication Guide. Changes feature a black box warning that concisely provides the most important prescribing information including a restriction of use to appropriate prescribers and patients for whom the benefit:risk profile is most favorable (women with diarrhea predominant irritable bowel syndrome who have failed to respond to conventional therapy).
- Implementation of a mandatory Patient-Physician Agreement document to ensure patient counseling by the prescriber regarding the benefits and risks of LOTRONEX.
- Recommendations for a lower initial dose.
- Modified packaging: 30 count bottle in a carton with Medication Guide affixed to the bottle. The proposed modifications are intended to correlate with the lower starting dose, facilitate more frequent physician-patient interaction, and facilitate delivery of important information via the Medication Guide.
- Communication of the RMP to health care providers.
- A double-check at the pharmacy level that the prescription was written in accordance with the RMP.
- Program evaluation to include collection of patient data and prescriber information to monitor implementation of the risk interventions in a real-world.
- Additional clinical research intended to obtain data that might facilitate greater optimization of use.
- Completion of population-based studies of the incidence and risk factors for ischemic colitis and complications of constipation and Phase IV studies to examine the occurrence of these events in LOTRONEX users as well as the utilization of LOTRONEX.

- Enhancements to GSK product surveillance activities.

1. OBJECTIVES OF THE GSK RMP FOR LOTRONEX

The goal of the 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. The RMP has been designed to help ensure that LOTRONEX is prescribed only to appropriate, informed patients and to specifically address the risk issues of complications of constipation and ischemic colitis.

Serious complications of constipation represent a rare but potentially avoidable risk. Severe outcomes may be mitigated by careful monitoring of signs and symptoms and timely intervention. Ischemic colitis is a serious, idiosyncratic event that has been associated with LOTRONEX. While ischemic colitis presents a risk for a small number of patients, severe outcomes may be mitigated by careful monitoring of signs and symptoms, by timely intervention and by providing information to patients and prescribers.

In recognition that some of the most serious post-marketing adverse event reports have been associated with inappropriate use of LOTRONEX or occurred in patients who did not receive prompt medical attention, the RMP includes elements intended to enhance appropriate patient selection and education of health care providers and patients. Under the proposed plan, access to LOTRONEX would be restricted under the provisions of 21 CFR 314 Subpart H. The RMP will restrict prescribing to only physicians knowledgeable and experienced in the diagnosis of IBS and diagnosis and management of ischemic colitis and complications of constipation. The key elements of the RMP components will be described within the boxed Warning section of the revised product labeling. In an attempt to minimize the risk of certain serious events, an initial lower starting dose will be implemented.

Physician and patient knowledge will be enhanced with modified labeling including a Medication Guide, a mandatory patient/physician agreement document, health care provider education, and modified packaging. Pharmacists will be instructed not to dispense initial LOTRONEX prescriptions without the required sticker. The sticker is affixed to the prescription by the prescriber and is intended as a real-time check for compliance with the elements of the RMP.

To measure the effectiveness of the RMP, GSK's outcome assessments will include patient based monitoring (conducted by Slone Epidemiology Unit of Boston University School of Medicine) and safety and utilization studies in the United Healthcare Database.

Additional clinical research activities will focus on optimal product use and epidemiology studies will seek to quantify the occurrence of ischemic colitis and complications of constipation in LOTRONEX users and evaluate risk factors for those events.

2. POPULATION FOR WHOM BENEFITS OUTWEIGH RISKS

In view of the possible risks that have been reported in association with treatment with LOTRONEX, GSK proposes to modify product use by restricting treatment to those patients who have exhausted other treatment options. Irritable bowel syndrome can be severely debilitating in some patients. Important new data further demonstrate the benefit of LOTRONEX in these patients. Restricting use under 21 CFR 314 Subpart H to only those patients for whom there is no reasonable therapeutic alternative raises the threshold for acceptance of possible risks.

Under the proposed program, patient restrictions would include the following:

- Indicated for women with diarrhea-predominant IBS who have failed traditional therapy;
- Patients would be educated about benefits and risks of LOTRONEX by the prescriber and would be required to review and sign a patient-physician agreement document (based on the content of the FDA approved Medication Guide) confirming delivery and their understanding of the key messages;
- The most important safety messages are reinforced by a FDA approved Medication Guide that Pharmacists are required by Federal law to provide at the time of dispensing;
- The dispensing of Medication Guides at the pharmacy level will be facilitated by introduction of new packaging.

3. APPROPRIATE PRESCRIBERS

The proposed RMP includes measures intended to restrict prescribing of LOTRONEX to only appropriate physicians who take appropriate, documented steps to counsel the patient. Restrictions under the proposed program are described below.

- The product labeling (boxed warning) will specify that prescribing is restricted to only physicians knowledgeable and experienced in the diagnosis and treatment of IBS and able to diagnose and manage ischemic colitis and complications of constipation.
- Physicians must sign an attestation statement located on the patient-physician agreement document confirming appropriate knowledge/experience.
- Physicians must counsel patients on benefits-risks and key safety monitoring issues.

- Physicians must obtain confirmation of patient education via signed patient-physician agreement.
- Physicians must provide a copy of the agreement document to the patient and place a copy in the patient's medical record.
- New prescriptions must be conveyed in writing only. Physicians must affix a special sticker to the written prescription to provide notice to pharmacists that the prescription was written in accordance with the RMP plan.
- Given the history of product withdrawal and intense media attention focusing on the safety profile of the drug, prescribers are expected to be highly motivated to comply with the provisions of the RMP.

4. MODIFIED LABELING

Package Insert and Medication Guide

GlaxoSmithKline is proposing labeling changes that describe a restricted use program under 21 CFR 314.520. The changes proposed for the package insert and the Medication Guide reflect changes made following receipt of the Agency's input. The proposed Package Insert with Medication Guide and Patient/Physician Agreement Documents are provided in **Attachments 1 and 2**.

The key elements of the proposed labeling changes are as follows:

- A Black Box Warning has been prominently placed at the beginning of the package insert (PI). At FDA's suggestion, this boxed warning has been drafted in a manner intended to concisely convey the most important prescribing information.
- The Indication section has been modified to reflect that LOTRONEX should be used only in women with Diarrhea Predominant Irritable Bowel Syndrome (D-IBS) who have failed to respond to conventional therapy (i.e. second line therapy) and who have signed the Patient-Physician Agreement.
- The labeling has been modified to include a warning regarding use in elderly and/or debilitated patients.
- The Warnings section includes language reflecting additional safety information received since the labeling was approved in August 2000. Specific changes include:
 - Rewording of the Warning section further emphasizes the most important safety information;
 - Enhanced directions to monitor for constipation;

- Information about the incidence of serious complications of constipation in clinical trials;
 - Telephone numbers have been added for GSK and FDA to facilitate prescriber reports of adverse events;
 - A warning has been added regarding use of concomitant medications that can cause constipation.
- The Information for Patients section has been enhanced to add detail regarding the patient counseling and agreement process.
 - The Dosage and Administration section has been modified to include a 4-week low-dose initial treatment period (1 mg daily), to help identify patients, who may be susceptible to constipating effects of LOTRONEX. If a patient tolerates this dose and responds positively, the patient will remain on the low dose. If the patient tolerates this dose but does not achieve an adequate response, the dose will be increased to 1 mg BID. Based on anecdotal reports from marketing experience, it is expected that some individual patients might actually receive clinical benefit at the lower starting dose. Increasing the dose for these patients may not be desirable given possible risks that could be associated with a higher dose. Accordingly, the proposed labeling advises physicians to consider maintaining the low starting dose for individual patients if IBS symptoms are adequately controlled at the 1mg daily dose.
 - The Medication Guide has been modified to be consistent with the modified PI.

Patient-Physician Agreement

GSK is proposing a Patient-Physician Agreement document (**Attachment 2**) that will be a mandatory component of the RMP. FDA provided comments and suggested changes on the proposed Patient-Physician Agreement. The GSK proposed Patient-Physician Agreement is consistent with the recommendations of the Agency. As discussed previously, GSK proposes a combined Patient-Physician Agreement form, to include physician attestation, rather than a Patient-Physician Agreement and a separate document to provide physician attestation.

5. MODIFIED PACKAGING

The packaging configuration previously marketed for LOTRONEX Tablets, 1 mg, was a 60 tablets packed in a 50-cc blue HDPE bottle with a child-resistant closure.

GSK intends to pursue the following changes to this configuration as an intervention to improve safety by facilitate dispensing of the Medication Guide, limiting the amount of drug provided at any one time, and to facilitate physician/patient interaction:

- Unit-of-use dispensing with Medication Guide and bottle enclosed within a sealed carton;
- Change from 60 to 30 count bottle as soon as practicable.

The bottle was distributed, previously, without a carton and the package insert was affixed to the outside of the bottle with the Medication Guide behind the package insert. Extra copies of the Medication Guide were distributed to Pharmacists. In order to minimize the potential that LOTRONEX might be inadvertently dispensed without the Medication Guide, GSK proposes that the packaging be changed to a configuration consisting of a bottle and Medication Guide packaged within a carton to be dispensed as a unit-of use. The package insert would be affixed to the outside of the carton.

As mentioned above, the proposed changes to labeling include an initial trial period when patients will be directed to take 1 mg per day for 4 weeks rather than the currently approved dose of 1mg BID. Some patients who receive benefit may continue on this dose without increasing to the current recommended dose of 1 mg BID. Accordingly, GSK believes that a pack size of 30-count bottle is more appropriate for the primary package for distribution.

6. COMMUNICATION OF RISK

The communication of risk component of the RMP has been developed in recognition of the intense media attention regarding GlaxoSmithKline's withdrawal of the product and potential risks associated with treatment with LOTRONEX. The proposed plan provides the following primary features:

- Designed to help ensure LOTRONEX is prescribed only to appropriate, informed patients;
- GSK will provide substantial educational opportunities to health care providers (HCP);
- Involves Pharmacists as a real-time double check that the provisions of the program are being followed;
- Medical education to be promoted and posted on-line.

Specific elements of the communication component of the plan include the following

- Dear Healthcare Professional (HCP) Letter: Announces re-introduction via communication that includes a letter, new PI, new Medication Guide, and a sample copy of the new Patient /Physician Agreement form. Also included will be a sample of a prescription sticker. These stickers will be affixed to the prescription for LOTRONEX by the physician and will serve as notice to a pharmacist that the physician has written the prescription in accordance with the RMP. Pharmacists will be instructed in their communication materials not to dispense an initial prescription for LOTRONEX unless a sticker is affixed to the written prescription.
- Target audience will be pharmacies and appropriate HCPs:
- Re-Introduction Patient/Physician Agreement Kit: Contains a letter outlining the re-introduction program. The kit includes: new package insert, tear-off pad with 25 copies of the new Medication Guide, and second tear-off pad with 25 copies of the Patient/Physician Agreement Form along with prescription stickers outlined above. The kit will also include a list of product specific and IBS Disease Awareness materials list that HCPs can order for their patients.
- The kit will be available to HCPs who request it from 1-800 number, and a website. It will also be delivered by sales representatives to physicians believed to have been among the most frequent prescribers of the drug while it was previously marketed.
- Sales representative: will be trained on changes to the Package Insert/Medication Guide and on the introduction of the Patient/Physician Agreement Form and stickers.
- Product /IBS Disease Awareness: Product specific and IBS disease materials will be available via a GSK sales force.
- Package Insert/MedGuide/Patient-Physician Agreement Form with Stickers Formulary Kit-Managed Care.
- Product monograph on disk.
- Website: Includes downloadable Package Insert, Medication Guide and instructions on how to order Patient/Physician Agreement Forms and Stickers.
- Patient Education Brochure: How to use LOTRONEX as well as IBS information
- IBS/GI AGA Disease Materials.

7. DEFINITION OF RISK

Additional Clinical Trials

The RMP for LOTRONEX includes an integrated program of clinical and epidemiological research. Additional clinical trials to be conducted following reintroduction include studies involving exploration of different doses and alternative dose regimens that might avoid constipation associated with treatment with LOTRONEX. FDA has suggested that GSK conduct a study that would evaluate the benefit of LOTRONEX on a functional endpoint with a randomized withdrawal component.

Concept protocols for the following studies are intended to serve as the basis for further discussion with FDA prior to protocol finalization.

- A Twenty-four Week, Randomized, Double Blind, Placebo-Controlled, Crossover Study to Assess the Effect of Alosetron 1.0mg BID on Work/Main Activity Productivity in Female Subjects with Diarrhea-Predominant IBS (Concept protocol provided as **Attachment 3**).
- A 12-Week, Randomized, Double-blind, Placebo Controlled, Dose-titration, Study of Alosetron in Female Subjects with Diarrhea-Predominant Irritable Bowel Syndrome (Concept protocol provided as **Attachment 4**).
- A Twelve-Week, Randomized, Double-Blind, Placebo-Controlled Study to Compare Methods of Constipation Management in Female Diarrhea-Predominant Irritable Bowel Syndrome Subjects Treated with Open-Label Alosetron (Concept protocol provided as **Attachment 5**).
- A Twelve-Week, Randomized, Double Blind, Placebo-Controlled, Study to Assess the Safety and Efficacy of 0.5mg BID and 1mg QD of Alosetron in Female, Diarrhea-Predominant, IBS Subjects (Concept protocol provided as **Attachment 6**).

Epidemiologic Research

An extensive program of epidemiologic research is ongoing. These studies are being conducted as part of the Phase IV commitments agreed to at the time of approval of the original NDA. The studies included in this program are intended to generate population-based data to quantify the occurrence of ischemic colitis and complications of constipation in LOTRONEX users and to evaluate risk factors for those events. The studies fall into two categories: 1) studies specifically designed to evaluate ischemic colitis and severe constipation in populations including LOTRONEX users, and 2) studies designed to improve our understanding of the background incidence and risk factors for these events in the general IBS population.

8. PROGRAM EVALUATION

Two studies have been designed to evaluate program compliance via monitoring of utilization and patient-based monitoring.

LOTRONEX Utilization and Safety Studies – United Healthcare

Within the currently ongoing Phase IV study, all patients who receive LOTRONEX will be characterized by “appropriateness for LOTRONEX therapy.” The following data will be collected:

- Demography
- Relevant GI medical history in the six months prior to the first dispensing of LOTRONEX
- Whether care was provided by a gastroenterologist
- Frequency of visits to the gastroenterologist
- Prescription drug dispensing in the six months prior to LOTRONEX

A safety evaluation will also be conducted. For patients with selected serious adverse events, charts will be abstracted for additional information (concept protocol provided in **Attachment 7**).

Patient-Based Monitoring: Slone Epidemiology Unit (SEU) – Boston University School of Medicine Post Marketing Study of LOTRONEX

This is a prescription-based approach to the study of LOTRONEX in collaboration with the Slone Epidemiology Unit and a large national pharmacy chain. Within one week of being dispensed a prescription for LOTRONEX or an appropriate comparison drug, patients will be contacted and asked to participate in the study. The following information will be collected at baseline:

- Demography
- IBS history and severity
- Appropriateness for treatment with LOTRONEX
- Medications used prior to LOTRONEX
- Whether counseling was provided and Patient-Physician Agreement was signed

- Receipt of the Medication Guide

Safety data will be collected in a follow-up contact.

(Concept protocol for the study is provided in **Attachment 8**).

9. ENHANCEMENTS TO SAFETY MONITORING

- Following market reintroduction, GSK agrees to voluntarily expedite reporting of “targeted events.” A specific proposal regarding the procedures to be included as part of the RMP for LOTRONEX is provided as **Attachment 9**.
- GSK intends to utilize an Expert Review Board (ERB) to provide an independent, expert evaluation of the evolving safety data, should the product be reintroduced under a restricted use program. Under the proposed plan, the ERB would conduct periodic evaluations of new safety data from various sources and provide expert counsel to medical representatives of GSK. The ERB will be comprised of external gastrointestinal experts who will provide GSK with assessments regarding key safety issues including ischemic colitis, complications of constipation, and other gastrointestinal events.
- It will be important for GSK and FDA to establish a common understanding of the baseline safety data prior to implementation of the RMP interventions and reintroduction of LOTRONEX. GSK envisions that this will necessitate meetings to discuss the available safety data. Following reintroduction, regular meetings (e.g., quarterly) will be held between FDA and GSK to review the evolving safety information.

10. POST-MARKETING COMMITMENTS

The NDA for LOTRONEX (NDA 21-107) was approved on February 9, 2000. Included in the approval letter was a description of post-marketing commitments made by the company. Prior to its decision to withdraw LOTRONEX from the market, GSK made continued progress to complete each of the studies and provided status updates in the NDA Annual Report. Should LOTRONEX be reintroduced, GSK is prepared to comply with these prior commitments, if possible under the terms of the reintroduction. However, in view of the product withdrawal, GSK will need to reach agreement with the Agency on the time frame to complete any outstanding activities as well as any new requirements.

11. PROMOTIONAL ACTIVITIES

Any product specific promotional materials will be submitted to FDA for pre-approval. GlaxoSmithKline has no plans at this time to distribute patient starts (drug samples) or conduct a Direct to Consumer (DTC) campaign.

Risk Management Plan

Attachment 1

1 **PRODUCT INFORMATION**

2 **LOTRONEX[®]**

3 **(alose tron hydrochloride)**

4 **Tablets**

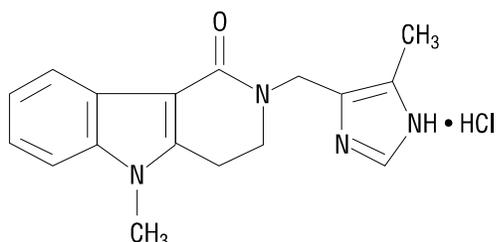
5
6
7 **WARNING:** Serious gastrointestinal events, some fatal, have been reported in association with
8 the use of LOTRONEX. These events, including ischemic colitis and serious complications of
9 constipation, have resulted in hospitalization, blood transfusion, and/or surgery.

- 10 • **Only physicians who are knowledgeable and experienced in the diagnosis and treatment of**
11 **irritable bowel syndrome (IBS), able to diagnose and manage ischemic colitis and**
12 **complications of constipation, and who have signed a Patient-Physician Agreement for**
13 **each patient, should prescribe LOTRONEX.**
- 14 • **LOTRONEX is indicated only for women with diarrhea-predominant IBS who have failed**
15 **to respond to conventional therapy. Before receiving an initial prescription for**
16 **LOTRONEX, the patient must read and understand the Medication Guide and must sign**
17 **the Patient-Physician Agreement (see PRECAUTIONS: Information for Patients).**
- 18 • **LOTRONEX should be discontinued immediately in patients who develop constipation or**
19 **symptoms of ischemic colitis. Physicians should instruct patients to immediately report**
20 **constipation or symptoms of ischemic colitis. LOTRONEX should not be resumed in**
21 **patients who develop ischemic colitis. Physicians should instruct patients who report**
22 **constipation to immediately contact them if the constipation does not resolve after**
23 **discontinuation of LOTRONEX. Patients with resolved constipation should resume**
24 **LOTRONEX only on the advice of their treating physician.**

25
26 **DESCRIPTION:** The active ingredient in LOTRONEX Tablets is alosetron hydrochloride (HCl), a
27 potent and selective antagonist of the serotonin 5-HT₃ receptor type. Chemically, alosetron is
28 designated as 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-
29 b]indol-1-one, monohydrochloride. Alosetron is achiral and has the empirical formula:

LOTRONEX[®] (alose tron hydrochloride) Tablets

30 C₁₇H₁₈N₄O•HCl, representing a molecular weight of 330.8. Alose tron is a white to beige solid that
31 has a solubility of 61 mg/mL in water, 42 mg/mL in 0.1M hydrochloric acid, 0.3 mg/mL in pH 6
32 phosphate buffer, and <0.1 mg/mL in pH 8 phosphate buffer. The chemical structure of alose tron is:



33
34 LOTRONEX Tablets for oral administration contain 1.124 mg alose tron HCl equivalent to 1 mg
35 of alose tron. Each tablet also contains the inactive ingredients lactose (anhydrous), magnesium
36 stearate, microcrystalline cellulose, and pregelatinized starch. The blue film-coat contains
37 hydroxypropyl methylcellulose, titanium dioxide, triacetin, and indigo carmine.

38 39 **CLINICAL PHARMACOLOGY:**

40 **Pharmacodynamics: Mechanism of Action:** Alose tron is a potent and selective 5-HT₃
41 receptor antagonist. 5-HT₃ receptors are nonselective cation channels that are extensively
42 distributed on enteric neurons in the human gastrointestinal tract, as well as other peripheral and
43 central locations. Activation of these channels and the resulting neuronal depolarization affect the
44 regulation of visceral pain, colonic transit and gastrointestinal secretions, processes that relate to the
45 pathophysiology of irritable bowel syndrome (IBS). 5-HT₃ receptor antagonists such as alose tron
46 inhibit activation of non-selective cation channels which results in the modulation of the enteric
47 nervous system.

48 The cause of IBS is unknown. IBS is characterized by visceral hypersensitivity and hyperactivity
49 of the gastrointestinal tract, which lead to abnormal sensations of pain and motor activity. Following
50 distention of the rectum, IBS patients exhibit pain and discomfort at lower volumes than healthy
51 volunteers. Following such distention, alose tron reduced pain and exaggerated motor responses,
52 possibly due to blockade of 5-HT₃ receptors.

LOTRONEX® (alosetron hydrochloride) Tablets

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

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

65 **Pharmacokinetics:** The pharmacokinetics of alosetron have been studied after single oral doses
66 ranging from 0.05 mg to 16 mg in healthy men. The pharmacokinetics of alosetron have also been
67 evaluated in healthy women and men and in patients with IBS after repeated oral doses ranging from
68 1 mg twice daily to 8 mg twice daily.

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

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

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

80 **Metabolism and Elimination:** Plasma concentrations of alosetron increase proportionately
81 with increasing single oral doses up to 8 mg and more than proportionately at a single oral dose of
82 16 mg. Twice-daily oral dosing of alosetron does not result in accumulation. The terminal

LOTRONEX® (alose tron hydrochloride) Tablets

83 elimination half-life of alose tron is approximately 1.5 hours (plasma clearance is approximately
84 600 mL/min). Population pharmacokinetic analysis in IBS patients confirmed that alose tron
85 clearance is minimally influenced by doses up to 8 mg.

86 Renal elimination of unchanged alose tron accounts for only 6% of the dose. Renal clearance is
87 approximately 94 mL/min.

88 Alose tron is extensively metabolized in humans. The biological activity of these metabolites is
89 unknown. A mass balance study was performed utilizing an orally administered dose of unlabeled
90 and ¹⁴C-labeled alose tron. This study indicates that on a molar basis, alose tron metabolites reach
91 additive peak plasma concentrations 9-fold greater than alose tron and that the additive metabolite
92 AUCs are 13-fold greater than alose tron's AUC. Plasma radioactivity declined with a half-life
93 2-fold longer than that of alose tron, indicating the presence of circulating metabolites.

94 Approximately 73% of the radiolabeled dose was recovered in urine with another 24% of the dose
95 recovered in feces. Only 7% of the dose was recovered as unchanged drug. At least 13 metabolites
96 have been detected in urine. The predominant product in urine was a 6-hydroxy metabolite (15% of
97 the dose). This metabolite was secondarily metabolized to a glucuronide that was also present in
98 urine (14% of the dose). Smaller amounts of the 6-hydroxy metabolite and the 6-O-glucuronide also
99 appear to be present in feces. A bis-oxidized dicarbonyl accounted for 14% of the dose and its
100 monocarbonyl precursor accounted for another 4% in urine and 6% in feces. No other urinary
101 metabolite accounted for more than 4% of the dose. Glucuronide or sulfate conjugates of unchanged
102 alose tron were not detected in urine.

103 In studies of Japanese men, an N-desmethyl metabolite was found circulating in plasma in all
104 subjects and accounted for up to 30% of the dose in one subject when alose tron was administered
105 with food. The clinical significance of this finding is unknown.

106 Alose tron is metabolized by human microsomal cytochrome P450 (CYP), shown in vitro to
107 involve enzymes 2C9 (30%), 3A4 (18%), and 1A2 (10%). Non-CYP mediated Phase I metabolic
108 conversion also contributes to an extent of about 11% (see PRECAUTIONS: Drug Interactions).

109 **Population Subgroups: Age:** In some studies in healthy men or women, plasma concentrations
110 were elevated by approximately 40% in individuals 65 years and older compared to young adults.
111 However, this effect was not consistently observed in men (see WARNINGS).

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112 **Gender:** Plasma concentrations are 30% to 50% lower and less variable in men compared to
113 women given the same oral dose. Population pharmacokinetic analysis in IBS patients confirmed
114 that alosetron concentrations were influenced by gender (27% lower in men).

115 **Reduced Hepatic Function:** No pharmacokinetic data are available in this patient group (see
116 PRECAUTIONS: Hepatic Insufficiency and DOSAGE AND ADMINISTRATION: Patients with
117 Hepatic Impairment).

118 **Reduced Renal Function:** Renal impairment (creatinine clearance 4 to 56 mL/min) has no
119 effect on the renal elimination of alosetron due to the minor contribution of this pathway to
120 elimination. The effect of renal impairment on metabolite kinetics and the effect of end-stage renal
121 disease have not been assessed (see DOSAGE AND ADMINISTRATION: Patients with Renal
122 Impairment).

123
124 **CLINICAL TRIALS:** Two 12-week treatment, multicenter, double-blind, placebo-controlled,
125 dose-ranging studies were conducted to determine the dosage of oral LOTRONEX for subsequent
126 evaluation in efficacy studies.

127 In women, of the doses studied, 1 mg of LOTRONEX twice daily was significantly more
128 effective than placebo in providing relief of IBS pain and discomfort, decreasing the proportion of
129 days with urgency, decreasing stool frequency, and producing firmer stools. Efficacy in men, as
130 assessed by producing adequate relief of IBS pain and discomfort, was not demonstrated at any dose
131 of LOTRONEX.

132 The efficacy and safety of 1 mg of oral LOTRONEX twice daily for 12 weeks was studied in 2
133 US multicenter, double-blind, placebo-controlled trials of identical design (Studies 1 and 2) in non-
134 constipated women with IBS meeting the Rome Criteria¹ for at least 6 months. For enrollment into
135 the studies, patients were required to meet entry pain and stool consistency criteria. An average pain
136 score of at least mild pain, as collected during a 2-week screening period, was required. Women
137 with severe pain were excluded. An entry stool consistency requirement was also incorporated to
138 target women whose predominant bowel symptom was diarrhea or in which diarrhea was a
139 prominent feature in their alternating pattern. Women with a history of severe constipation were
140 excluded. Men were not included in these studies.

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141 The primary efficacy measure in these studies was the woman's weekly assessment of adequate
142 relief of IBS pain and discomfort. Key secondary measures included percentage of days with
143 urgency and daily assessment of stool frequency and consistency. Study 1 enrolled 647 women
144 (71% diarrhea-predominant, 28% alternating between diarrhea and constipation, and 1%
145 constipation-predominant) while Study 2 enrolled 626 women (71% diarrhea-predominant, 27%
146 alternating between diarrhea and constipation, and 2% constipation-predominant). At entry into the
147 studies, most women reported mild to moderate pain intensity and stool consistency of formed to
148 loose.

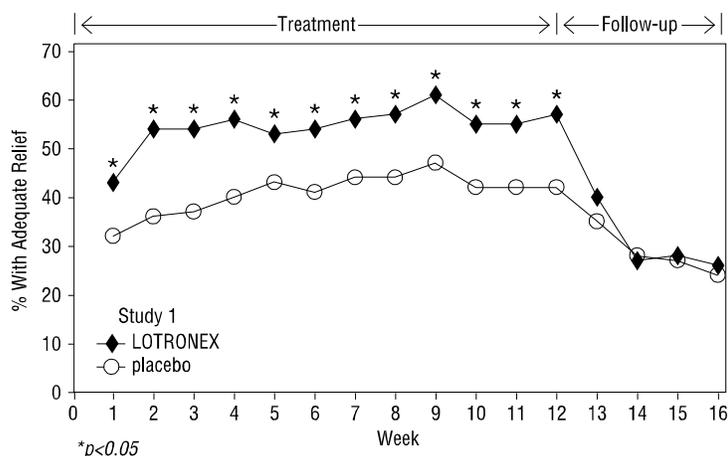
149 In both trials, LOTRONEX 1 mg administered twice daily was significantly more effective than
150 placebo in providing relief of IBS pain and discomfort.

151 In both Study 1 and Study 2, the beneficial effect on IBS pain and discomfort was demonstrated
152 only in women with diarrhea-predominant IBS. Data in Figures 1 and 2 are presented for this
153 subgroup. In Study 1, significantly more women reported relief of their abdominal pain and
154 discomfort within 1 week of starting alosecron therapy than those who received placebo (Figure 1).
155 In Study 2, this treatment effect was observed within 4 weeks (Figure 2). Once attained, significant
156 treatment effect persisted throughout the remainder of the treatment period. Upon discontinuing
157 LOTRONEX, symptoms returned. Within 1 week after discontinuing therapy, there was no
158 difference between placebo- and alosecron-treated women.

159

160 **Figure 1: Percentage of Women (Diarrhea-Predominant)**
161 **Reporting Relief of IBS Pain and Discomfort in Study 1**

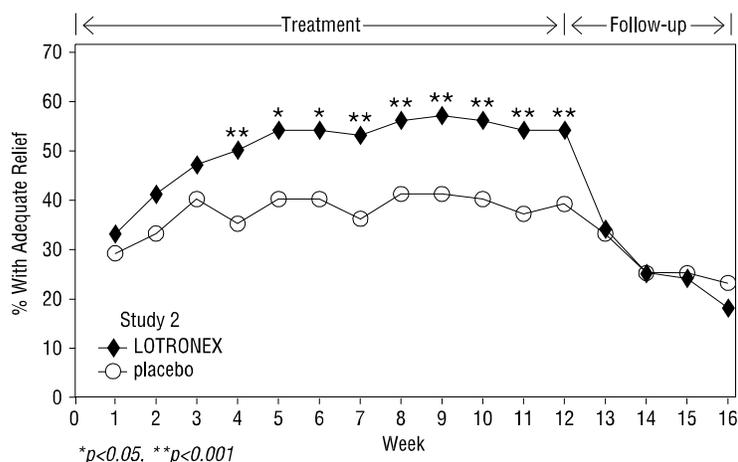
162



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



168
169

170 In each study, women who received LOTRONEX reported a significant decrease in the
171 percentage of days with urgency as compared to those who received placebo. Treatment with
172 LOTRONEX also resulted in firmer stools and a significant decrease in stool frequency. Significant
173 improvement of these symptoms occurred within the first week of treatment and persisted
174 throughout the 12 weeks of therapy. Upon discontinuance of treatment these symptoms returned.
175 Within 1 week after discontinuing therapy, there was no difference between placebo- and alosetron-
176 treated patients.

177

178 **INDICATIONS AND USAGE:** LOTRONEX is indicated only for women with diarrhea-
179 predominant irritable bowel syndrome (IBS) who have failed to respond to conventional therapy and
180 who have signed the Patient-Physician Agreement (see BOXED WARNING,
181 CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

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

184

185 **CONTRAINDICATIONS:**

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

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187 LOTRONEX is contraindicated in patients:

- 188 • With a history of chronic or severe constipation or with a history of sequelae from
189 constipation.
- 190 • With a history of intestinal obstruction, stricture, toxic megacolon, gastrointestinal
191 perforation, and/or adhesions.
- 192 • With a history of ischemic colitis or impaired intestinal circulation.
- 193 • With current or a history of Crohn's Disease or ulcerative colitis.
- 194 • With active diverticulitis or a history of diverticulitis.
- 195 • Who are unable to understand or comply with the Patient-Physician Agreement.
- 196 • With known hypersensitivity to any component of the product.

197

198 **WARNINGS:** (see **BOXED WARNING** and **DOSAGE AND ADMINISTRATION**)

199 Prescribers should report adverse events to GlaxoSmithKline at 1-888-825-5249 or to the
200 Food and Drug Administration MedWatch Program at 1-800-FDA-1088.

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

203 **Constipation:** Serious complications of constipation, including obstruction, perforation,
204 impaction, toxic megacolon, and secondary ischemia, have been reported in association with
205 administration of LOTRONEX. In some cases these complications have required intestinal
206 surgery, including colectomy. In clinical trials, the frequency of serious complications of
207 constipation was approximately 1 in 1500 patients. Clinical trial and postmarketing
208 experience suggest that patients who are elderly, debilitated, or taking additional medications
209 that decrease gastrointestinal motility, may be at greater risk for complications of
210 constipation.

211 **Ischemic Colitis:** Ischemic colitis has been reported in patients receiving LOTRONEX in
212 clinical trials as well as during marketed use of the drug. In clinical trials, the frequency of
213 ischemic colitis in women receiving LOTRONEX was approximately 1 in 700 patients.
214 Patients with a history of ischemic colitis should not take LOTRONEX.

215 LOTRONEX should be discontinued immediately in patients with signs of ischemic colitis
216 such as rectal bleeding, bloody diarrhea, or new or worsening abdominal pain. Because

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217 **ischemic colitis can be life-threatening, patients with signs or symptoms of ischemic colitis**
218 **should be evaluated promptly and have appropriate diagnostic testing performed. Treatment**
219 **with LOTRONEX should not be resumed in patients who develop ischemic colitis.**

220

221 **PRECAUTIONS:**

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

224 PHYSICIANS MUST:

- 225 • Counsel the patient about the potential risks and benefits of LOTRONEX given the patient's
226 response to other treatments and how much IBS symptoms interfere with the patient's life.
- 227 • Give the patient a copy of the Medication Guide, which outlines the potential risks and benefits of
228 LOTRONEX and instruct the patient to carefully read the Medication Guide. Answer all
229 questions the patient may have about LOTRONEX. The complete text of the Medication Guide
230 is printed at the end of this document.
- 231 • Review the Patient-Physician Agreement with the patient, answer all questions, and confirm that
232 the patient has signed the Agreement.
- 233 • Sign the Patient-Physician Agreement, give a copy of the signed Agreement to the patient, and
234 put the original in the patient's medical record.
- 235 • Provide each patient with appropriate instructions for taking LOTRONEX.

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

238 PATIENTS WHO ARE PRESCRIBED LOTRONEX SHOULD BE INSTRUCTED TO:

- 239 • Read the Medication Guide before starting LOTRONEX and each time they refill their
240 prescription.
- 241 • Not start taking LOTRONEX if they are constipated.
- 242 • Immediately discontinue LOTRONEX and contact their physician if they become constipated, or
243 have symptoms of ischemic colitis such as new or worsening abdominal pain, bloody diarrhea,
244 or blood in the stool. Immediately contact their physician again if their constipation does not
245 resolve after discontinuation of LOTRONEX. Resume LOTRONEX only if their constipation
246 has resolved and after discussion with and the agreement of their treating physician.

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- 247 • Stop taking LOTRONEX and contact their physician if LOTRONEX does not adequately
248 control IBS symptoms after 4 weeks of taking one tablet twice a day.

249 **Drug Interactions:** In vitro human liver microsome studies and an in vivo metabolic probe study
250 demonstrated that alosetron did not inhibit CYP enzymes 2D6, 3A4, 2C9, or 2C19. In vitro, at total
251 drug concentrations 27-fold higher than peak plasma concentrations observed with the 1-mg dosage,
252 alosetron inhibited CYP enzymes 1A2 (60%) and 2E1 (50%). In an in vivo metabolic probe study,
253 alosetron did not inhibit CYP2E1 but did produce 30% inhibition of both CYP1A2 and N-
254 acetyltransferase. Although not studied with alosetron, inhibition of N-acetyltransferase may have
255 clinically relevant consequences for drugs such as isoniazid, procainamide, and hydralazine. The
256 effect on CYP1A2 was explored further in a clinical interaction study with theophylline and no
257 effect on metabolism was observed. Another study showed that alosetron had no clinically
258 significant effect on plasma concentrations of the oral contraceptive agents ethinyl estradiol and
259 levonorgestrel (CYP3A4 substrates). A clinical interaction study was also conducted with alosetron
260 and the CYP3A4 substrate cisapride. No significant effects on cisapride metabolism or QT interval
261 were noted. The effect of alosetron on monoamine oxidases and on intestinal first pass secondary to
262 high intraluminal concentrations have not been examined. Based on the above data from in vitro and
263 in vivo studies, it is unlikely that alosetron will inhibit the hepatic metabolic clearance of drugs
264 metabolized by the major CYP enzyme 3A4, as well as the CYP enzymes 2D6, 2C9, 2C19, 2E1, or
265 1A2.

266 Alosetron does not appear to induce the major cytochrome P450 (CYP) drug metabolizing
267 enzyme 3A. Alosetron also does not appear to induce CYP enzymes 2E1 or 2C19. It is not known
268 whether alosetron might induce other enzymes.

269 Because alosetron is metabolized by a variety of hepatic CYP drug-metabolizing enzymes,
270 inducers or inhibitors of these enzymes may change the clearance of alosetron. The effect of
271 induction or inhibition of individual pathways on metabolite kinetics and pharmacodynamic
272 consequences has not been examined.

273 **Hepatic Insufficiency:** Due to the extensive hepatic metabolism and first pass metabolism of
274 alosetron and metabolites, increased exposure to alosetron is likely to occur in patients with hepatic
275 insufficiency.

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276 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** In 2-year oral studies, alosetron was
277 not carcinogenic in mice at doses up to 30 mg/kg/day or in rats at doses up to 40 mg/kg/day. These
278 doses are, respectively, about 60 to 160 times the recommended human dose of alosetron of
279 2 mg/day (1 mg twice daily) based on body surface area. Alosetron was not genotoxic in the Ames
280 tests, the mouse lymphoma cell (L5178Y/TK[±]) forward gene mutation test, the human lymphocyte
281 chromosome aberration test, the ex vivo rat hepatocyte unscheduled DNA synthesis (UDS) test, or
282 the in vivo rat micronucleus test for mutagenicity. Alosetron at oral doses up to 40 mg/kg/day (about
283 160 times the recommended daily human dose based on body surface area) was found to have no
284 effect on fertility and reproductive performance of male or female rats.

285 **Pregnancy: Teratogenic Effects:** Pregnancy Category B. Reproduction studies have been
286 performed in rats at doses up to 40 mg/kg/day (about 160 times the recommended human dose based
287 on body surface area) and rabbits at oral doses up to 30 mg/kg/day (about 240 times the
288 recommended daily human dose based on body surface area). These studies have revealed no
289 evidence of impaired fertility or harm to the fetus due to alosetron. There are, however, no adequate
290 and well-controlled studies in pregnant women. Because animal reproduction studies are not always
291 predictive of human response, LOTRONEX should be used during pregnancy only if clearly needed.

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

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

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

299
300 **ADVERSE REACTIONS:** Table 1 summarizes adverse events from 22 repeat-dose studies in
301 patients with IBS who were treated with 1 mg of LOTRONEX twice daily for 8 to 24 weeks. The
302 adverse events in Table 1 were reported in 1% or more of patients who received LOTRONEX and
303 occurred more frequently on LOTRONEX than on placebo. A statistically significant difference was
304 observed for constipation in patients treated with LOTRONEX compared to placebo (p<0.0001).

305
306

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

Body System Adverse Event	LOTRONEX 1 mg B.I.D. (n = 8328)	Placebo (n = 2363)
Gastrointestinal		
Constipation	29%	6%
Abdominal discomfort and pain	7%	4%
Nausea	6%	5%
Gastrointestinal discomfort and pain	5%	3%
Abdominal distention	2%	1%
Regurgitation and reflux	2%	2%
Hemorrhoids	2%	1%

307

308 **Gastrointestinal:** Constipation is a frequent and dose-related side effect of treatment with
309 LOTRONEX (see WARNINGS). In clinical studies (including 2 long-term studies not included in
310 Table 1 but discussed under “Long-Term Safety”), constipation was reported in approximately 29%
311 of IBS patients treated with LOTRONEX 1 mg twice daily (n = 9316). This effect was statistically
312 significant compared to placebo (p<0.0001). Eleven percent (11%) of patients treated with
313 LOTRONEX 1 mg twice daily withdrew from the studies due to constipation. Although the number
314 of IBS patients treated with LOTRONEX 0.5 mg twice daily is relatively small (n = 243), only 11%
315 of those patients reported constipation and 4% withdrew from clinical studies due to constipation.
316 Among the patients treated with LOTRONEX 1 mg twice daily who reported constipation, 75%
317 reported a single episode and most reports of constipation (70%) occurred during the first month of
318 treatment with the median time to first report of constipation onset of 8 days. Occurrences of
319 constipation in clinical trials were generally mild to moderate in intensity, transient in nature, and
320 resolved either spontaneously with continued treatment or with an interruption of treatment.
321 However, serious complications of constipation have been reported in clinical studies and in
322 postmarketing experience (see BOXED WARNING and WARNINGS). In Studies 1 and 2, 9% of
323 patients treated with LOTRONEX reported constipation and 4 consecutive days with no bowel

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324 movement (see CLINICAL TRIALS). Following interruption of treatment, 78% of the affected
325 patients resumed bowel movements within a 2-day period and were able to re-initiate treatment with
326 LOTRONEX.

327 **Hepatic:** A similar incidence in elevation of ALT (>2-fold) was seen in patients receiving
328 LOTRONEX or placebo (1.0% vs. 1.2%). A single case of hepatitis (elevated ALT, AST, alkaline
329 phosphatase, and bilirubin) without jaundice was reported in a 12-week study. A causal association
330 with LOTRONEX has not been established.

331 **Long-Term Safety:** The pattern and frequency of adverse events in 2 long-term, placebo-
332 controlled studies in which patients with IBS (n = 988) were treated with LOTRONEX 1 mg twice
333 daily for up to 12 months were essentially the same as observed in the 8- to 24-week clinical trials.
334 There were no reports of ischemic colitis or serious complications of constipation in the patients
335 treated with LOTRONEX in these 2 studies.

336 **Other Events Observed During Clinical Evaluation of LOTRONEX:** During its assessment
337 in clinical trials, multiple and single doses of LOTRONEX were administered resulting in 11,874
338 subject-exposures in 86 completed clinical studies. The conditions, dosages, and duration of
339 exposure to LOTRONEX varied between trials, and the studies included healthy male and female
340 volunteers as well as male and female patients with IBS and other indications.

341 In the listing that follows, reported adverse events were classified using a standardized coding
342 dictionary. Only those events that an investigator believed were possibly related to alosetron,
343 occurred in at least 2 patients, and occurred at a greater frequency during treatment with
344 LOTRONEX than during placebo administration are presented. Serious adverse events occurring in
345 at least 1 patient for which an investigator believed there was reasonable possibility that the event
346 was related to alosetron treatment and which occurred at a greater frequency in LOTRONEX than
347 placebo-treated patients are also presented.

348 In the following listing, events are categorized by body system. Within each body system, events
349 are presented in descending order of frequency. The following definitions are used: *Infrequent*
350 adverse events are those occurring on one or more occasion in 1/100 to 1/1000 patients; *Rare*
351 adverse events are those occurring on one or more occasion in fewer than 1/1000 patients.

352 Although the events reported occurred during treatment with LOTRONEX, they were not
353 necessarily caused by it.

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

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

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

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

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

363 **Eye: Rare:** Light sensitivity of eyes.

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

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

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

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

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

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

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

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

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

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

388 **Observed During Clinical Practice:** In addition to adverse events reported from clinical trials,
389 the following events have been identified during use of LOTRONEX in clinical practice and from
390 noncontrolled investigational use. Because they are reported voluntarily from a population of
391 unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion
392 due to a combination of their seriousness, frequency of reporting, or potential causal connection to
393 LOTRONEX.

394 **Gastrointestinal:** Constipation, ileus, impaction, obstruction, perforation, ulceration, ischemic
395 colitis (characterized by new or worsening abdominal pain, bloody diarrhea, or rectal bleeding) (see
396 WARNINGS).

397 **Neurological:** Headache.

398 **Skin:** Rash.

399

400 **DRUG ABUSE AND DEPENDENCE:** LOTRONEX has no known potential for abuse or
401 dependence.

402

403 **OVERDOSAGE:** There is no specific antidote for overdose of LOTRONEX. Patients should be
404 managed with appropriate supportive therapy. Individual oral doses as large as 16 mg have been
405 administered in clinical studies without significant adverse events. This dose is 8 times higher than
406 the recommended total daily dose. Inhibition of the metabolic elimination and reduced first pass of
407 other drugs might occur with overdoses of alosetron (see PRECAUTIONS: Drug Interactions).
408 Single oral doses of LOTRONEX at 15 mg/kg in female mice and 60 mg/kg in female rats (30 and
409 240 times, respectively, the recommended human dose based on body surface area) were lethal.
410 Symptoms of acute toxicity were labored respiration, subdued behavior, ataxia, tremors, and
411 convulsions.

412

413 **DOSAGE AND ADMINISTRATION:**

414 **Only physicians who are knowledgeable and experienced in the diagnosis and treatment of**
415 **irritable bowel syndrome (IBS), able to diagnose and manage ischemic colitis and**
416 **complications of constipation, and who have signed a Patient-Physician Agreement for each**
417 **patient should prescribe LOTRONEX.**

418
419 **Usual Dose in Adults:** LOTRONEX should be started at a dosage of 1 mg orally once a day for
420 4 weeks. This dosage may be less constipating than a regimen of 1 mg twice a day (see
421 WARNINGS). Although the efficacy of the 1 mg once a day dosage in treating diarrhea-
422 predominant IBS has not been evaluated in clinical trials, consideration should be given to
423 continuing this dosage if well tolerated and IBS symptoms in the individual patient are adequately
424 controlled. If, after 4 weeks, the 1 mg once a day dosage is well tolerated but does not adequately
425 control IBS symptoms, then the dosage can be increased to 1 mg twice a day, which was the dosage
426 shown to be effective in controlled clinical trials (see CLINICAL TRIALS).

427 LOTRONEX should be discontinued immediately in patients who develop constipation. If the
428 constipation resolves and the physician and patient agree to restart LOTRONEX, the dosage should
429 be individualized to meet the needs of the patient. Although not evaluated in clinical trials, reduction
430 of dosage or intermittent dosing can be considered as potential options to meet the needs of
431 individual patients (see WARNINGS, CONTRAINDICATIONS, and ADVERSE REACTIONS:
432 Gastrointestinal).

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

437 **LOTRONEX should be discontinued in patients who have not had adequate control of IBS**
438 **symptoms after four weeks of treatment with 1 mg twice a day.**

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

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

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

447 **Patients with Hepatic Impairment:** No studies have been conducted in patients with hepatic
448 impairment (see PRECAUTIONS: Hepatic Insufficiency and CLINICAL PHARMACOLOGY:
449 Population Subgroups: Reduced Hepatic Function).

450

451 LOTRONEX can be taken with or without food.

452

453 **HOW SUPPLIED:** LOTRONEX Tablets, 1 mg (1.124 mg alosetron HCl equivalent to 1 mg
454 alosetron), are blue, oval, film-coated tablets debossed with GX CT1 on one face in bottles of 60
455 (NDC 0173-0690-00) with child-resistant closures. [Note to FDA: This section will be revised
456 pending approval of a 30-count bottle.]

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

459

460 **REFERENCE:**

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

463



464

465 GlaxoSmithKline

466 Research Triangle Park, NC 27709

467

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470

471 (Date of issue)

RL-

472 **MEDICATION GUIDE**

473
474 **LOTRONEX[®] (LOW-trah-nex) Tablets**

475 **alosetron hydrochloride**

476
477 **Do not take LOTRONEX unless you understand its possible risks and benefits, have signed**
478 **the Patient-Physician Agreement your doctor will give you, and are willing and able to follow**
479 **the instructions in this Medication Guide.** Read this Medication Guide carefully before you sign
480 the Patient-Physician agreement and before you start to take LOTRONEX. Read the Medication
481 Guide you get with each refill for LOTRONEX. There may be new information. This information
482 does not take the place of talking with your doctor.

483
484 **What is the most important information I should know about LOTRONEX?**

- 485 • LOTRONEX is only for women who have irritable bowel syndrome (IBS) with diarrhea as their
486 main symptom and who have not been helped by other treatments. Women who have
487 constipation as their main IBS symptom should **not** use LOTRONEX. LOTRONEX has not
488 been shown to help men with IBS.
- 489 • **Some patients (about 1 in 1500) develop serious side effects of constipation. These may**
490 **result in hospitalization, blood transfusions, surgery, and rarely death. Because of this:**
- 491 • **Do not start taking LOTRONEX if you are constipated.**
 - 492 • **If you get constipated while taking LOTRONEX, stop taking it right away and call**
493 **your doctor.**
 - 494 • **If your constipation does not get better after you have stopped taking LOTRONEX,**
495 **call your doctor again.**
 - 496 • **Do not start taking LOTRONEX again until your doctor has told you to do so.**
- 497 • Some patients (about 1 in 700) develop ischemic colitis. This condition may require being
498 hospitalized, needing blood transfusions, or surgery. Because of this, **you must stop taking**
499 **LOTRONEX right away and call your doctor right away if you have any of these signs of**
500 **ischemic colitis:**
- 501 • **new or worsening abdominal (lower stomach area) pain**

LOTRONEX® (alosetron hydrochloride) Tablets

- 502 • **bloody diarrhea or blood in your stools (bowel movements)**
- 503 • Serious constipation or ischemic colitis can happen without warning. Older patients, or patients
504 who have other health problems or who take other medicines that may cause constipation, may
505 be more likely to have serious side effects of constipation. Before deciding if LOTRONEX is
506 right for you, be certain that you understand the possible benefits and risks of LOTRONEX for
507 you. You should discuss with your doctor how much your IBS symptoms interfere with your
508 life. You also should discuss other treatments you have tried for IBS and how well they worked,
509 as well as those you have not tried.
- 510 • Only doctors who know about IBS and the possible side effects of LOTRONEX should prescribe
511 LOTRONEX.
- 512 • You must sign a Patient-Physician Agreement after you have read this Medication Guide for the
513 first time and have fully discussed your situation with your doctor. Signing the Agreement
514 means that you understand the risks and benefits of LOTRONEX and that you are willing and
515 able to follow the instructions in this Medication Guide.

516

517 **What is LOTRONEX?**

518 LOTRONEX is a medicine that slows the movement of stools (bowel movements) through the large
519 intestine. LOTRONEX does not cure IBS and it will not help every person who takes it. For those
520 who are helped, LOTRONEX reduces lower abdominal (stomach area) pain, abdominal discomfort,
521 urgency (sudden need to have a bowel movement), and diarrhea of IBS. If you stop taking
522 LOTRONEX, your IBS symptoms may return within 1 or 2 weeks.

523

524 **Who should not take LOTRONEX?**

- 525 • **LOTRONEX is not right for everyone. Do not ever take LOTRONEX if you:**
 - 526 • are constipated most of the time or have ever had a serious problem from constipation.
 - 527 • have ever had ischemic colitis or intestinal circulation problems.
 - 528 • have ever had Crohn's Disease, ulcerative colitis, or diverticulitis. These are all types of
529 inflammation of the intestine.
 - 530 • are allergic to LOTRONEX or any of its ingredients (see the list of ingredients at the end of
531 this Medication Guide).

532
533 **If you can take LOTRONEX, do not start taking it if you are constipated. Wait until you have**
534 **diarrhea again to start taking LOTRONEX.**

535
536 **Before taking LOTRONEX tell your doctor**

- 537 • about any other illnesses you have or medicines you take or plan to take. This includes both
538 prescription and non-prescription medicines, including supplements and herbal remedies. Some
539 illnesses and medicines cause constipation in some people. If you have these illnesses or take
540 these medicines, taking LOTRONEX may increase your risk of getting the serious side effects of
541 constipation.
- 542 • if you are pregnant, planning to get pregnant, or breast feeding.

543
544 **How should I take LOTRONEX?**

- 545 • Take LOTRONEX exactly as your doctor prescribed it. LOTRONEX can be taken with or
546 without food.
- 547 • If you miss a dose of LOTRONEX, just skip that dose. Do **not** take 2 doses the next time. Wait
548 until the next scheduled dosing time and take your normal dose.
- 549 • Begin with 1 tablet a day for 4 weeks to see how you respond to LOTRONEX. Although the
550 effect of 1 tablet a day on IBS symptoms has not been studied, you and your doctor may decide
551 that you should keep taking this dose if it adequately controls your IBS symptoms and you have
552 not become constipated or had ischemic colitis while taking LOTRONEX.
- 553 • If 1 tablet a day does not adequately control your symptoms after 4 weeks and you have not
554 become constipated or had ischemic colitis, tell your doctor. Your doctor may increase your
555 dose to 1 tablet 2 times a day, the dose that was studied and shown to be effective in clinical
556 studies.
- 557 • Stop taking LOTRONEX right away and call your doctor if you become constipated or have any
558 signs of ischemic colitis, such as new or worsening abdominal pain, bloody diarrhea, or blood in
559 your stools. If you have constipation and it goes away, you and your doctor may consider
560 restarting LOTRONEX. Before restarting LOTRONEX, talk with your doctor. Your doctor may

LOTRONEX® (alosetron hydrochloride) Tablets

561 consider a lower dose of LOTRONEX to see if that could work for you. You should not restart
562 LOTRONEX if you had ischemic colitis while taking LOTRONEX.

- 563 • **Stop taking LOTRONEX and call your doctor if your IBS symptoms have not improved**
564 **after taking 1 tablet 2 times a day for 4 weeks.**

565

566 **What are the possible side effects of LOTRONEX?**

567 **Read the section “What is the most important information I should know about**
568 **LOTRONEX?” at the beginning of this Medication Guide for information about potential**
569 **serious side effects of LOTRONEX and what to do if you become constipated or have any**
570 **signs of ischemic colitis.**

571

572 This Medication Guide does not tell you about all the possible side effects of LOTRONEX. Your
573 doctor or pharmacist can give you a more complete list.

574

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

580

581 **Active Ingredient:** alosetron hydrochloride

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

585

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

587



588

589 GlaxoSmithKline

LOTRONEX[®] (alosetron hydrochloride) Tablets

590 Research Triangle Park, NC 27709

591

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594

595 (Date of issue)

MG-

596

Risk Management Plan

Attachment 2

PATIENT-PHYSICIAN AGREEMENT FOR LOTRONEX

Lotronex is only for women who have irritable bowel syndrome (IBS) with diarrhea as their main symptom and who have not been helped by other treatments. Women who have constipation as their main IBS symptom should **not** use Lotronex. Lotronex has not been shown to help men with IBS, women with conditions other than IBS, or women under 18.

Some patients taking Lotronex develop serious intestinal conditions, including serious constipation and ischemic colitis. Constipation can be serious when it blocks movement of stools (bowel movement) through the intestines. Serious problems resulting from constipation occurred in about 1 in 1500 patients in clinical studies. Ischemic colitis (which occurred in about 1 in 700 patients in clinical studies) happens when the flow of blood to the intestines is reduced. These conditions can lead to hospitalization, blood transfusions, surgery, and even death. Serious constipation or ischemic colitis can happen without warning. Older patients, or patients who have other health problems or who take other medicines that may cause constipation, may be more likely to develop a serious intestinal condition while taking Lotronex.

IBS itself is not life-threatening and usually does not result in a need for hospitalization or surgery. My doctor and I have discussed how much my IBS symptoms interfere with my life and whether the possible benefits of Lotronex for me are greater than its possible risks. Because of the serious risks associated with Lotronex, only patients whose IBS symptoms have not been helped by other treatments should use Lotronex.

- Before taking Lotronex I will tell my doctor
 - about any illnesses or other medicines, prescription or non-prescription, that I am taking or plan to take.
 - if I am constipated most of the time, am constipated now, or have had a serious problem from constipation.
 - if I have ever had ischemic colitis or intestinal circulation problems.
 - if I have ever had Crohn's Disease, ulcerative colitis, or diverticulitis.
- I will stop taking Lotronex right away and call my doctor right away if I become constipated. If my constipation does not get better, I will call my doctor right away. I will talk to my doctor before I take Lotronex again.
- I will stop taking Lotronex right away and call my doctor right away if
 - I have new or worsening abdominal (lower stomach area) pain.
 - I get bloody diarrhea or blood in my stool (bowel movement).
- I will stop taking Lotronex and call my doctor if my IBS symptoms have not improved after 4 weeks of taking one tablet twice a day.

I have read and understand the Medication Guide for Lotronex. My doctor answered all my questions about treatment with Lotronex. If I see other doctors about my IBS or possible side effects from Lotronex, I will tell my doctor who prescribed Lotronex. I will take Lotronex exactly as my doctor prescribed it. I understand that only doctors who know about IBS and the

potential side effects of Lotronex should prescribe Lotronex.

My signature below indicates I have read, understood, and agree with ALL the statements made above. I authorize my doctor to begin treatment with Lotronex.

Name of Patient (print)

Signature

Date

SECTION FOR THE PHYSICIAN

I am knowledgeable and experienced in the diagnosis and treatment of irritable bowel syndrome (IBS) and able to diagnose and manage ischemic colitis and complications of constipation.

I have reviewed the complete Prescribing Information for Lotronex and am thoroughly familiar with the important information in the Boxed Warning, Indications and Usage, Contraindications, Warnings, Precautions, Adverse Reactions, Dosage and Administration, and Medication Guide sections. I have also reviewed and am familiar with all the components of the Patient-Physician Agreement for Lotronex.

I know that Lotronex has been approved for use by FDA, and proven to give treatment benefits, ONLY in adult women with diarrhea-predominant IBS. Treatment benefits in other populations have not been established.

I have given the patient named above:

- a copy of the Medication Guide for Lotronex, and instructed them to read it carefully before signing this Agreement and to take it home.
- counseling about the potential risks and benefits of Lotronex given the patient's response to other treatments and how much IBS symptoms interfere with the patient's life.
- appropriate instructions for taking Lotronex.

The patient signed the Patient-Physician Agreement in my presence after I counseled the patient, asked if he/she had any questions about treatment with Lotronex, and answered all questions to the best of my ability.

Name of Physician (print)

Signature

Date

After the patient and the physician sign this Patient-Physician Agreement, give one copy to the patient and put one copy in the patient's medical record.

Risk Management Plan

Attachment 3

A Twenty-four Week, Randomized, Double Blind, Placebo-Controlled, Crossover Study to Assess the Effect of Alosetron 1.0mg BID on Work/Main Activity Productivity in Female Subjects with Diarrhea-Predominant IBS

Background

Irritable bowel syndrome (IBS) is a chronic recurrent disorder characterized by abdominal pain and discomfort with an associated alteration in bowel function. The alterations in bowel function may manifest primarily as diarrhea, constipation, or as an alternation between the two. Alosetron has been shown to significantly reduce the multiple symptoms of IBS in female patients with diarrhea-predominant disease.

The symptoms of IBS can be severe and result in limiting the functional productivity of the individual at work or in doing their main activities. The therapeutic goal of IBS treatment is to reduce abdominal pain and discomfort, as well as normalize bowel function. Successful treatment should allow individuals to be more functionally productive. In the Phase III alosetron studies, individuals, who were unable to perform their main activity for at least 2 weeks per month due to IBS, or who had to cut-back on their main activity for at least 2 weeks per month, were able to reduce the number of days unable to perform their main activity by 5 days a month.

Study Rationale

Alosetron treatment of diarrhea-predominant IBS in female subjects who are compromised in performing their main activity should result in a significant improvement in the days in which the subjects could not perform these activities.

Study Design

This is a 24-week, randomized, double-blind, placebo-controlled crossover study to compare 1.0mg BID alosetron vs. placebo in female subjects with diarrhea predominant IBS. Following 12 weeks of randomized treatment in Period 1, subjects will receive 12 weeks of treatment in Period 2 according to the following scheme:

<u>Period 1 (12 weeks)</u>	<u>Period 2 (12 weeks)</u>
Placebo	Alosetron 1.0mg BID
Alosetron 1.0mg BID	Placebo
Alosetron 1.0mg BID	Alosetron 1.0mg BID

Ambulatory, outpatient, female subjects, at least 18 years of age, with at least 6 months of recurrent symptoms meeting the Rome II criteria for IBS, classified by the investigator as having diarrhea-predominant IBS and who indicate that they were not able to attend their work/school/main activity or had to cut back on work/school/main activity for at

least 2 of the last 4 weeks will be eligible for screening. Subjects will record their stool frequency and consistency scores daily for a 2-week screening period via a touch-tone telephone data entry system. Subjects who are not constipated and meet all screening requirements of an average daily stool consistency score of ≥ 3.0 (5-point scale; 1=very hard, 5=watery), an average daily stool frequency of ≥ 2.0 , and all other inclusion/exclusion criteria will be equally randomized to one of three treatment sequences consisting of Period 1 for 12 weeks followed by Period 2 for another 12 weeks. The 24-week treatment phase will be followed by a 4-week follow-up phase with no treatment.

During the screening phase, subjects will record daily self-assessments of stool frequency and stool consistency. During treatment and follow-up subjects will use a touch-tone telephone data entry system to record their daily symptoms, whether or not they were able to attend to their major activity that day, whether or not they had to cut back their major activity that day (i.e., started late or had to end early), and to rate their level of productivity that day (100 point scale; 0=no productivity, 100=normal productivity). During treatment, subjects will return to the clinic every six weeks for evaluation. Total study duration will be 30 weeks.

Planned Sample Size

A total of 225 female subjects will be randomly allocated in a ratio of 1:1:1 for the three treatment sequences:

<u>Period 1</u>	<u>Period 2</u>	<u>N</u>
Placebo	Alosetron 1.0mg BID	75
Alosetron 1.0mg BID	Placebo	75
Alosetron 1.0mg BID	Alosetron 1.0mg BID	75

The sample size is based on reducing the number of days subjects are unable to perform their main activity in Period 1 with alosetron by 5 days more than placebo and a standard deviation of 9 days with 90% power at the $\alpha=0.05$ significance level, plus an allowance of approximately 20% for dropouts in each period. Subjects will receive treatment on an outpatient basis at approximately 75 sites in the United States.

Study Drugs and Dosages

Subjects will be randomized to treatment in a ratio of 1:1:1 to receive one of the following sequences:

<u>Period 1 (12 weeks)</u>	<u>Period 2 (12 weeks)</u>	<u>N</u>
Placebo	Alosetron 1.0mg BID	75
Alosetron 1.0mg BID	Placebo	75
Alosetron 1.0mg BID	Alosetron 1.0mg BID	75

Study Objective(s)

Primary Objectives:

1. The primary objective is to compare the alosetron 1.0mg BID treatment group to placebo during treatment Period 1 for changes in the number of days unable to attend work/school/main activity, changes in the number of days cut back on work/school/main activity, and changes in productivity at work/school/main activity.
2. In addition, changes in the number of days unable to attend work/school/main activity, changes in the number of days cut back on work/school/main activity, and changes in productivity will be compared between periods within the 3 treatment sequences.
3. Compare the safety and tolerability between treatment groups and within treatment sequences for adverse events, in particular constipation, and abnormalities of laboratory tests.

Study Endpoint(s)**Primary Efficacy Endpoint:**

The primary efficacy endpoint is the change from baseline in the number of days unable to attend work/school/main activity due to IBS symptoms during the past 4 weeks in treatment Period 1.

Secondary Efficacy Endpoints:

1. Changes in the number of days cut back on work/school/main activity during the past 4 weeks due to IBS during treatment Period 1.
2. Changes in productivity at work/school/main activity during the past 4 weeks during treatment Period 1.
3. Changes in the number of days unable to attend work/school/main activity, days cut back on work/school/main activity, and productivity between treatment periods within the 3 treatment sequences.
4. Changes in lower GI symptoms within the treatment sequence compared to the follow-up phase.

Other Endpoints:

Summary of laxative usage and reason for use.

Safety Endpoints:

1. Incidence of constipation.
2. Incidence of adverse events grouped by body system.

3. Changes in laboratory values.

Study design issues:

In case of constipation at any time during the course of the study, subjects will stop their randomized treatment and be allowed to take a laxative. A laxative (bisacodyl 5mg tablets, labeled for 2 tablets once daily for constipation) will be provided by Glaxo Wellcome (GW) or subjects can use a laxative (or bulking agent) of their choice for the management of constipation. Laxative use will be recorded on a daily basis onto a laxative use diary card.

Subjects whose constipation is not resolved after two days of stopping therapy, with or without laxative therapy, will be dropped from the study. Subjects who experience severe constipation must contact the study site and will be discontinued from treatment immediately.

Subjects experiencing no stool for 2 or more days during screening or who report constipation during screening will be contacted by the study site and discontinued from the study.

Risk Management Plan

Attachment 4

A 12-Week, Randomized, Double-blind, Placebo Controlled, Dose-titration, Study of Alosetron in female subjects with Diarrhea-Predominant Irritable Bowel Syndrome

Background

Irritable bowel syndrome (IBS) is a chronic recurrent disorder characterized by abdominal pain and discomfort associated with altered bowel function. The alterations in bowel function may manifest primarily as diarrhea, primarily as constipation or as an alternation between the two. The therapeutic goal of IBS treatment is to reduce pain and normalize bowel function.

Alosetron 1mg BID has proven to be effective in reducing the abdominal pain and discomfort of IBS in females with diarrhea predominant IBS, as well as improving urgency, stool frequency, and stool consistency. In addition, alosetron increases colonic compliance and slows colonic transit in IBS patients.

As a consequence of alosetron's ability to slow colonic transit, constipation can develop. In the pivotal studies, constipation occurred at the rate of 28% with 1 mg BID alosetron. This constipation occurs typically in the first month of therapy, is transient (lasting about 1 week), and usually occurs only once during therapy. Study data also indicate that the constipation is dose-related (0.5 mg BID = 13% constipation rate).

Study Rationale

Alosetron is a potent and highly selective 5-HT₃ receptor antagonist and in clinical studies constipation occurred in 25-30% of subjects treated with alosetron 1mg BID.

Anecdotal information received from subjects taking alosetron indicates subjects can titrate their own dose to control adequate relief and the side effect of constipation. The current study is being conducted to further evaluate the efficacy and safety of alosetron in the treatment of female diarrhea predominant IBS subjects while allowing the subject to titrate their dose.

Study Design

This is a 12-week, randomized, double-blind, placebo-controlled multi-center study to compare 0-4 tablets daily of 0.5 mg alosetron PO or placebo PO in female diarrhea predominant Irritable Bowel Syndrome.

Ambulatory, outpatient, female Subjects, at least 18 years of age, with at least 6 months of recurrent symptoms meeting the Rome II criteria for IBS and are classified by the investigator as having diarrhea-predominant IBS will be eligible for screening. Subjects will record their abdominal pain or discomfort scores, stool frequency and consistency

scores and sense of urgency daily for a 2-week screening period via a touch-tone telephone data entry system. Subjects who are not constipated and meet all screening requirements of an average pain score of ≥ 1.0 (5-point scale; 0=none, 1=mild, 2=moderate, 3=intense, 4=severe), an average daily stool consistency score of ≥ 3.0 (5-point scale; 1=very hard, 2=hard, 3=formed, 4=loose, 5=watery), an average stool frequency of ≥ 2.0 bowel movements per day and all other inclusion/exclusion criteria will be randomized to either alosetron 0.5 mg or placebo.

Randomized subjects will be instructed to administer 0-2 tablets of alosetron 0.5 mg or placebo once or twice per day. Subjects will be instructed to titrate their dosage based on their symptoms. Subjects will enter the number of tablets taken or not daily via the touch-tone telephone data entry system. The treatment phase will be followed by a four-week follow-up phase for post-treatment observation and collection of both IBS pain and discomfort data, global improvement, and GI symptoms. During the screening, treatment and follow-up phases, subjects will record daily self-assessments of pain and discomfort, and lower GI symptoms. Daily and weekly during the treatment and follow-up phases, subjects will record adequate relief data and monthly self-ratings of IBS global improvement. Subjects will use a touch-tone telephone data entry system to record their symptoms. Safety and tolerability will be evaluated via reporting of adverse events and monitoring of routine laboratory tests. Total study duration will be 18 weeks.

Planned Sample Size

A total of 500 female subjects (250 per treatment group) with diarrhea predominant IBS will be randomized in the study. The sample size is based on detecting a 10-point difference in adequate relief rates favoring alosetron and a standard deviation of 40 points with 80% power at the $\alpha=0.05$ significant level. Subjects will receive treatment on an outpatient basis at approximately 100 investigator sites in the US.

Study Drugs and Dosages

Subjects will be randomized to 12 weeks of treatment in a ratio of 1:1 to receive one of the following:

1. alosetron 0.5mg, 0-2 tablets once or twice per day PO (n = 250 subjects)
2. placebo, 0-2 tablets once or twice per day PO (n = 250 subjects)

Study Objective(s)

Primary Objectives:

1. Compare the two treatment groups with respect to self-rating of an IBS global improvement question.
2. Compare the tolerability of the two treatments with respect to the incidence of adverse events and abnormalities of laboratory tests.

Secondary Objectives:

1. Compare the two treatment groups with respect to adequate relief of IBS pain and discomfort.
2. Compare the two treatment groups with respect to adequate relief of IBS pain and discomfort based on the numbers of tablets taken each day.
3. Compare the two treatment groups with respect to self-ratings of the following lower GI functions:
 - a. sense of urgency
 - b. stool frequency
 - c. stool consistency
4. Compare overall satisfaction with treatment at Week 12/Final Visit to the satisfaction received from the previously used treatment prior to the study.

Study Endpoint(s)

Primary Efficacy Endpoint:

1. Difference between the treatment groups in the IBS global improvement question is the primary efficacy endpoint.

Secondary Efficacy Endpoints:

1. The average weekly adequate relief rate of IBS pain and discomfort during the treatment phase.

As supportive endpoints to the adequate relief endpoint, the weekly (Week 1–Week 16) and daily (first 7 days on treatment) adequate relief rates will be assessed.

2. Changes in lower GI symptoms during the treatment phase.

As supportive endpoints to the lower GI symptoms endpoints, the changes of lower GI symptoms at each week (Week 1 – Week 16) will be assessed.

3. Overall satisfaction with treatment compared to previously used treatment prior to the study.

Safety Endpoints:

1. Incidence of constipation
2. Adverse events grouped by body system.
3. Changes in laboratory values.

Study design issues:

In case of constipation at any time during the course of the study, subjects will stop they randomized treatment and be allowed to take a laxative. A laxative (bisacodyl 5mg tablets, labeled for 2 tablets once daily for constipation) will be provided by Glaxo Wellcome (GW) or subjects can use a laxative (or bulking agent) of their choice for the management of constipation. Laxative use will be recorded on a daily basis onto a laxative use diary card.

Subjects whose constipation is not resolved after two days of stopping therapy, with or without laxative therapy, will be dropped from the study. Subjects who experience severe constipation must contact the study site and will be discontinued from treatment immediately.

Subjects experiencing no stool for 2 or more days during screening or who report constipation during screening will be contacted by the study site and discontinued from the study.

Risk Management Plan

Attachment 5

A Twelve-Week, Randomized, Double-Blind, Placebo-Controlled Study to Compare Methods of Constipation Management in Female Diarrhea-Predominant Irritable Bowel Syndrome Subjects Treated with Open-Label Alosetron.

Background

Irritable bowel syndrome (IBS) is a chronic recurrent disorder characterized by abdominal pain and discomfort with associated alterations in bowel function. The alterations in bowel function may manifest primarily as diarrhea, primarily as constipation, or as an alternation between the two. The therapeutic goal of IBS treatment is to reduce pain and normalize bowel function.

Study Rationale

As a class effect, 5-HT₃ antagonists induce constipation. In clinical studies, this expected effect of constipation occurred in 25-30% of subjects treated with alosetron 1mg BID. The median onset of constipation occurred within 10 days of starting treatment and had a median duration of 6 days. About three-fourths of subjects who experienced constipation had only one occurrence. Most subjects categorized their constipation as mild to moderate in severity. In the Phase III studies, subjects were instructed to interrupt treatment if they experienced no passing of stool for 4 consecutive days. Subjects were allowed up to a four-day interruption of therapy until stool passage resumed, and in most subjects (88%) interruption of therapy resulted in return of stool. If a subject continued to have absence of stool for 8 consecutive days, the subject was withdrawn from the study. Less than 1% of subjects had 8 days without passing a stool. In these studies subjects were not allowed to take laxatives. Therefore, this study seeks to determine an effective management strategy for constipation in subjects who report constipation during treatment with open-label alosetron 1mg BID.

Study Design

This is a 12-week, randomized, double-blind, placebo-controlled, multi-center study to compare 4 methods of constipation management in female diarrhea predominant IBS subjects who develop constipation while treated with open-label alosetron 1mg BID. Four constipation management strategies will be evaluated: interruption of alosetron treatment; a reduction of the dose of alosetron to 1mg QD and adding a laxative (bisacodyl); reduction of the alosetron dose to 1mg QD; or maintaining alosetron 1mg BID and adding a laxative (bisacodyl).

Ambulatory, outpatient, female subjects at least 18 years of age, with recurrent symptoms meeting the Rome II criteria for IBS, and classified by the investigator as having diarrhea-predominant IBS will be eligible for screening. Subjects must have a colonic evaluation within 1 year of study entry. Subjects will record their stool frequency and consistency scores and sense of urgency daily for a 1-week screening period via a touch-tone telephone data entry system. Subjects not reporting constipation and meeting all other inclusion/exclusion criteria will receive open-label alosetron 1mg BID for 12

weeks. At this time subjects will also be randomized to 1 of 4 constipation treatment groups, as noted above. Subjects will continue to record stool parameters daily using the phone system during the treatment period, and will return to clinic every 4 weeks. Four weeks after completing treatment, subjects will receive a telephone call from the site to assess concurrent medications and adverse events.

If a subject reports constipation, she will be instructed to stop taking open-label alosetron and begin taking the constipation management medication until constipation resolves. Once constipation resolves, the subject will be instructed to resume taking open-label alosetron. Subjects are allowed up to 3 events of constipation during the 12-week treatment phase; otherwise, if a fourth event is reported the subject must be withdrawn from the study. If a single episode of constipation does not resolve within 8 days, the subject will be withdrawn from the study.

Planned Sample Size

To assess the effectiveness of the constipation management methods, 800 subjects will be needed to experience constipation and initiate constipation management treatment. Assuming a 40% incidence rate of constipation, 2000 female subjects will need to be enrolled and randomized to one of the constipation management groups (a 40% constipation rate was seen in the bowel urgency study (S3B30011) in which laxative use was allowed and is assumed for this study since patients will be asked each day about constipation during the open-label phase). Subjects will receive treatment on an outpatient basis at approximately 200 investigational sites in the US.

Various estimates for the 4-day resolution rate of constipation for the active arms in the trial were considered, compared to the historical rate with no intervention from previous trials. From the previous trials, the 4-day resolution rate for no intervention was 33% (78/235). Estimates for the active arms of this trial were chosen as follows:

- A. Interruption of treatment: 88%
- B. Alosetron 1mg QD and laxative: 75%
- C. Alosetron 1mg BID and laxative: 65%
- D. Alosetron 1mg QD: 50%

The estimate for group C (65%) is based on results of the bowel urgency study (S3B30011) in which laxative use was allowed. Estimates for treatment groups B and D were chosen intuitively as about midway between A and C, and midway between C and the historical control of no intervention, respectively. Comparisons between the historical rate with no intervention and the 4 active arms are reasonably addressed with superiority comparisons such that a sample size of 200 constipated females per treatment group would provide at least 80% power to detect differences for the pairwise comparisons between the historical control rate with no intervention from previous trials (33%) and any of the four constipation management groups at the $\alpha=(0.05/4)=0.0125$ level of significance. In addition, comparisons among the 4 active arms are reasonably

addressed with non-inferiority comparisons using 99% confidence intervals around the treatment differences and a non-inferiority margin of $\pm 13\%$ (which is $\frac{1}{4}$ of the superiority margin between A and the historical rate) for the smaller of the two rates.

Study Drugs and Dosages

Open-label alosetron: alosetron 1mg BID for 12 weeks

Constipation management medication: Four constipation management groups as follows:

- Placebo alosetron and placebo laxative (dose interruption)
- Alosetron 1mg QD and laxative
- Alosetron 1mg BID and laxative
- Alosetron 1mg QD and placebo laxative

Study Objective(s)

Primary Objectives:

1. To compare the historical control group of alosetron 1mg BID (no intervention), placebo alosetron/placebo laxative (dose interruption), alosetron 1mg QD and laxative; alosetron 1mg BID and laxative, and alosetron 1mg QD and placebo laxative in the management of constipation.
2. To evaluate the safety and tolerability of study drug treatment in female subjects with diarrhea-predominant IBS.

Secondary Objectives:

1. Compare 4 constipation management groups with respect to improvement in the characteristics of constipation:
 - duration and severity of constipation events
 - stool frequency and stool consistency
 - urgency
 - bloating
 - straining
 - study withdrawal due to constipation

Other Objectives:

1. Assess subject's perception of constipation.
2. Compare lower GI functions during and not during the constipation event (stool frequency and stool consistency; urgency; bloating; straining).

Study Endpoint(s)

Primary Efficacy Endpoint:

The proportion of subjects whose first constipation event resolves within 4 days of starting constipation management therapy.

Secondary Efficacy Endpoints:

1. Changes in the characteristics of constipation and lower GI function:
 - duration and severity of constipation events
 - stool frequency and stool consistency
 - urgency
 - bloating
 - straining
 - study withdrawal due to constipation

Other Endpoints:

1. Perception of constipation.
2. Differences in lower GI function during and not during the constipation event.

Safety Endpoints:

1. Nature and frequency of adverse events.
2. Changes in laboratory values.

Study design issues:

A subject may report constipation by 3 different methods: 1) reporting feeling constipated via the phone system, 2) reporting 4 consecutive days of not passing a stool via the phone system, 3) reporting constipation during a clinic visit.

If a subject reports 8 consecutive days of not passing a stool, the subject should discontinue study medication and be withdrawn from the study.

Risk Management Plan

Attachment 6

A Twelve-Week, Randomized, Double Blind, Placebo-Controlled, Study to Assess the Safety and Efficacy of 0.5mg BID and 1mg QD of Alosetron in Female, Diarrhea-Predominant, IBS Subjects

Background

Irritable bowel syndrome (IBS) is a chronic recurrent disorder characterized by abdominal pain and discomfort with associated alterations in bowel function. The alterations in bowel function may manifest primarily as diarrhea, primarily as constipation, or as an alternation between the two. The therapeutic goal of IBS treatment is to reduce pain and normalize bowel function.

Study Rationale

As a class effect, 5-HT₃ antagonists cause constipation. In clinical studies, constipation occurred in 25-28% of subjects treated with alosetron 1mg BID. The median onset of constipation occurred within 9 days of starting treatment and had a median duration of 5 days. About three-fourths of subjects experienced only one occurrence of constipation. Constipation was generally characterized as mild to moderate in severity.

Data from subjects that received 0.5mg BID in the IBS dose-ranging study S3BP12, reported an incidence of constipation (13%) that was lower than that experienced by subjects receiving 1mg BID in the Phase II and III 12-week studies (28%). Serious gastrointestinal events, including complications of constipation, have been infrequently reported with administration of alosetron. This study is being conducted to determine the efficacy and constipation rates of alosetron 0.5mg BID and alosetron 1mg QD.

Study Design

This is a 12-week, randomized, double-blind, placebo-controlled study to compare alosetron 0.5 mg BID PO and alosetron 1mg QD PO to placebo BID PO in female diarrhea predominant Irritable Bowel Syndrome.

Ambulatory, outpatient, female Subjects, at least 18 years of age, with at least 6 months of recurrent symptoms meeting the Rome II criteria for IBS and are classified by the investigator as having diarrhea-predominant IBS will be eligible for screening. Subjects will record their abdominal pain or discomfort scores, stool frequency and consistency scores and sense of urgency daily for a 2-week screening period via a touch-tone telephone data entry system. Subjects meeting all screening requirements of an average pain score of ≥ 1.0 (5-point scale; 0=none, 1=mild, 2=moderate, 3=intense, 4=severe), an average daily stool consistency score of ≥ 3.0 (5-point scale; 1=very hard, 2=hard, 3=formed, 4=loose, 5=watery), an average stool frequency of ≥ 2.0 stools per day and all other inclusion/exclusion criteria will be equally randomized to alosetron 0.5mg BID PO alosetron 1mg QD PO or placebo BID PO for the 12 -week treatment phase.

The 12-week treatment phase will be followed by a 4-week follow-up phase of no treatment. Assessment of IBS pain and discomfort, global improvement, and lower GI symptoms will occur during this post treatment observation period.

During the screening, treatment and follow-up phases, subjects will record daily self-assessments of pain and discomfort and lower GI symptoms. During the treatment and follow-up phases, subjects will record weekly self-assessment of adequate relief and monthly self-ratings of IBS global improvement. Subjects will use a touch-tone telephone data entry system to record their daily symptoms, weekly adequate relief, and monthly global improvement. During treatment, subjects will return to the clinic every four-weeks for evaluation. Total study duration will be 18 weeks.

Planned Sample Size

A total of 900 female subjects (300 per treatment group) with diarrhea predominant IBS will be randomized in the study.

The sample size is based on detecting a 10-point difference in adequate relief rates favoring either dose of alosetron versus placebo and a standard deviation of 40 points with 80% power at the $\alpha=0.025$ significance level. Subjects will receive treatment on an outpatient basis at approximately 200 sites in the United States.

Study Drugs and Dosages

Subjects will be randomized to treatment in a ratio of 1:1:1 to receive one of the following regimens:

- alosetron 0.5mg BID (n = 300 subjects)
- alosetron 1mg QD (n = 300 subjects)
- placebo (n = 300 subjects)

Study Objective(s)

Primary Objectives:

1. The primary objective is to compare each dose of alosetron to placebo for adequate relief of IBS pain and discomfort.
2. Compare the safety and tolerability of the three treatments with respect to incidence of adverse events, in particular constipation, and abnormalities of laboratory tests.

Secondary Objectives:

1. Comparisons between each dose of alosetron and placebo with respect to the following lower GI symptoms
 - a. sense of urgency

- b. stool frequency
 - c. stool consistency
2. Comparisons between each dose of alosetron and placebo with respect to self-rating of an IBS global improvement question.

Study Endpoint(s)

Primary Efficacy Endpoint:

The primary efficacy endpoint is the average weekly adequate relief rate of IBS pain and discomfort during Weeks 1 - 12 of treatment.

Secondary Efficacy Endpoints:

1. Changes in lower GI symptoms
2. Response to the IBS global improvement question.

Other Endpoints:

1. Amount and reason for laxative use.

Safety Endpoints:

1. Incidence of constipation for each dose.
2. Incidence of adverse events grouped by body system.
3. Changes in laboratory values.

Study design issues:

In case of constipation at any time during the course of the study, subjects will stop they randomized treatment and be allowed to take a laxative. A laxative (bisacodyl 5mg tablets, labeled for 2 tablets once daily for constipation) will be provided by GlaxoSmithKline (GSK) or subjects can use a laxative (or bulking agent) of their choice for the management of constipation. Laxative use will be recorded on a daily basis onto a laxative use diary card.

Subjects whose constipation is not resolved after two days of stopping therapy, with or without laxative therapy, will be dropped from the study. Subjects who experience severe constipation must contact the study site and will be discontinued from treatment immediately.

Subjects experiencing no stool for 2 or more days during screening or who report constipation during screening will be contacted by the study site and discontinued from the study.

Risk Management Plan

Attachment 7

CONCEPT PROTOCOL: DRAFT

ADMINISTRATIVE INFORMATION

Protocol Title: Lotronex Utilization Study: A Cohort Study in the United Healthcare Research Database

Protocol Number: EPI-40060

Drug Name:

Lotronex

GW Protocol contact person:

Suzanne F. Cook, PhD
Worldwide Epidemiology

Collaborating Investigator:

Alexander Walker, MD,
Ingenix Pharmaceutical
Services, Epidemiology
Division, A UnitedHealth
Group Company

Study Timelines:

TBD

Estimated enrollment date for the
first subject:

TBD

Estimated date of study completion:

TBD

Use of central clinical laboratory:

N

Collection of Genotyping samples:

N

TABLE OF CONTENTS

	Page
1. INTRODUCTION	5
2. OBJECTIVES	5
3. METHODOLOGY	6
3.1. Study Design.....	6
3.2. Data Source	6
3.3. Patient Confidentiality	8
3.4. Exposure Definition and Measures.....	8
3.5. Epidemiologic Measures	8
3.6. Adverse Experiences	8
3.7. Data Management.....	9
3.8. Validation Procedures	9
3.9. Data Analysis	9
3.10 Strengths & Limitations	10
4. STUDY MANAGEMENT	10
4.1. Approval and Consent.....	10
4.2. Study Closure	10
4.3. Project Management	10
4.4. Study Reporting and Publication	11
APPENDIX 1. TABLE SHELLS	12
TABLE 1: Demographic Characteristics of Lotronex Users With at Least Six Months of Membership in UHC Prior to their First Lotronex Dispensing (Eligibles)	12
TABLE 2: Demographic Characteristics of Lotronex Users With Less than Six Months of Membership in UHC Prior to Their First Lotronex Dispensing (Not eligible for study)	13
TABLE 3: Fifteen Most Frequently Recorded Outpatient Diagnoses Among Users of Lotronex	14
TABLE 4: Fifteen Most Frequently Recorded Inpatient Diagnoses Among Users of Lotronex	15
TABLE 5: GI Related Inpatient Diagnoses Among Users of Lotronex	16
TABLE 6: GI Related Outpatient Procedures Performed Among Users of Lotronex	17
TABLE 7: GI Related* Inpatient Procedures Performed Among Users of Lotronex	19

TABLE 8: Medical History of Users of Lotronex With At Least One Claim Carrying a Diagnosis of 564.1	21
TABLE 9: Medical History of Users of Lotronex With No Claims Carrying a Diagnosis of 564.1	25
TABLE 10: Combinations of Claims Diagnoses found Among Patients with Constipation or Complications of Constipation in the Six Months Prior to First Lotronex Dispensing	29
TABLE 11. Health Care Utilization Among Users of Lotronex	31
TABLE 12: Fifteen Most Frequent Outpatient Drug Dispensings Among Users of Lotronex	32
TABLE 13: Medication History Among Users of Lotronex*	33
APPENDIX 2. List of Abbreviations and Definitions of Terms	34
APPENDIX 3. ICD-9 code for irritable colon (564.1)	35
APPENDIX 4. Diagnoses and diagnostic codes used in the study of the health care utilization of Lotronex users	36
APPENDIX 5. GI Related Procedures	38
APPENDIX 6. Medication Categories Used in the Study of the Health Care Utilization of Lotronex Users	39

1. INTRODUCTION

Lotronex is a potent and selective 5-HT₃ receptor antagonist. Lotronex was approved by the FDA for the treatment of irritable bowel syndrome (IBS) in women whose predominant symptom is diarrhea. Lotronex was marketed in the US between March 1, 2000 and November 28, 2000.

As part of its post-marketing commitments for Lotronex, GlaxoSmithKline initiated a Phase IV Study entitled “An Epidemiologic Study of Ischemic Colitis and Complications of Constipation in Patients Receiving Lotronex, Patients with IBS not Receiving Lotronex and the General Population in the UnitedHealthcare (UHC) Research Database”. One component of this Phase IV study is a Utilization Study of patients receiving Lotronex. The concept protocol for the Phase IV Study was submitted to FDA for review on May 17, 2000, June 29, 2000, August 31, 2000 and October 11, 2000.

GSK has conducted this Utilization Study for the time period March 1, 2000 through November 28, 2000. This report is entitled “Utilization Patterns of Lotronex Users March – November 2000” and is submitted in the sNDA.

This concept protocol expands upon the Utilization Study protocol submitted in this sNDA. . Most notably, the Utilization Study now includes a prospective component, whereby patients with a dispensing for Lotronex are followed forward for one year to examine such information as Lotronex usage patterns and dispensings of selected concomitant medications.

Patients will be characterized by age, gender, medical history of comorbid conditions and/or concomitant medications affecting the gastrointestinal tract within 6 months prior to the dispensing of Lotronex, medical conditions contraindicative for Lotronex, duration of IBS diagnosis, total healthcare costs within 3 months prior to the dispensing of Lotronex, and geographic region the patient resides in. Patients will be further characterized based on the frequency of physician visits and associated health care for IBS in the 6 months prior to the dispensing of Lotronex. Patients will be followed forward for one year for to evaluate Lotronex usage patterns and dispensings of selected concomitant medications.

2. OBJECTIVES

The study objectives are as follows:

1. Describe the utilization of Lotronex by describing and characterizing a 10,000 patient cohort who receive Lotronex.
2. Characterize the demographics of Lotronex users by age, gender and geographic location at the time of the first Lotronex dispensing.
3. Characterize the medical history of Lotronex users based on inpatient and outpatient medical service claims incurred within six months before the first dispensing of

- Lotronex. There will be a special focus on medical conditions affecting gastrointestinal motility and absorption, thrombostasis and vascular insufficiency, and medical conditions contraindicative for Lotronex. Identify whether care for these conditions was provided by gastroenterologists.
4. Characterize the frequency of visits to gastroenterologists in the six-month period before the first use of Lotronex.
 5. Characterize the prescription drug dispensings in the six-month period before the first Lotronex dispensing, with a special focus on medications affecting gastrointestinal motility and absorption, thrombosis, and vascular insufficiency.
 6. Characterize the usage patterns of Lotronex and dispensing of selected prescription medications in the one year period following the first prescription for Lotronex.

3. METHODOLOGY

3.1. Study Design

All Lotronex users in 23 health plans from 18 states in the United Healthcare Research Database following the reintroduction of Lotronex up to 10,000 patients will be identified. All potential study subjects will have at least one pharmacy dispensing claim during this period with an NDC code for Lotronex (00173069000).

Patients will have at least 6 months of continuous enrollment in UnitedHealthcare prior to their first Lotronex dispensing in order to characterize their medical history and past drug use. For the purpose of this study, "eligible" patients are those with at least 6 months of continuous prior enrollment and "ineligible" patients are those with less than 6 months of enrollment. Data on "ineligible" users will be summarized only as described in Objective 2.2.

3.2. Data Source

The UnitedHealthcare Research Database (UHC) is the data source for this study. The study will use automated health insurance claims data from the UHC Research Database. Ingenix Pharmaceutical Services, Epidemiology Division, the contractor of this study, utilizes these data for a wide range of safety, utilization and economic analyses.

UHC is the second largest health care company in the United States with more than 300,000 physicians contracted to provide health services to over 14 million members.

The UHC Research Database, a subset of the UHC database, is comprised of a total of 8 million members since 1990 who have medical and prescription coverage. The Research Database has been designed to facilitate drug safety and outcomes research. The Research Database includes information from 25 affiliated health plans for about 4,600,000 people in 1999 from the 19 following states: Florida, Georgia, Illinois, Massachusetts, Michigan, Missouri, Nebraska, Mississippi, Ohio, North Carolina, Rhode Island, South Carolina, Alabama, Arizona, Arkansas, Tennessee, Louisiana, Texas and Utah.

Although all ages are represented in the data, UnitedHealthcare, like most US managed care organizations, enrolls relatively few persons over the age of 65, due to the availability of Medicare coverage for the elderly. The elderly found in the UnitedHealthcare Research Database include those who are still employed or are not eligible for Medicare. Thus, in this database, the elderly will account for a smaller proportion of patients than would be found in the general US population.

The database has encrypted patient and physician identifiers that maintain confidentiality yet also allow linkage of records. The raw data represent records of claims transactions, which may be original claims for reimbursement, or transactions involving financial adjustments (debits or credits) to patient accounts.

Member enrollment files record demographic information on all health plan enrollees, including date of birth, gender, place of employment, and benefit package. Legal restrictions preclude health insurers from collecting data on race. A unique identifier is assigned to each member at the time of enrollment. The identifier is structured to allow longitudinal follow-up of the subscribers and their household members.

Detailed transactions include all services, whether they occur in a doctor's office or a medical facility. Each facility service record contains information on up to 9 diagnoses, recorded with ICD-9 codes, 9th Revision and up to 6 procedure codes (CPT) or Health Care Financing Agency (HCFA) Common Procedure Coding System (HCPCS) codes. Sites of care include hospital emergency room, hospital outpatient, hospital inpatient, doctor's office, long-term care facility, ambulatory surgery center, and other sites. The facility transactions contain each service category that the facility listed on its claim for reimbursement, such as surgeries, laboratory tests, room and board charges and other billed items. In general, these data do not include drugs administered in the hospital. Total amounts charged by the provider and costs paid by the insurer, the patient, and any other third party are available, thus enabling calculations of costs from both the insurer and patient perspectives.

Claims from individual providers such as physicians are recorded in ICD-9 diagnosis codes, and CPT, ICD-9CM or HCPCS procedure codes. Each doctor service record contains information in up to 4 diagnoses, recorded with ICD-9 diagnosis codes, and one procedure code recorded using ICD-9 procedure codes, CPT or HCPCS codes.

Prescription drugs are identified and selected by National Drug Code (NDC), brand name, generic name, or therapeutic class. Information is available on drug strength (days), total daily dose, route of administration and whether the dispensing was an original prescription or refill.

The Research Database receives new information about enrollment, pharmacy and medical claims on an ongoing basis. Pharmacy claims are included in the computerized database within about 6 weeks of their occurrence. Incorporation of medical claims is more variable, with approximately six months required to capture 95% of paid claims.

The data undergo audits by the insurer and by Ingenix Pharmaceutical Services, Epidemiology Division. The validity of the UnitedHealthcare claims has also been documented through review of source medical records

3.3. Patient Confidentiality

Patient confidentiality will be maintained throughout the study. Neither GSK nor Ingenix will receive any patient-identifiable information. Procedures in place at UnitedHealthcare will be used to ensure adherence to confidentiality safeguards.

3.4 Exposure Definition and Measures

The target cohort size is 10,000 patients who have a computer-recorded dispensing of Lotronex.

All UnitedHealthcare plans in the Research Database will be searched for plan members having both medical and prescription drug coverage and who have a dispensing of Lotronex as recorded in the computerized pharmacy records. We will capture all dispensings of Lotronex until 10,000 patients who have received Lotronex have been identified. The first date that Lotronex is dispensed will be referred to as the index exposure.

All eligible subjects found among the 10,000 Lotronex patients, with a computer-recorded dispensing will be entered into the study cohort irrespective of patient age, gender or reason Lotronex is prescribed. IBS sub-type will not be characterised, as this information is not captured by ICD-9 codes.

In the event a patient in the cohort terminates enrolment in the UHC plan in the year following the first dispensing date of Lotronex, the available data will be analyzed using a person-time approach.

The rate of accrual of patients into the 10,000 patient cohort will depend on prescribing patterns for Lotronex. The rate of accrual will be continuously monitored.

3.5. Epidemiologic Measures

The epidemiologic measures that will be collected include :

- Demographics
- Medical history with a special focus on conditions affecting the gastrointestinal tract
- Frequency of visits to gastroenterologists with an ICD-9 code for IBS
- Duration of IBS diagnosis
- Prescription drug dispensings, with a special focus on medications affecting the gastrointestinal tract
- Total health care costs within 3 months prior to the dispensing of Lotronex
- Lotronex usage patterns
- Selected prescriptions during the year following the first dispensing of Lotronex

3.6. Adverse Experiences

Adverse experiences will not be collected in this component of the Phase IV study.

3.7. Data Management

Data management will be carried out by Ingenix Pharmaceutical Services.

3.8. Validation Procedures

Data will be cleaned before they are entered into the analytic data set. Reversals of claims, and duplicate claims will be deleted from the data set before its use in analysis. Data from a subject who may have accessed benefits under different membership identification numbers (because of a change in employment status, for example) will be linked to a single member identification number. In addition, a series of verification measures will be used at each stage in the preparation of the analytic data file. The verification process will assure that occasional records with an untenable claims history are removed from analysis.

3.9. Data Analysis

The data output will be comprised of a descriptive analysis of the characteristics of Lotronex patients that are in the cohort of eligible patients identified among the 10,000 patients with a dispensing of Lotronex. Appendix 1 (Tables 1-18) are examples of the tables to be used in the final report.

All patients in the cohort will be described by age, gender, medical history and concomitant medications affecting the gastrointestinal tract within 6 months prior to the dispensing of Lotronex, duration of IBS diagnosis, total healthcare costs within 3 months prior to the dispensing of Lotronex, and geographic region in which the patient resides. Patients will be further characterized based on the frequency of physician visits and associated health care for IBS in the 6 months prior to the dispensing of Lotronex. Within the groups of Lotronex users with and without 6 months of continuous prior enrollment, the number and percent of patients by age and gender as well as by geographic location at the time of the first Lotronex claim will be tabulated. In addition, the average membership time in UnitedHealthcare prior to their first Lotronex dispensing and whether the provider who first prescribed Lotronex was identified as a gastroenterologist, other internist, or a family practitioner on the dispensing claim will be reported.

During the six month period prior to the initiation of Lotronex (including the day of initiation), we will characterize all eligible Lotronex users according to the presence of the following diagnoses on an inpatient or outpatient claim associated with a visit to any physician and a visit to a gastroenterologist: irritable colon, diarrhea, nonspecific colitis, Crohn's disease, conditions affecting gastrointestinal motility, conditions affecting gastrointestinal absorption, constipation and its complications, vascular insufficiency of the intestine, and diagnoses of abdominal pain and bloody diarrhea that occur on the same day. Diagnoses occurring on the same day as the first Lotronex dispensing are thought to reflect prior or continuing medical conditions and are thus included in our assessment of diagnoses (but not procedures). We will also characterize users according to the presence of claims for symptoms involving the digestive system, abdomen, and pelvis. The specific diagnoses/symptoms within each category as well as the ICD-9 codes associated with each are provided in Appendices 3 and 4.

The top 15 most frequently recorded diagnoses for inpatient and outpatient services as well as procedures related to the gastrointestinal system during the six month period prior to the initiation of Lotronex will be calculated.

Using the drug claims in the six months preceding the initiation of Lotronex, we will tabulate the top 15 most frequently dispensed medications among eligible patients. In addition, we will calculate the frequency of use of the following categories of drugs; drugs that may induce constipation as a side effect, antidiarrheal drugs, drugs that may induce diarrhea, drugs that may affect gastrointestinal absorption, and drugs that may produce thrombosis. Appendix 6 displays a list of generic drug names and drug classes within each category.

The cohort of eligible patients will be followed for one year following the first Lotronex prescription. Lotronex usage patterns and dispensings of selected concomitant medications will be characterized and described.

3.10 Strengths & Limitations

Strengths

One of the major strengths of this study is the fact that all patients who are dispensed Lotronex will enter the observational cohort thus, the cohort will reflect actual prescribing patterns for Lotronex.

Limitations

The measurement of exposure to Lotronex will be determined by a computer-coded dispensing of Lotronex from a pharmacy. Dispensing of Lotronex or any of the concomitant medications does not indicate actual use of the medications or compliance with the dosing instructions; however dispensing of a medication is a stronger indication of use than a record of a prescription being written.

4. STUDY MANAGEMENT

4.1. Approval and Consent

The protocol will receive the necessary approvals as required by GlaxoSmithKline and UHC, including IRB approval, as required by UHC.

4.2. Study Closure

The study will be closed after the target cohort of 10,000 patients who have been dispensed Lotronex has been reached in the observational cohort study. Enrollment in the cohort will end after 10,000 patients are entered.

4.3. Project Management

Ingenix Pharmaceutical Services, Epidemiology Division, a UHC company, will conduct the study, data analyses and prepare the study reports. Alexander Walker MD, DrPH,

Senior Vice President, Ingenix Pharmaceutical Services Epidemiology Division, is the Principal Investigator.

4.4. Study Reporting and Publication

Periodic interim reports and a final report of study results will be provided by UHC to GlaxoSmithKline based on an agreed-to format and schedule. Interim reports will be provided to the Agency every 6 months. A manuscript summarizing the study and findings will be submitted to an appropriate journal.

Appendix 1. Table shells

TABLE 1: Demographic Characteristics of Lotronex Users With at Least Six Months of Membership in UHC Prior to their First Lotronex Dispensing (Eligibles)							
Characteristic	Gender		%	Male		%	Total
	Female						
Membership Time Prior to First Lotronex Dispensing (Days)							
Mean							
Median							
Age* Category (mean= , median=)							
<20							
21-30							
31-40							
41-50							
51-60							
61-70							
71-80							
80+							
Total							
First Lotronex Dispensing Prescribed by:							
Gastroenterologist							
Other internist							
Family practitioner							
Other doctor							
Total							
Geographic location of each Member's Health Plan							
Alabama							
Arizona							
Arkansas							
Florida							
Georgia							
Illinois							
Louisiana							
Massachusetts							
Michigan							
Mississippi							
Missouri							
N. Carolina							
Nebraska							
Ohio							
Rhode Island							
S. Carolina							
Tennessee							
Texas							
Utah							
Total							
*Age on the date of first Lotronex dispensing.							

TABLE 2: Demographic Characteristics of Lotronex Users With Less than Six Months of Membership in UHC Prior to Their First Lotronex Dispensing (Not eligible for study)

Characteristic	Gender				Total	%
	Female	%	Male	%		
Membership Time Prior to First Lotronex Dispensing (Days)						
Mean						
Median						
Age* Category (mean= , median=)						
<20						
21-30						
31-40						
41-50						
51-60						
61-70						
71-80						
80+						
Total						
First Lotronex Dispensing Prescribed by						
Gastroenterologist						
Other internist						
Family practitioner						
Other doctor						
Total						
Geographic location of each Member's Health						
Alabama						
Arizona						
Arkansas						
Florida						
Georgia						
Illinois						
Louisiana						
Massachusetts						
Michigan						
Mississippi						
Missouri						
N. Carolina						
Nebraska						
Ohio						
Rhode Island						
S. Carolina						
Tennessee						
Texas						
Utah						
Total						
*Age on the date of first Lotronex dispensing.						

TABLE 3: Fifteen Most Frequently Recorded Outpatient Diagnoses Among Users of Lotronex

	Number and percent of patients with diagnosis			
	Females		Males	
	N	%	N	%
3-Digit ICD-9 Diagnoses*				
564: Functional Digestive Disorder NEC				
789: Other Abdomen/Pelvis Symptoms				
787: GI System Symptoms				
780: General Symptoms				
401: Essential Hypertension				
461: Acute Sinusitis				
530: Diseases of Esophagus				
477: Allergic Rhinitis				
786: Respiratory System/Other Chest Symptoms				
558: Other Noninfectious Gastroenteritis				
272: Disorder Lipoid Metabolism				
729: Disorders of Soft Tissues				
466: Acute Bronchitis/Bronchiolitis				
724: Back Disorder				
465: Acute URI				

* Diagnoses associated with an evaluation and management visit (CPT procedure code beginning with 992, 993, or 994). Diagnoses recorded for services performed in the 183 days prior to the first Lotronex dispensing or on the date of first Lotronex dispensing. Diagnoses are not mutually exclusive. Patients may have more than one diagnosis.

TABLE 4: Fifteen Most Frequently Recorded Inpatient Diagnoses Among Users of Lotronex

3-Digit ICD-9 Diagnoses**	Number and percent of patients with diagnosis			
	Females		Males	
	N	%	N	%
789: Other Abdomen/Pelvis Symptoms				
787: GI System Symptoms				
564: Functional Digestive Diseases NEC				
786: Respiratory System/Other Chest Symptoms				
276: Fluid/Electrolyte Disord				
401: Essential Hypertension				
530: Diseases of Esophagus				
305: Nondependent Drug Abuse				
558: Other Noninfectious Gastroenteritis				
780: General Symptoms				
311: Depressive Disorder NEC				
493: Asthma				
625: Female Genital Symptoms				
250: Diabetes Mellitus				
278: Obesity and Hyperalimentation NEC				

**Diagnoses recorded during hospitalizations that occurred in the 6 months prior to the first Lotronex dispensing or on the date of first Lotronex dispensing. Diagnoses are not mutually exclusive. Patients may have more than one diagnosis.

TABLE 5: GI Related Inpatient Diagnoses Among Users of Lotronex

	Number and percent of hospitalizations with diagnosis			
	Females		Males	
	hospitalizations		hospitalizations	
ICD-9 Diagnosis Categories*	N	%	N	%
530-537: Diseases of Esophagus, Stomach, and Duodenum				
540-543: Appendicitis				
550-553: Hernia of Abdominal Cavity				
555-558: Noninfectious Enteritis and Colitis				
560-569: Other Diseases of Intestines and Peritoneum				
570-579: Other Diseases of Digestive System				
787: Symptoms involving Digestive System				
At least one of the above related diagnoses				
*Diagnoses recorded during hospitalizations that occurred in the 6 months prior to the first Lotronex dispensing or on the date of first Lotronex dispensing. Diagnoses are not mutually exclusive. Patients may have more than one diagnosis.				

TABLE 6: GI Related Outpatient Procedures Performed Among Users of Lotronex

Procedure Description	CPT or ICD-9 Procedure Code	Number and percent of patients with procedure			
		Females		Males	
		N	%	N	%
Blood, occult, feces, 1-3 simultaneous determinations	82270				
Colonoscopy, flexible, proximal to splenic flexure, with biopsy	45380				
Colonoscopy, flexible, proximal to splenic flexure	45378				
Closed (endoscopic) biopsy of large intestine	4525				
Esophagogastroduodenoscopy (EGD) with closed biopsy	4516				
Colonoscopy	4523				
X-ray, small bowel	74250				
Sigmoidoscopy, flexible, diagnostic	45330				
Endoscopic polypectomy of large intestine	4542				
X-ray, upper GI tract with small bowel follow-through, air contrast, with specific high density barium	74249				
Colonoscopy, flexible, proximal to splenic flexure, with removal of tumors, polyps, or other lesions by hot biopsy forceps or bipolar cautery	45385				
Colonoscopy, flexible, proximal to splenic flexure, with removal of tumors, polyps, or other lesions by snare technique	45384				
Other endoscopy of small intestine	4513				
X-ray, upper GI tract with small bowel	74245				
X-ray upper GI tract, air contrast, with specific high density barium	74246				
Laparoscopic cholecystectomy	5123				
X-ray, colon; barium enema	74270				
Sigmoidoscopy, flexible, diagnostic, with biopsy	45331				
X-ray, colon; barium enema, air contrast with specific high density barium	74280				
X-ray, upper GI tract	74240				
Closed (endoscopic) biopsy of rectum	4824				
Flexible sigmoidoscopy	4524				
Intraoperative cholangiogram	8753				
Cinema X-ray, swallowing function, pharynx and/or esophagus	74230				
X-ray, esophagus	74220				
(Endoscopic) polypectomy of rectum	4836				
Breath hydrogen test (e.g. for detection of lactase deficiency)	91065				
CAT scan of abdomen	8801				
Cholangiography and/or pancreatography, intraoperative	74300				
Colonoscopy, flexible, proximal to splenic flexure, with ablation of tumors, polyps, or other lesions	45383				
Esophagus, acid reflux test, prolonged recording	91033				
X-ray upper GI tract, with KUB, air contrast, with specific high density barium	74247				

TABLE 6 (cont): GI Related* Outpatient Procedures Performed Among Users of Lotronex

Procedure Description	CPT or ICD-9 Procedure Code	Number and percent of patients with procedure			
		Females		Males	
		N	%	N	%
<i>(continued)</i>					
Small intestinal endoscopy, enteroscopy, not including ileum, with biopsy	44361				
Small intestinal endoscopy, enteroscopy, including ileum, with biopsy	44377				
Closed (endoscopic) biopsy of small intestine	4514				
Esophageal motility study	91010				
X-ray, small bowel, via enteroclysis tube	74251				
X-ray, upper GI tract, with KUB	74241				
X-ray, combined endoscopic catheterization of the biliary and pancreatic ductal systems	74330				
Cholangiography and/or pancreatography, postoperative	74305				
Excision of hemorrhoids	4946				
Laparoscopy	5421				
Laparoscopic lysis of peritoneal adhesions	5451				
Anal fistulectomy	4912				
Anal fistulotomy	4911				
Other anal sphincterotomy	4959				
Diagnostic ultrasound of digestive system	8874				
Endoscopic destruction of other lesion or tissue of large intestine	4543				
Endoscopic insertion of stent (tube) into bile duct	5187				
Endoscopic sphincterotomy and papillotomy	5185				
Endoscopic retrograde cholangiopancreatography (ERCP)	5110				
Excision or destruction of peritoneal tissue	544				
Gastric motility (manometric) studies	91020				
Ileoscopy, through stoma, diagnostic	44380				
Intraluminal Dilation of strictures and/or obstructions	74360				
Introduction of long gastrointestinal tube	44500				
Open biopsy of large intestine	4526				
Other local excision or destruction of lesion or tissue of anus	4939				
Pelvic opaque dye contrast radiography	8811				
Rigid Proctosigmoidoscopy	4823				
Sigmoidoscopy, flexible, with ablation of tumors, polyps, or other lesions	45339				
Duodenography, hypotonic	74260				
* See Appendix II for description of GI related outpatient procedures.					

TABLE 7: GI Related* Inpatient Procedures Performed Among Users of Lotronex

Procedures	CPT or ICD-9 Procedure Code	Number and percent of patients with procedure			
		Females		Males	
		N	%	N	%
Esophagogastroduodenoscopy (EGD) with closed biopsy	4516				
Closed (endoscopic) biopsy of large intestine	4525				
Colonoscopy, flexible, proximal to splenic flexure, with biopsy	45380				
Other lysis of peritoneal adhesions	5459				
Colonoscopy, flexible, proximal to splenic flexure	45378				
Other endoscopy of small intestine	4513				
X-ray, small bowel	74250				
Laparoscopic cholecystectomy	5123				
Laparoscopic lysis of peritoneal adhesions	5451				
Colonoscopy	4523				
Laparoscopy	5421				
X-ray, upper GI tract with small bowel	74245				
Blood, occult, feces, 1-3 simultaneous determinations	82270				
Sigmoidoscopy, flexible, diagnostic	45330				
Endoscopic polypectomy of large intestine	4542				
Other incidental appendectomy	4719				
Enterolysis (freeing of intestinal adhesion)	44005				
Colectomy, partial	44140				
Colectomy, partial, with coloproctostomy	44145				
Endoscopy of large intestine through artificial stoma	4522				
Flexible sigmoidoscopy	4524				
Sigmoidoscopy, flexible, diagnostic, with biopsy	45331				
Colonoscopy, flexible, proximal to splenic flexure, with removal of	45384				
Colonoscopy, flexible, proximal to splenic flexure, with removal of	45385				
Left Hemicolectomy	4575				
Closed (endoscopic) biopsy of rectum	4824				
Incision of Perirectal Tissue	4881				
Endoscopic retrograde cholangiopancreatography (ERCP)	5110				
Cholecystectomy	5122				
Endoscopic sphincterotomy and papillotomy	5185				
Closed biopsy of intra-abdominal mass	5424				
Excision/destruction of lesion or tissue of abdominal wall or umbilicus	543				
Cinema X-ray, swallowing function, pharynx and/or esophagus	74230				
X-ray, upper GI tract	74240				
X-ray, upper GI tract, with KUB	74241				
X-ray upper GI tract, air contrast, with specific high density barium	74246				

Table 7 (cont): GI Related* Inpatient Procedures Performed Among Users of Lotronex

Procedures	CPT or ICD-9 Procedure Code	Number and percent of patients with procedure			
		Females		Males	
<i>(continued)</i>		N	%	N	%
X-ray, upper GI tract with small bowel follow-through, air contrast, with specific high density barium	74249				
X-ray, colon; barium enema	74270				
X-ray, endoscopic catheterization of the pancreatic ductal system	74329				
CAT scan of abdomen	8801				
* See Appendix V for description of GI related outpatient procedures.					

TABLE 8: Medical History of Users of Lotronex With At Least One Claim Carrying a Diagnosis of 564.1

Diagnosis*	Number and percent of patients with diagnosis on a visit to any physician				Number and percent of patients with diagnosis on a visit to a gastroenterologist			
	Females		Males		Females		Males	
	N	%	N	%	N	%	N	%
Functional digestive disorders, not elsewhere classified (564)								
Constipation (564.0) (<i>also appears under Constipation and Complications of Constipation</i>)								
Irritable colon (564.1)								
Functional diarrhea (564.5)								
Symptoms involving the digestive system (787)								
Nausea and vomiting (787.0)								
Heartburn (787.1)								
Dysphagia (787.2)								
Flatulence, eructation, and gas pain (787.3)								
Visible peristalsis (787.4)								
Abnormal bowel sounds (787.5)								
Incontinence of feces (787.6)								
Abnormal feces (787.7)								
Other symptoms involving digestive system (787.9)								
Unspecified 787 (with no 4th or 5th digit specified)								

Table 8 (cont): Medical History of Users of Lotronex With At Least One Claim Carrying a Diagnosis of 564.1

Diagnosis*	Number and percent of patients with diagnosis on a visit to any physician				Number and percent of patients with diagnosis on a visit to a gastroenterologist			
	Females		Males		Females		Males	
	N	%	N	%	N	%	N	%
<i>(continued)</i>								
Other symptoms involving abdomen and pelvis (789)								
Abdominal pain (789.0)								
Hepatomegaly (789.1)								
Splénomegaly (789.2)								
Abdominal or pelvic swelling, mass, or lump (789.3)								
Abdominal rigidity (789.4)								
Ascites (789.5)								
Abdominal tenderness (789.6)								
Other symptoms involving abdomen and pelvis (789.9)								
Unspecified symptoms involving abdomen and pelvis (i.e. no 4th or 5th digit specified)								
Diarrhea (009.2, 009.3, 564.5, or 787.91)								
Abdominal pain and bloody diarrhea on the same day (789.0 & 787.91)								
Non-specific colitis (558)								
Gastroenteritis and colitis due to radiation (558.1)								
Toxic gastroenteritis and colitis (558.2)								
Other and unspecified noninfectious gastroenteritis and colitis								
Other (558 without 4th or 5th digit specified)								
Crohn's disease/ulcerative colitis (555, 556)								
Vascular insufficiency of intestine (557)								

Table 8 (cont): Medical History of Users of Lotronex With At Least One Claim Carrying a Diagnosis of 564.1

	Number and percent of patients with diagnosis on a visit to any physician				Number and percent of patients with diagnosis on a visit to a gastroenterologist			
	Females		Males		Females		Males	
	N	%	N	%	N	%	N	%
Diagnosis*								
<i>(continued)</i>								
Conditions affecting gastrointestinal motility								
Diabetes (250)								
Gastroparesis (536.3)								
Dyspepsia (536.8, 536.9)								
Hirschsprung's disease or Aganglionic megacolon (751.3)								
Conditions affecting gastrointestinal absorption								
Intestinal malabsorption (579)								
Malignant neoplasm of small intestine (152)								
Enteritis of small intestine (555.0, 555.2, 555.9)								
Diverticula of small intestine (562.0)								
Atresia of small intestine (751.1)								
Cholelithiasis (574)								

Table 8 (cont): Medical History of Users of Lotronex With At Least One Claim Carrying a Diagnosis of 564.1

	Number and percent of patients with diagnosis on a visit to any physician				Number and percent of patients with diagnosis on a visit to a gastroenterologist			
	Females		Males		Females		Males	
Diagnosis*	N	%	N	%	N	%	N	%
<i>(continued)</i>								
Constipation and Complications of Constipation								
Constipation (564.0)								
Impaction of colon (560.30, 560.39)								
Bowel perforation (569.83, 569.89)								
Bowel obstruction (560.9)								
Megacolon (564.7)								
Paralytic ileus (560.1)								
Non-operative alimentary tract irrigation, cleaning, and local instillation – removal of impacted feces** (96.38)								
Anal fissure and fistula (565)								
Rectal prolapse (569.1)								
Solitary rectal ulcer syndrome (569.41)								
* Claims diagnoses based upon services performed in the 6 months prior to or on the day of the first Lotronex dispensing.								

TABLE 9: Medical History of Users of Lotronex With No Claims Carrying a Diagnosis of 564.1

	Number and percent of patients with diagnosis on a visit				Number and percent of patients with diagnosis on a visit to a gastroenterologist			
	Females		Males		Females		Males	
	N	%	N	%	N	%	N	%
Diagnosis*								
Functional digestive disorders, not elsewhere classified (564)								
Constipation (564.0) <i>(also appears under Constipation and Irritable colon (564.1))</i>								
Functional diarrhea (564.5)								
Symptoms involving the digestive system (787)								
Nausea and vomiting (787.0)								
Heartburn (787.1)								
Dysphagia (787.2)								
Flatulence, eructation, and gas pain (787.3)								
Visible peristalsis (787.4)								
Abnormal bowel sounds (787.5)								
Incontinence of feces (787.6)								
Abnormal feces (787.7)								
Other symptoms involving digestive system (787.9)								
Unspecified 787 (with no 4th or 5th digit specified)								

Table 9 (cont): Medical History of Users of Lotronex With No Claims Carrying a Diagnosis of 564.1

Diagnosis*	Number and percent of patients with diagnosis on a visit				Number and percent of patients with diagnosis on a visit to a gastroenterologist			
	Females		Males		Females		Males	
	N	%	N	%	N	%	N	%
<i>(continued)</i>								
Other symptoms involving abdomen and pelvis (789)								
Abdominal pain (789.0)								
Hepatomegaly (789.1)								
Splenomegaly (789.2)								
Abdominal or pelvic swelling, mass, or lump (789.3)								
Abdominal rigidity (789.4)								
Ascites (789.5)								
Abdominal tenderness (789.6)								
Other symptoms involving abdomen and pelvis (789.9)								
Unspecified symptoms involving abdomen and pelvis (i.e. no 4th or								
Diarrhea (009.2, 009.3, 564.5, or 787.91)								
Abdominal pain and bloody diarrhea on the same day (789.0 &								
Non-specific colitis (558)								
Gastroenteritis and colitis due to radiation (558.1)								
Toxic gastroenteritis and colitis (558.2)								

Table 9 (cont): Medical History of Users of Lotronex With No Claims Carrying a Diagnosis of 564.1

Diagnosis*	Number and percent of patients with diagnosis on a visit				Number and percent of patients with diagnosis on a visit to a gastroenterologist			
	Females		Males		Females		Males	
	N	%	N	%	N	%	N	%
<i>(continued)</i>								
Other and unspecified noninfectious gastroenteritis and colitis (558.9)								
Other (558 without 4th or 5th digit specified)								
Crohn's disease/ulcerative colitis (555, 556)								
Vascular insufficiency of intestine (557)								
Conditions affecting gastrointestinal motility								
Diabetes (250)								
Gastroparesis (536.3)								
Dyspepsia (536.8, 536.9)								
Hirschsprung's disease or Aganglionic megacolon (751.3)								
Conditions affecting gastrointestinal absorption								
Intestinal malabsorption (579)								
Malignant neoplasm of small intestine (152)								
Enteritis of small intestine (555.0, 555.2, 555.9)								
Diverticula of small intestine (562.0)								
Atresia of small intestine (751.1)								
Cholelithiasis (574)								

Table 9 (cont): Medical History of Users of Lotronex With No Claims Carrying a Diagnosis of 564.1

	Number and percent of patients with diagnosis on a visit				Number and percent of patients with diagnosis on a visit to a gastroenterologist			
	Females		Males		Females		Males	
Diagnosis*	N	%	N	%	N	%	N	%
<i>(continued)</i>								
Constipation and Complications of Constipation								
Constipation (564.0)								
Impaction of colon (560.30, 560.39)								
Bowel perforation (569.83, 569.89)								
Bowel obstruction (560.9)								
Megacolon (564.7)								
Paralytic ileus (560.1)								
Non-operative alimentary tract irrigation, cleaning, and local instillation – removal of impacted feces** (96.38)								
Anal fissure and fistula (565)								
Rectal prolapse (569.1)								
Solitary rectal ulcer syndrome (569.41)								
* Claims diagnoses based upon services performed in the 6 months prior to or on the day of the first Lotronex dispensing.								
** ICD-9 procedure code								

TABLE 11. Health Care Utilization Among Users of Lotronex								
	Number and percent of patients/visits							
	0-3 months before Lotronex				4-6 months before Lotronex			
	Females		Males		Females		Males	
Health care utilization variable	N	%	N	%	N	%	N	%
Among those with at least one claim for 564.1								
Number of patients								
With at least one visit to a gastroenterologist								
With at least one visit to any provider								
No. of visits to any provider								
No. of visits to gastroenterologists								
Among those with no claims for 564.1								
Number of patients								
With at least one visit to a gastroenterologist								
With at least one visit to any provider								
No. of visits to any provider								
No. of visits to gastroenterologists								
Total								
Number of patients								
With at least one visit to a gastroenterologist								
With at least one visit to any provider								
No. of visits to any provider								
No. of visits to gastroenterologists								

TABLE 12: Fifteen Most Frequent Outpatient Drug Dispensings Among Users of Lotronex					
		Number and percent of patients with drug			
		Females		Males	
Generic Name	Therapeutic Class	N	%	N	%
Hyoscyamine Sulfate	Antispasmodics				
Azithromycin	Macrolides				
Conjugated Estrogens	Estrogens				
Hydrocodone Bitartrate/APAP	Opiate Agonists				
Lansoprazole	Misc. GI Drugs				
Amoxicillin	Penicillins				
Dicyclomine	Antispasmodics				
Propoxyphene Napsylate/APAP	Opiate Agonists				
Diphenoxylate/Atropine Sulfate	Antidiarrheal Drugs				
Levothyroxine	Thyroid Agents				
Ciprofloxacin	Quinolones				
Alprazolam	Benzodiazepines				
Fluconazole	Antifungal Antibiotics				
Fluoxetine	Antidepressants				
Estradiol	Estrogens				
* Drugs dispensed in the 183 days prior to the first Lotronex dispensing. Patients may have claims for more than one drug.					

TABLE 13: Medication History Among Users of Lotronex*

	Number and percent of patients with drug dispensings			
	Females		Males	
	N	%	N	%
Medication Category**				
Drugs that may induce constipation				
As a side effect				
Antidiarrheal drugs				
Drugs that may induce diarrhea				
Drugs that may affect GI absorption				
Drugs that may produce thrombosis				

* Drugs dispensed in the 183 days prior to the first Lotronex dispensing. Patients may have claims for more than one drug.

** See Appendix VI for description of medication categories

APPENDIX 2. List of Abbreviations and Definitions of Terms

1. The UnitedHealthcare Research Database (UHC)

The UnitedHealthcare Research Database (UHC) is the datasource for this study. The UHC database is described in detail in Section 3.2.

2. Ingenix Pharmaceutical Services, Epidemiology Division

Ingenix Pharmaceutical Services, Epidemiology Division, is the contractor for this study. Ingenix Pharmaceutical Services is a UnitedHealth Group Company.

APPENDIX 3. ICD-9 code for irritable colon (564.1)

Colitis:

- Adaptive
- Enterospasm
- Membranous
- Irritable bowel syndrome
- Mucous
- Spastic colon

APPENDIX 4. Diagnoses and diagnostic codes used in the study of the health care utilization of Lotronex users

<u>Diagnostic Category/Diagnosis</u>	<u>ICD-9 Diagnosis Code(s)</u>
Conditions affecting gastrointestinal absorption:	
Intestinal malabsorption	579
Malignant neoplasm of small intestine	152
Secondary malignant neoplasm of small intestine	197.4
Enteritis of small intestine	555.0, 555.2, 555.9
Diverticula of small intestine	562.0
Atresia of small intestine	751.1
Cholelithiasis	574
Conditions affecting gastrointestinal motility:	
Diabetes	250
Gastroparesis	536.3
Dyspepsia	536.8, 536.9
Hirschprung's disease/Aganglionic megacolon	751.3
Constipation and its complications:	
Constipation	564.0
Impaction of colon	560.30, 560.39
Bowel perforation	569.83, 569.89
Bowel obstruction	560.9
Megacolon	564.7
Paralytic ileus	560.1
Anal fissure and fistula	565
Rectal prolapse	569.1
Nonoperative alimentary tract irrigation, cleaning and local instillation-removal of impacted feces	96.38*
Solitary rectal ulcer syndrome	569.41
Crohn's disease/ulcerative colitis	555, 556
Diarrhea	009.2, 009.3, 564.5, 787.91
Diagnosis of abdominal pain and bloody diarrhea (on the same day)	789.0 & 787.91 & 578.1
Functional digestive disorders, not elsewhere classified (564)	
Constipation (already listed above)	564.0
Irritable colon	564.1
Functional diarrhea	564.5
Nonspecific colitis	558

Appendix 4. (continued)

<u>Diagnostic Category/Diagnosis</u>	<u>ICD-9 Diagnosis Code(s)</u>
Symptoms involving the digestive system	787
Symptoms involving the abdomen and pelvis	789
Vascular insufficiency of intestine	557

* ICD-9 Procedure Code

APPENDIX 5. GI Related Procedures

CPT Codes

Radiology procedures of the gastrointestinal tract (74210-74363)

Occult fecal blood test (82270, 82273)

Medicine/Gastroenterology Section (91000-91299)

Surgeries on the Digestive System

- Incisions (44000-44055)
- Excisions (44100-44160)
- Laparoscopies (44200-44209)
- Enterostomies (44300-44346)
- Endoscopies (44360-44394)
- Introduction (44500)
- Repair (44600-44680)
- Other procedures on the intestines (44700-44799)
- Colonoscopies and sigmoidoscopies (45330-45383)

ICD-9 Volume III Procedure Codes

Operations on the Digestive System (42-54)

- Incision, excision, and anastomosis of intestine (45)
- Other operations on intestine (46)
- Operations on appendix (47)
- Operations on rectum, rectosigmoid, and perirectal tissue (48)
- Operations on anus (49)
- Operations on liver (50)
- Operations on gallbladder and biliary tract (51)
- Operations on pancreas (52)
- Repair of hernia (53)
- Other operations on abdominal region (54)

Miscellaneous Diagnostic and Therapeutic Procedures

- Biliary tract x-ray (87.5)
- Other x-ray of digestive system (87.6)
- Soft tissue x-ray of abdomen (88.0)
- Other x-ray of abdomen (88.1)
- Diagnostic ultrasound of digestive system (88.74)
- Microscopic examination of specimen from lower gastrointestinal tract and of stool (90.9)
- Nonoperative removal of therapeutic device from digestive system (97.5)
- Nonoperative Removal of intraluminal foreign body from digestive system without incision (98.0)

APPENDIX 6. Medication Categories Used in the Study of the Health Care Utilization of Lotronex Users

A. Drugs that may induce constipation:

Antidiarrheal drugs:

- Antimuscarinics/Antispasmodics
- Antidiarrheals

As a side effect:

- Antiparkinsonism anticholinergic
- Calcium channel blockers
- Narcotics
- MAO Inhibitors
- Other Antispasmodics
- Sodium polystyrene sulfonate

B. Drugs that may induce diarrhea

Antibiotics and other anti-infectives

- Chloramphenicols
- Macrolides
- Tetracyclines
- Miscellaneous Antibiotics
- Sulfonamides

Antacids and Adsorbents

(not including calcium carbonate, aluminum carbonate, aluminum hydroxide sodium bicarbonate)

Antidepressants (not including SSRIs)

Antilipemic Agents

- Bile salt sequestrants
- Lipotropics (not including statins)

Antivirals

Cardiac drugs

- Digitalis Glycosides
- Antiarrhythmics
- Beta-adrenergic Blocking Agents

Cathartics and Laxatives

Cholinergic Agents

Colchicine

Pancreatic Enzyme Supplements

C. Drugs that may affect GI absorption:

Antineoplastics

Bile salt sequestrants

Neomycin

Orlistat

Phenobarbital

Phenytoin

Primidone

Risk Management Plan

Attachment 8

CONCEPT PROTOCOL:DRAFT

ADMINISTRATIVE INFORMATION

Protocol Title: A Pharmacy-based Post Marketing Surveillance Study of Lotronex

Protocol Number EPI-40134

Under a classification by a Regulatory Agency Yes

If so, state the agency classification IND 48,487

Drug Name Lotronex

GSK Protocol Contact Person Suzanne F. Cook, Ph.D.
Worldwide Epidemiology

Collaborating Investigator Carol Louik, Sc.D.
Slone Epidemiology Unit

Study Timeline TBD

Estimated date of enrollment of first subject TBD

Estimated date for study completion TBD

Use of a central laboratory N

Collection of genotyping samples N

TABLE OF CONTENTS

	PAGE
1. INTRODUCTION.....	4
2. OBJECTIVES.....	4
2.1. Pilot Study.....	4
2.2. Full study.....	5
3. METHODOLOGY.....	5
3.1. Study Design.....	5
3.1.1. Pilot Study.....	6
3.1.2. Full Study.....	7
3.2. Patient Confidentiality.....	7
3.3. Exposure Definition and Measures.....	8
3.4. Epidemiologic Measures.....	8
3.5. Data Source and Eligibility.....	8
3.6. Adverse Experiences.....	8
3.7. Data Management.....	8
3.8. Sample Size.....	8
3.9. Data Analysis.....	9
3.9.1. Pilot Study.....	9
3.9.2. Full Study.....	9
3.10. Strengths and Limitations.....	9
4. STUDY MANAGEMENT.....	10
4.1. Approval and Consent.....	10
4.2. Study Closure.....	10
4.3. Study Reporting and Publication.....	10
5. LIST OF ABBREVIATIONS.....	11

1. INTRODUCTION

This concept protocol describes a novel, pharmacy-based approach to a post-marketing epidemiologic study of Lotronex. The study will be conducted by the Slone Epidemiology Unit (SEU) at Boston University School of Medicine in collaboration with Eckerd Corporation and the Department of Epidemiology at GlaxoSmithKline. The study can be initiated soon after the re-introduction of Lotronex.

The primary objectives of the study are to describe the characteristics of patients receiving Lotronex, to assess appropriateness of treatment with Lotronex and to evaluate the patients' knowledge and awareness of the risks and benefits of the drug. To accomplish these goals, we will elicit information from patients by self-administered questionnaires regarding their history of IBS and therapies used prior to Lotronex. We will inquire about such items as whether the patient received physician counselling about Lotronex, signed the Physician-Patient Agreement Form and received the Medication Guide. These data will be collected in the initial questionnaire. Data on usage patterns and serious gastrointestinal adverse events will be collected in a follow up questionnaire with the patient.

Patients will be enrolled through the Eckerd pharmacy chain, which has over 1,700 retail pharmacies located in the southern and western United States. Within one week of receiving a prescription for Lotronex or an appropriate comparison drug, patients will be contacted in writing or by phone by Eckerd and invited to participate in the study.

The study will be carried out in two phases: a six-month pilot study and a full study. A pilot study of 2000 patients who are dispensed a first prescription for Lotronex or a comparison drug through the Eckerd pharmacy chain will be conducted to validate and refine the methodology. The pilot data will also provide preliminary substantive data for the development of the full study. The full study, capturing a sample of patients who are dispensed a first prescription for Lotronex or an appropriate comparison drug through the Eckerd pharmacy chain for a period of 2 years, will be initiated after analysis of the pilot data.

2. OBJECTIVES

2.1. Pilot Study

The pilot study will assess the overall feasibility of the methods and will also test a variety of options in the conduct of the study. In addition, the pilot study will provide preliminary data on the same variables to be assessed in the full study, as described in Section 2.2.

Specifically, the objectives of the pilot study are to:

- a. Assess the feasibility and refine the methodologic approach of the study

- b. Examine the utility of using an initial telephone contact versus a mail contact to enroll patients
- c. Determine the utility of a small financial payment to enhance participation in the study

2.2. Full study

The primary objectives of the full study are to describe the characteristics of patients receiving Lotronex, assess the appropriateness of treatment with Lotronex, assess awareness of the risks and benefits associated with treatment and to examine usage patterns the occurrence of serious gastrointestinal adverse events.

This will be accomplished through an initial and follow up questionnaires that seek information in the following areas:

- 1. Demographic characteristics
- 2. History and severity of IBS
- 3. IBS therapies used prior to Lotronex
- 4. Appropriateness of treatment with Lotronex
- 5. Receipt of physician counselling
- 6. Signing and receipt of the Physician-Patient Agreement Form
- 7. Receipt of the Medication Guide
- 8. Understanding of the gastrointestinal adverse events possibly associated with Lotronex
- 9. Understanding of appropriate action to take if a gastrointestinal adverse event occurs
- 10. Patterns of usage and compliance with usage instructions
- 11. Occurrence of serious gastrointestinal adverse events

3. METHODOLOGY

3.1. Study Design

This study will identify, enroll, and follow two cohorts of patients, defined by the use of Lotronex or an appropriate comparison drug. Eligible patients will be contacted by trained Eckerd pharmacy personnel to determine their willingness to participate. The

initial contact with the patient will be made within one week of the dispensing of Lotronex or the comparison drug.

This study will be designed and conducted by the Slone Epidemiology Unit of Boston University School of Public Health. The plan is to proceed with the full study based on the results of the pilot study. For the full study, an Advisory Committee will be established by the SEU to provide guidance and expertise.

3.1.1. Pilot Study

a) Patient Enrollment

To achieve the desired sample size of 2000, 500 patients will be approached each week for four weeks. All patients receiving Lotronex through Eckerd Pharmacies will be approached and invited to participate. Since the number of patients receiving Lotronex is anticipated to be fewer than 500, each week the Eckerd Corporation will use its existing computerized randomization process to select sufficient patients receiving the comparison drug to attain the total of 500 subjects per week. Potential study subjects will be contacted by Eckerd personnel to determine their willingness to participate. During the pilot phase, a variety of approaches to subjects will be evaluated. The initial contact, by mail or by telephone, will be made within one week of filling the prescription and will be done by random assignment.

b) Written Contact

Written contact will consist of 1) a cover letter from Eckerd, 2) materials prepared by Boston University describing the study, 3) the initial study questionnaire, to be completed by the participant and returned to Boston University, and 4) a self-addressed, stamped envelope.

c) Telephone Contact

Telephone contact will be made by pharmacy technicians employed by Eckerd Corporation. The technicians will be provided a script, developed by Boston University, which will include a brief description of the study, and an invitation to participate. Contact will be attempted with each selected study subject on four occasions, which will include both weekends and weekdays, during both day and evening hours. If no contact has been made after these attempts, the subject will be declared unreachable and will be replaced with another eligible subject. If the subject is contacted and agrees to participate, the same procedures will be used to contact him/her. If the subject is ambivalent, he/she will be asked if further information can be provided. If the subject agrees, the same materials will be sent. If the subject is unwilling to receive additional materials, he/she will be classified as a refusal.

Whether subjects are initially approached by mail or phone, they will be given 10 days to respond following the mailing of study materials. If they fail to respond within this time

period, they will be followed with a second mailing. Failure to respond to the second mailing will constitute refusal to participate.

Information derived from the initial questionnaire will be used in the full study to identify typical usage patterns for the drug which will affect the timing of the subsequent questionnaires. In the absence of this information during the pilot phase we plan to send a second mailed questionnaire approximately two months after commencement of treatment. The follow up questionnaire will focus on usage patterns and serious gastrointestinal adverse events. In addition, it will enable us to estimate the proportion of subjects who can be successfully followed with subsequent questionnaires. Although the pilot study will be limited to two questionnaires, we would ultimately seek to follow participants on a regular basis to examine patterns and changes in medication usage among subjects taking Lotronex in the full study.

d) Financial Payment

During the six-month pilot study period, the usefulness of a small monetary payment will be tested. On a random basis, half of each group contacted (mail and phone) will be offered a small (\$5) payment, to be sent to the participant upon receipt by Boston University of the completed questionnaire; the other half will receive no financial payment. No payment will be offered for any subsequent follow-up questionnaires.

3.1.2. Full Study

The study design for the full study will be essentially the same as the pilot study. Based on pilot results, decisions will be made with respect to initial patient approach (phone or mail) and use of a small payment. Appropriate sample sizes will be determined based on pilot results.

3.2. Patient Confidentiality

Patient confidentiality is a major concern and will be protected in a number of ways. GlaxoSmithKline will not receive any patient-identifiable data. In addition, procedures in place at the Slone Epidemiology Unit and Eckerd Corporation will be used to ensure adherence to confidentiality safeguards. All patient information will be maintained in locked files and password-protected databases. Employees are instructed about the importance of maintaining confidentiality and sign an agreement to do so.

The study protocol will be submitted for approval by Boston University's Institutional Review Board to insure protection of human subjects participating in research studies. The contract between GlaxoSmithKline and Boston University will stipulate that no information that can identify an individual patient will be released by the University to GlaxoSmithKline or any other party without the consent of the individual involved. In addition, we will apply for a Federal Certificate of Confidentiality, which will protect information obtained from subpoena.

3.3. Exposure Definition and Measures

Exposure to Lotronex or the comparison drug will be identified by through computerized pharmacy records at Eckerd Corporation.

3.4. Epidemiologic Measures

The initial and follow up questionnaires will elicit information in the following general areas:

- Demographic characteristics
- IBS history
- Therapies used prior to Lotronex
- Appropriateness of treatment with Lotronex
- Receipt of physician counselling
- Signing and receipt of the Patient Agreement Form
- Receipt of the Medication Guide
- Understanding of gastrointestinal adverse events possibly associated with Lotronex
- Understanding of appropriate actions to take if a gastrointestinal adverse event occurs
- Patterns of usage
- Occurrence of serious gastrointestinal events

3.5. Data Source and Eligibility

Eligible patients will be identified through the Eckerd pharmacy database. Patients will be considered eligible for enrollment if they are over the age of 18 and have filled a new prescription for Lotronex through Eckerd.

3.6. Adverse Experiences

Safety data, focusing on serious gastrointestinal events, will be collected in a follow up contact with participating patients.

3.7. Data Management

The Slone Epidemiology Unit at Boston University School of Medicine will be responsible for all aspects of data management.

3.8. Sample Size

The primary comparisons for the pilot study will focus on enrollment rates in the two groups according to method of initial contact and further by offer of a payment. We seek to achieve a participation rate of at least 75%. Given this rate, a sample size of approximately 500 in each of the four groups (mail and phone, with and without

payment) should allow us to detect meaningful differences in response rates between the two enrollment methods and between the presence or absence of an payment. For example, we would have 90% power to detect a reduction in the response rate to 65%. If the highest response rate achieved is only 60%, we would still have 80% power to detect a reduction of 50%. If response rates are higher than anticipated, it may be possible to draw conclusions regarding appropriate methods earlier.

3.9. Data Analysis

3.9.1. Pilot Study

For the pilot study, the primary analyses will be directed toward assessing the feasibility of the various methods under study. The critical factor in determining feasibility will be the enrollment rate. As indicated above, we will compare enrollment rates a) overall for each of the two methods (mail and telephone), b) for use of an payment overall, and c) within enrollment method, for presence or absence of payment . Rate ratios and rate differences for each of the four study groups will be calculated to evaluate the relative efficiency of each approach

We will also compare enrolled and unenrolled subjects with respect to age, sex, zip code of residence, and payment method (i.e. insurance or self-pay).

In addition to enrollment rate, we will also evaluate losses to follow-up in each of the groups defined above, and we will also evaluate these losses with respect to the characteristics described.

A third critical measure of the success of the pilot will be the quality of information obtained. This will be assessed in two ways. First, we will judge quality by exploring the number of non-responses or unknown responses to specific questions. Second, we aim to compare selected variables obtained from the questionnaire with equivalent variables available in the Eckerd database (e.g. use of other prescription medications).

3.9.2. Full Study

Rates for outcomes such as signing the Physician-Patient Agreement Form, receipt of the Medication Guide, and appropriateness of treatment will be calculated overall and according to subject characteristics to identify subgroups of patients who may be at risk of having incomplete information. Other analyses comparing patient characteristics and patient knowledge related to the two study drugs may also be conducted as appropriate.

3.10. Strengths and Limitations

The Eckerd system offers the opportunity to enroll and follow a large cohort of patients under the conditions in which the drugs are actually used. Enrollment of comparison cohorts is carried out in the identical setting. Because the only condition for study

eligibility is filling a prescription, subjects approached should represent a broad spectrum of patient characteristics such as age, sex, and medical history.

A notable advantage of this approach is the opportunity for direct patient contact, which can provide information that would not be available in a monitoring of prescriptions or review of computerized data, including detailed and accurate information about compliance, possible reasons for non-compliance, and data on important outcomes such as serious gastrointestinal adverse events.

With regard to validity, the Eckerd database will allow us to assess the representativeness of the enrolled population with regard to characteristics that are available through the Eckerd system, such as age, sex, zip code of residence, and payment method (i.e. insurance or self-pay).

Finally, from the methodological perspective, the successful completion of the pilot study will demonstrate the feasibility of a new method of postmarketing surveillance, which can be applied to many other topics in the future.

4. STUDY MANAGEMENT

The Slone Epidemiology Unit will be responsible for all aspects of the study design, conduct, data analyses and preparation of study reports and manuscripts. The Principal Investigator at the Slone Epidemiology Unit is Carol Louik, ScD. Suzanne F. Cook, PhD at the Department of Epidemiology at GlaxoSmithKline will serve as technical advisor and study collaborator. The Eckerd Corporation will participate as a contractor to provide access to potential patient participants.

4.1. Approval and Consent

The protocol will receive the necessary approvals as required by GlaxoSmithKline, the Slone Epidemiology Unit and Eckerd Pharmacy, including IRB approval.

4.2. Study Closure

The pilot study will conclude after 2000 patients have been entered into the study. It is estimated that the full study will take 3 years to complete.

4.3. Study Reporting and Publication

Periodic interim reports and a final report of study results will be provided by SEU to GlaxoSmithKline and made available to the FDA. Interim reports will be provided to the Agency every 6 months. Manuscripts summarising the study findings will be submitted to appropriate journals.

5. LIST OF ABBREVIATIONS

IBS	Irritable Bowel Syndrome
SEU	Slone Epidemiology Unit
GSK	GlaxoSmithKline

Risk Management Plan

Attachment 9

Voluntary Expedited Reporting of Post-Marketing, Spontaneous Adverse Events

The NDA for Lotronex Tablets was approved on February 9, 2000. In May of 2000, FDA raised concerns regarding reports of ischemic colitis following treatment with Lotronex and requested that Glaxo Wellcome voluntarily expedite reporting of all cases of ischemic colitis even if these cases did not meet the regulatory criteria for expedited reporting. Glaxo Wellcome verbally agreed to this request during a teleconference on May 26, 2000 and subsequently confirmed the agreement in writing. On November 28, 2000, Glaxo Wellcome informed FDA representatives that, effective that day, it would voluntarily cease sale and distribution of Lotronex. The decision to voluntarily cease further sale and distribution was documented in Glaxo Wellcome's letter to NDA 21-107 dated December 21, 2000. As part of this letter, Glaxo Wellcome documented the history of FDA's request for voluntary expedited reporting of cases of ischemic colitis and informed the Agency that since the product had been withdrawn from sale, it would discontinue the voluntary reporting procedures but to continue to comply with codified reporting requirements.

In January 2001, representatives of FDA and GlaxoSmithKline (GSK) renewed discussions regarding Lotronex with a goal of exploring the feasibility of resuming sale of the product under a mutually acceptable risk management plan. On March 29, 2001 FDA verbally requested that GlaxoSmithKline voluntarily submit as alert reports all spontaneous cases meeting the following criteria:

- All cases of ischemic colitis;
- Ischemic changes or necrosis of the colon as determined by clinical judgment, endoscopic changes or pathology report;
- Constipation or suspected constipation leading to Emergency Room visit or hospitalization; or complications of constipation including (but not limited to) fecal impaction, obstruction, necrosis, or rupture.

GlaxoSmithKline understands that the Agency is interested in rapid receipt of reports meeting these criteria, irrespective of reporting criteria specified in 21 CFR 314.80. Accordingly, upon reintroduction of Lotronex to the market, GSK agrees to provide FDA, as expedited 15 day alert reports, information regarding the cases described below, even though these events are all described in the approved product labeling for Lotronex, and might not meet the regulatory definition of serious. For processing purposes, we will consider such reports to be "other serious" to designate special medical interest, rather than the usual use of this classification. Usually, this designation on FDA form 3500A is intended to identify adverse events that, based on appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the other serious outcomes.

This agreement applies to spontaneous post-marketing reports only.

GSK is prepared to begin this voluntary expedited reporting, if and when commercial distribution of Lotronex resumes, as to the following described cases:

- All spontaneous cases of ischemic colitis;
- All spontaneous cases involving ischemic changes, ischemia, or necrosis of the colon;
- All spontaneous cases involving constipation requiring hospitalization or Emergency Room visit resulting in intervention by a health care provider;
- All spontaneous cases involving the following possible complications of constipation: obstruction, perforation, intestinal ulceration, toxic megacolon, ileus, or impaction requiring hospitalization or Emergency Room visit resulting in intervention by a health care provider.

IV. SUMMARY AND OVERALL CONCLUSIONS

GSK believes that the benefits of LOTRONEX outweigh the possible risks in those patients without therapeutic alternatives. Although data from clinical trials and post-marketing experience have identified complications of constipation and ischemic colitis as possible risks following LOTRONEX treatment, these risks must be assessed against the substantial benefits provided to patients who have failed conventional therapy and, therefore, do not have therapeutic alternatives.

For the vast majority of patients, constipation can be detected early and will resolve with cessation of therapy and supportive care including laxatives as needed. While complications of constipation represent a serious potential risk, sequelae can be mitigated with appropriate patient selection, careful monitoring, and adequate patient education.

Ischemic colitis also represents a clinically significant risk. The relative incidence and nature of reports of ischemic colitis in clinical trials has remained essentially unchanged since approval of the NDA. Nevertheless, even taking into account that approximately 4 times the number of subjects were treated with alosetron in IBS clinical trials versus placebo (11,874 versus 3500), ischemic colitis was reported at a disproportionately greater frequency following treatment with alosetron (16/11,874) than following treatment with placebo (1/3500). Ischemic colitis has also been reported in patients following treatment with marketed product. Therefore, it is essential that all prescribers and patients be appropriately informed of this possible risk since careful monitoring will allow prompt medical management that may ameliorate possible sequelae.

A mechanism linking alosetron to ischemic colitis has not been elucidated. An evaluation of available safety data does not reveal specific risk factors including constipation or use of estrogen or NSAIDs. However, recent data from population-based studies of IBS patients not treated with alosetron suggests that a diagnosis of IBS may be a risk factor for the occurrence of acute colon ischemia. Drugs that induce constipation also are associated with colon ischemia.

A proposed Risk Management Plan (RMP) has been outlined as part of the sNDA that has been developed with the intention of providing a balance between managing the potential for serious risks and allowing access by appropriate patients without creating extraordinary barriers. Since January of 2001, representatives of FDA and GSK have held numerous discussions intended to explore options that might allow GSK to resume the sale of LOTRONEX under a mutually acceptable RMP. These discussions have focused on the following common goals:

- Access to LOTRONEX by patients without therapeutic alternatives;
- Careful use of LOTRONEX in appropriately informed patients;
- Prescribing only by physicians with appropriate knowledge and experience regarding the diagnosis of IBS and managing risks associated with LOTRONEX.

The GSK supplemental new drug application requests FDA approval of new labeling defining a restricted use program intended to limit the drug to specific prescribers and appropriate patients for whom the benefits/risk ratio of LOTRONEX is most favorable; i.e. those who lack therapeutic alternatives. Under the proposed market reintroduction plan, access to LOTRONEX would occur only in association with defined risk management interventions. The intention of the RMP is to provide market controls that will allow appropriate and informed patients access to LOTRONEX while risks are appropriately managed.

The labeling and proposed RMP included in the sNDA have been developed in accordance with substantial new data that have become available since the drug was originally approved for marketing and input received from FDA during the discussions that have transpired over the last year. Supporting the GSK proposals for changes in the conditions of use are:

- New benefit and safety information derived from the cumulative database from all clinical trials conducted as part of the global development program for LOTRONEX;
- A comprehensive assessment of post-marketing safety data;
- New information from ongoing epidemiologic studies regarding the incidence and risk factors for ischemic colitis and complications of constipation in relation to IBS.

In conclusion, GlaxoSmithKline believes that market reintroduction of LOTRONEX with restrictions is appropriate on the basis of the substantial new body of data included in the supplemental new drug application. GlaxoSmithKline also believes that the proposed RMP described in this submission will allow appropriate, informed patients access to LOTRONEX while risks are appropriately managed; striking a balance between the need to mitigate the risk of infrequent but serious adverse events and the need to make the drug available without placing extraordinary burdens on patients and prescribers.

Appendix I: Table of Clinical Trials

TABLE OF CLINICAL TRIALS

Protocol (report #) # Invest. Public.*	Study Design	Treatment Dose(s)	Duration of Drug Treatment	Number for Each Treatment (enrolled)	Age Range in Years (mean)	%M/F (B/W/O)	Status (Date of First Dose)	Country Code	When Submitted*
CONTROLLED CLINICAL STUDIES FOR THE TREATMENT OF IRRITABLE BOWEL SYNDROME									
Studies with Concurrent Placebo Control									
S3B-P12 (GGN/94/022) 43 Inv Aliment Pharmacol Ther 2000; 14: 23-34	Rand, MC, DB, Par, PC, RD	-Alosetron 0.1mg BID -Alosetron 0.5mg BID -Alosetron 2mg BID -Placebo	12 weeks	115 116 114 117	18-74 (43)	27/73 (2/97/1)	Completed (08/08/93)	Belgium, Canada, Denmark, France, Germany, Netherlands, Poland, Sweden, UK	NDA
S3BA2001 (RM1997/004 36/02) 71 Inv Aliment Pharmacol Ther 1999; 13: 1149- 1159	Rand, MC, DB, Par, PC, RD	-Alosetron 1mg BID -Alosetron 2mg BID -Alosetron 4mg BID -Alosetron 8mg BID -Placebo	12 weeks	72 74 76 68 80	18-94 (45)	30/70 (3/94/3)	Completed (12/20/95)	Canada, Germany, Netherlands, UK, US	NDA
S3B20023 (RM2001/000 23/00) 186 Inv	Rand, MC, DB, Par, PC, RD	Alosetron 0.5mg BID Alosetron 1mg BID -Alosetron 2mg BID -Alosetron 4mg BID -Placebo	12 Weeks	127 131 136 140 128	19-85 (44)	100/0 (2/93/5)	Completed (10/27/99)	Canada, US	SNDA

*NDA = June 29, 1999 (no Quality of Life Results were provided for any study)
SNDA = December 7, 2002

TABLE OF CLINICAL TRIALS

Protocol (report #) # Invest. Public.*	Study Design	Treatment Dose(s)	Duration of Drug Treatment	Number for Each Treatment (enrolled)	Age Range in Years (mean)	%M/F (B/W/O)	Status (Date of First Dose)	Country Code	When Submitted*
S3BA3001 (RM1998/004 29/00) (GC1998/000 08/00) 112 Inv Amer Jour of Gastro 2001;96: 455- 459. Arch Intern Med. 2001; 161:1733- 1740	Rand, MC, DB, Par, PC, RD	-Alosetron 1mg BID -Placebo	12 weeks	309 317	18-83 (45)	0/100 (7/88/5)	Completed (10/20/97)	US	NDA SNDA
S3BA3002 (RM1998/004 30/00) (GC1998/000 09/00) 120 Inv Lancet 2000; 355: 1035- 1040 Amer Jour of Gastro 2001; 96: 455-459	Rand, MC, DB, Par, PC, RD	-Alosetron 1mg BID -Placebo	12 weeks	324 323	19-83 (46)	0/100 (3/93/4)	Completed (10/02/97)	US	NDA sNDA

*NDA = June 29, 1999 (no Quality of Life Results were provided for any study)
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Protocol (report #) # Invest. Public.*	Study Design	Treatment Dose(s)	Duration of Drug Treatment	Number for Each Treatment (enrolled)	Age Range in Years (mean)	%M/F (B/W/O)	Status (Date of First Dose)	Country Code	When Submitted*
S3B30011 (RM2000/003 09/00) 180 Inv Amer jour of Gastro; in press	Rand, MC, DB, Par, PC, RD	-Alosetron 1mg BID -Placebo	12 weeks	532 269	18-85 (47)	0/100 (4/93/3)	Completed (09/13/99)	US	SNDA
S3B30013 (RM2000/005 14/00) 149 Inv	Rand, MC, DB, Par, PC, RD	-Alosetron 1mg BID -Placebo	12 weeks	280 281	18-100 (46)	0/100 (5/90/5)	Terminated (11/04/99)	US	SNDA
S3B30015 (RM2001/000 09/00) 25 Inv	Rand, MC, DB, Par, PC, RD	-Alosetron 1mg BID -Placebo	8 weeks	33 16	11-17 (14)	55/45 (0/98/2)	Terminated (2/29/00)	Belgium, Canada, Spain, Sweden, UK, US	SNDA
S3B30025 BP2001/ 00042/00 246 Inv	Rand, MC, DB, Par, PC, RD	-Alosetron 1mg BID -Placebo	24 weeks	1028 520	18-92 (47)	0/100 (<1/99/<1)	Terminated (05/30/00)	Canada, Europe, UK	SNDA
S3B30028 GM2001/ 00122/00 5 Inv	Rand, MC, DB, Par, PC, RD	-Alosetron 1mg BID -Placebo	12 weeks	2 9	25-64 (43)	0/100 (0/0/100)	Terminated (11/14/00)	Asia Pacific	SNDA
S3B30031 NN2001/ 00048/00 31 Inv	Part A: MC, OL, RD Part B: Rand, MC, DB, Par, PC, RD	Part A: Alosetron 1mg BID Part B: -Alosetron 1mg BID -Placebo	Part A: 8-12 weeks Part B: 8 weeks	Part A: 276 Part B: 30 33	19-84 (44)	0/100 (<1/98/2)	Terminated (07/17/00)	Canada	SNDA
S3B40031 (RM2001/001 22/00) 104 Inv	Rand, MC, DB, Par, PC, RD	-Alosetron 1mg BID -Placebo	12 weeks	246 246	19-84 (48)	0/100 (5/90/5)	Terminated (03/22/00)	US	SNDA

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TABLE OF CLINICAL TRIALS

Protocol (report #) # Invest. Public.*	Study Design	Treatment Dose(s)	Duration of Drug Treatment	Number for Each Treatment (enrolled)	Age Range in Years (mean)	%M/F (B/W/O)	Status (Date of First Dose)	Country Code	When Submitted*
Studies with Active Concurrent Control									
S3BB3001 (GM1999/001 31/00) 112 Inv Aliment Pharmacol Therap 1999; 13; 1419- 1427	Rand, MC, DB, Par, RD	-Alosetron 1mg BID -Mebeverine 135mg TID	12 weeks	319 304	17-75 (44)	0/100 (0/98/2)	Completed (12/12/97)	Australia, Europe, Israel, New Zealand, S. Africa, UK	sNDA
S3BB3002 (GM2000/000 29/00) 172 Inv	Rand, MC, DB, Par, RD	-Alosetron 1mg BID -Trimebutine 200mg TID	12 weeks	402 382	18-88 (44)	0/100 (<1/95/5)	Completed (06/04/98)	Canada, Europe, Mexico	sNDA
S3B30026 BP2001/ 00043/00 270 Inv	Part A: Rand, MC, DB, Par, RD Part B: MC, OL, RD	Part A: -Alosetron 1mg BID -Alosetron 2mg QD Part B: Alosetron 1mg BID	Part A: 8 weeks Part B: Up to 6 months	Part A: 485 472 Part B: 136	18-87 (49)	0/100	Terminated (04/14/00)	Australia Germany Switzerland	sNDA
S3B30033 BP2001/ 00044/00 177 Inv	Rand, MC, DB, Par, RD	-Alosetron 1mg BID -Mebeverine 135mg TID	12 weeks	94 86	18-82 (45)	0/100	Terminated (10/13/00)	Netherlands, UK	sNDA

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TABLE OF CLINICAL TRIALS

Protocol (report #) # Invest. Public.*	Study Design	Treatment Dose(s)	Duration of Drug Treatment	Number for Each Treatment (enrolled)	Age Range in Years (mean)	%M/F (B/W/O)	Status (Date of First Dose)	Country Code	When Submitted*
Long-Term Studies									
S3BA3003 (RM1998/004 87/00) (RM1999/ 00344/00) (RM1999/ 00476/00) (RM1999/ 00495/00) (RM2000/002 13/00) 131 Inv Amer Jour of Gastro 2001; 96: 803-811	Rand, MC, DB, Par, PC, RD	-Alosetron 1mg BID -Placebo	1 year	649 210	19-82 (47)	26/74 (4/92/4)	Completed (11/25/97)	US	NDA 205/001 Safety Update (24 Sept. 1999) Safety Update (17 Jan. 2000) sNDA sNDA
S3B30006 (RM2000/001 90/00) 138 Inv.	Rand, MC, DB, Par, PC, RD	-Alosetron 1mg BID -Placebo	48 weeks	351 363	19-79 (46)	0/100 (3/94/3)	Completed (12/18/98)	US	SNDA

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TABLE OF CLINICAL TRIALS

Protocol (report #) # Invest. Public.*	Study Design	Treatment Dose(s)	Duration of Drug Treatment	Number for Each Treatment (enrolled)	Age Range in Years (mean)	%M/F (B/W/O)	Status (Date of First Dose)	Country Code	When Submitted*
Open-Label Studies									
S3B30012 (RM2001/00046/00) 91 Inv	MC, OL, RD	-Alosetron 1mg BID	Part A 8 weeks Part B Cont. for additional 16 weeks	Part A 426 Part B 235	18-61 (40)	0/100 (5/89/6)	Completed (10/06/99)	US	SNDA
S3B30017 BP2001/ 00045/00 133 Inv	Part A: MC, OL, RD Part B: Rand, MC, DB, Par, PC, RD	Part A: Alosetron 1mg BID Part B: -Alosetron 1mg BID -Alosetron 2 mg BID	Part A: 8-12 weeks Part B: 12 weeks	Part A: 876 Part B: 53 53	18-93 (45)	0/100 (<1/>99/<1)	Terminated (05/15/00)	Australia, Europe, New Zealand	SNDA
S3B30019 (RM2001/ 00007/00) 72 Inv	MC, OL, RD	-Alosetron 1mg BID	16 weeks	8	12-17 (14)	38/62 (0/100/0)	Terminated (04/19/00)	Belgium, Canada, Spain, Sweden, US, UK	SNDA
S3B30020 RM2001/ 00035/00 426 Inv	MC, OL, RD	-Alosetron 1mg BID Traditional therapy	6 months	1819 889	18-91 (48)	0/100 (4/92/4)	Terminated (03/21/99)	US	SNDA
S3B40032 RM2001/ 00106/00 267 Inv	MC, OL, RD	Alosetron 1mg BID	12 weeks	587	18-94 (47)	0/100 (2/92/6)	Terminated (10/20/99)	US	SNDA

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TABLE OF CLINICAL TRIALS

Protocol (report #) # Invest. Public.*	Study Design	Treatment Dose(s)	Duration of Drug Treatment	Number for Each Treatment (enrolled)	Age Range in Years (mean)	%M/F (B/W/O)	Status (Date of First Dose)	Country Code	When Submitted*
CLINICAL PHARMACOLOGY STUDIES									
Bioavailability/Bioequivalence Studies									
GHP:89:44 (GPK/91/005) Dewland	Rand, SC, OL, CO	-Alosetron 4mg IV -Alosetron 4mg aqueous oral solution	SD	8 8	20-42 (30)	100/0	Completed (01/29/90)	UK	NDA
GHP:90:13 (GPK/91/007) Dewland	Rand, SC, OL, CO	-Alosetron 4mg IV -Alosetron 4mg tablet -Alosetron 4mg oral solution	SD	6 12 12	18-36 (25)	100/0	Completed (03/26/90)	UK	NDA
Pharmacokinetics: Single-Dose									
GHP:89:23 (GMH/89/024) Millson	Rand, SC, DB, PC, Ascending Dose, CO	-Alosetron 0.015mg IV -Alosetron 0.12mg IV -Alosetron 0.96mg IV -Alosetron 3.75mg IV -Alosetron 10mg IV -Placebo	SD	3 3 2 3 3 14	22-39 (32)	100/0	Completed (06/20/89)	UK	NDA
GHP:89:38 (GMH/90/004) Millson	Rand, SC, DB, PC, Ascending Dose, CO	-Alosetron 0.5mg -Alosetron 1mg -Alosetron 2mg -Alosetron 4mg -Alosetron 8mg -Alosetron 16mg -Placebo IV	SD	3 5 6 6 6 3 15	20-42 (28)	100/0	Completed (09/11/89)	UK	NDA
GHP:90:21 (GMH/91/002) Millson	OL	-Alosetron 4mg	SD	2	52-53 (52)	100/0	Completed (09/24/90)	UK	NDA

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TABLE OF CLINICAL TRIALS

Protocol (report #) # Invest. Public.*	Study Design	Treatment Dose(s)	Duration of Drug Treatment	Number for Each Treatment (enrolled)	Age Range in Years (mean)	%M/F (B/W/O)	Status (Date of First Dose)	Country Code	When Submitted*
GPK:90:01 (GPK/90/006) Weber	Rand, SC, OL, CO	-Alosetron 4mg tablet -Alosetron 4mg IV	SD	32 32	25-82 (50)	100/0 (0/100/0)	Completed (05/03/90)	Germany	NDA
C92-058 (GCP/92/058) Strobel	Rand, SC, OL, CO	-Alosetron 2mg IV -Alosetron 2mg tablet	SD	49 48	19-78 (49)	49/51	Completed (01/26/93)	Germany	NDA
C92-087 (GCP/92/087) Lawlor Analyst 1994; 199: 2395-2401	OL, SD	-Alosetron 1mg	SD	3	28-44 (35)	100/0 (0/100/0)	Completed (02/25/93)	UK	NDA
S3B10903 (NN2001/00012/00) 3 Inv	OL, SD, MC	-Alosetron 1mg	SD	5	7-9 (7)	60/40 (20/60/20)	Terminated (03/31/00)	US	sNDA
S3B10934 (NN2001/00017/00) 3 Inv	OL, SD, MC	-Alosetron 1mg	SD	21	12-17 (14)	43/57 (14/86/0)	Terminated (02/24/00)	US	sNDA
S3B10947 (NN2001/00047/00) Frazier- O'Bannon	OL, SD	-Alosetron 4mg -Oral Solution (10 ml)	SD	7	24-47 (35)	57/43 (0/86/14)	Terminated (08/15/00)	US	sNDA

*NDA = June 29, 1999 (no Quality of Life Results were provided for any study)
sNDA = December 7, 2002

TABLE OF CLINICAL TRIALS

Protocol (report #) # Invest. Public.*	Study Design	Treatment Dose(s)	Duration of Drug Treatment	Number for Each Treatment (enrolled)	Age Range in Years (mean)	%M/F (B/W/O)	Status (Date of First Dose)	Country Code	When Submitted*
Pharmacokinetics: Repeat-Dose									
GPK:90:02 (GPK/90/008) Houston	Rand, SC, DB, Par, PC, RD	-Alosetron 4mg BID -Placebo	9-1/2 days	12 4	19-30 (21)	100/0 (0/94/6)	Completed (04/11/90)	UK	NDA
S3B-101 (UCP/91/014) Kisicki	Rand, SC, DB, Par, PC, RD, Ascending Dose	-Alosetron 1mg BID -Alosetron 4mg BID -Alosetron 8mg BID -Alosetron 16mg BID -Placebo	3 1/2 days	9 9 9 9 12	19-40 (25)	100/0 (2/96/2)	Completed (05/18/90)	US	NDA
S3B-102 (UCP/92/019) Hunt	Rand, SC, DB, Par, PC, RD	-Alosetron 2mg BID -Placebo	27-1/2 days	36 12	19-82 (48)	75/25 (4/88/8)	Completed (02/05/91)	US	NDA
S3BB1011 (NN1998/0003/00) Laurent	OL, RD	-Alosetron 1mg BID	29-1/2 days	30	18-50 (33)	50/50 (3/74/23)	Completed (10/17/97)	US	NDA
Pharmacokinetics: Interaction Studies									
S3BA1001 (NN1999/00011/00) Girard	Rand, SC, DB, PC, CO, RD	-Alosetron 1mg BID + Cisapride 20mg QID -Placebo + Cisapride 20mg QID	4 days	12 12	19-44 (30)	50/50 (0/92/8)	Completed (11/09/98)	Canada	NDA
S3BA1002 (NN1999/00032/00) Serfaty	OL, SC, CO	-Min-Ovral -Alosetron 1mg BID + Min- Ovral	21 days	16 16	19-43 (30)	0/100 (6/94/0)	Completed (08/03/98)	Canada	NDA
S3BA1004 (NN1999/00025/00) Goldwater	Rand, SC, DB, PC, CO	-Alosetron 1mg BID + Theophylline 200mg BID -Placebo + Theophylline 200mg BID	15-1/2 days	13 12	18-44 (28)	0/100 (0/86/14)	Completed (12/01/98)	Canada	NDA

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TABLE OF CLINICAL TRIALS

Protocol (report #) # Invest. Public.*	Study Design	Treatment Dose(s)	Duration of Drug Treatment	Number for Each Treatment (enrolled)	Age Range in Years (mean)	%M/F (B/W/O)	Status (Date of First Dose)	Country Code	When Submitted*
S3BB1004 (NN1996/000 03/00) Pierce	Rand, SC, OL, CO	-Alosetron 4mg -Alosetron 4mg + food	SD	20 20	22-50 (35)	50/50 (0/100/0)	Completed (01/16/96)	Canada	NDA
S3B-201 (UCP/93/ 009) Marder, Meltzer, Miller J. Clin Pharmacol19 95;35: 202- 207	Rand, MC, DB, PC, CO, RD	-Alosetron 1mg + Haloperidol -Placebo + Haloperidol	14 days	11 13	26-62 (40)	85/15 (15/85/0)	Completed (05/24/92)	US	NDA
S3B10935 (NN2000/000 26/00) P. Leese Journ of Clin Pharm 2001; 41: 452-454	OL, CO	-Alosetron 1mg BID + Fluoxetine 20mg SD -Fluoxetine 20mg SD	14 days SD	12 15	21-50 (35)	40/60 (7/93/0)	Completed (10/09/99)	US	sNDA
S3B10936 (NN2000/000 27/00) P. Leese	OL, CO	-Alosetron 1mg BID + Amitriptyline 50mg SD -Amitriptyline 50 mg SD	5 days SD	12 12	18-48 (28)	33/67 (17/75/8)	Completed (11/02/99)	US	sNDA
S3B10937 (NN2000/000 28/00) P. Leese	OL, SD, RD	-Alosetron 1mg + -Vicodin 1 tablet	SD SD	12 12	20-48 (34)	33/67 (25/75/0)	Completed (11/12/99)	US	sNDA

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TABLE OF CLINICAL TRIALS

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S3B10938 (NN2000/000 29/00) P. Leese Journ of Clin Pharm 2001; 41: 455-458	OL, SC, RD	-Alosetron 1mg BID + 1 alprazolam 1 mg	2 days	13	20-49 (32)	31/69 (39/46/15)	Completed (12/01/99)	US	sNDA
		-Alprazolam 1mg	SD	13					
S3B10939 (NN2000/000 30/00) P. Leese	OL, SD, RD	-Alosetron 1mg + ibuprofen 600 mg	SD	12	18-49 (33)	31/69 (15/77/8)	Completed (10/26/99)	US	sNDA
		-Ibuprofen:	SD	12					
S3B10948 (NN2001/000 02/00) Hoelscher	OL,CO,SC	-Oral contraceptive (Alesse-21) OD	21 days	18	19-40 (28)	0/100 (0/72/28)	Completed (07/30/00)	US	sNDA
		-Alosetron 1mg BID	7 days	18					
		-OC OD + Alosetron 1mg BID	21days	18					
Pharmacodynamics: Effects on Intradermal 5-HT Induced Flare Response									
GHP:90:16 (GMH/91/ 007) Millson	Rand, SC, DB, PC, CO	-Alosetron 0.1mg IV	SD	12	21-46 (35)	100/0	Completed (06/19/90)	UK	NDA
		-Alosetron 1mg IV		12					
		-Alosetron 4mg IV		12					
		-Placebo IV		12					
GHP:90:27 (GMH/91/ 015) Sohail	Rand, SC, DB, PC, CO	-Alosetron 0.05mg	SD	12	24-44 (31)	100/0 (0/100/0)	Completed (11/05/90)	UK	NDA
		-Alosetron 0.25mg		12					
		-Alosetron 1mg		12					
		-Placebo		12					
Pharmacodynamics: Effects on Gastrointestinal Transit Time									
C92-057 (GCP/92/ 057) Sohail	Rand, SC, DB, PC, CO	-Alosetron 0.25mg	SD	12	21-50 (33)	100/0 (8/92/0)	Completed (11/16/92)	UK	NDA
		-Alosetron 4mg		12					
		-Placebo		12					
S3B-H03 (GGN/93/012) Read	Rand, SC, DB, PC, CO	-Alosetron 4mg -Placebo	SD	20 20	19-35 (27)	100/0 (0/100/0)	Completed (01/22/93)	UK	NDA

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TABLE OF CLINICAL TRIALS

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S3B-H05 (GGN/94/020) Whorwell Aliment Pharmacol Ther 2000; 14: 775-782	Rand, SC, DB, PC, CO, RD	-Alosetron 2mg BID -Placebo	8 days	11 12	20-37 (24)	100/0 (0/92/8)	Completed (08/23/93)	UK	NDA
S3B-H06 (GM1998/002 87/00) Whorwell Aliment Pharmacol Ther 2000; 14: 775-782	Rand, SC, DB, PC, CO, RD	-Alosetron 2mg BID -Placebo	8 days	12 13	23-56 (39)	36/64 (0/93/7)	Completed (02/17/94)	UK	NDA
S3BB2011 (GM1998/002 75/00) Camilleri Aliment Pharmacol Ther 2000; 14: 869-878	Rand, SC, DB, PC, Par, RD	-Alosetron 1mg BID -Alosetron 4mg BID -Placebo	4 weeks	10 10 6	19-64 (40)	27/73 (0/100/0)	Completed (04/24/97)	UK	NDA
S3B10906 (NN2000/000 67/00) Camilleri	SC, OL, RD	-Alosetron 1mg BID	6 weeks	32	18-67 (43)	47/53 (0/97/3)	Completed (07/15/99)	US	sNDA

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TABLE OF CLINICAL TRIALS

Protocol (report #) # Invest. Public.*	Study Design	Treatment Dose(s)	Duration of Drug Treatment	Number for Each Treatment (enrolled)	Age Range in Years (mean)	%M/F (B/W/O)	Status (Date of First Dose)	Country Code	When Submitted*
Pharmacodynamics: Effects on Esophageal, Small Bowel, and Colonic Motility									
C94-014 (GCP/95/ 048) Campbell	Rand, SC, DB, PC, CO, RD	-Alosetron 2mg BID -Placebo	7 days	21 19	30-79 (54)	68/32 (0/100/0)	Completed (09/02/94)	UK	NDA
S3BB1001 (GM1997/003 07/00) Wingate	Rand, SC, DB, PC, CO, RD	-Alosetron 4mg BID -Placebo	7-1/2 days	12 13	25-49 (32)	43/57 (7/50/43)	Completed (02/16/96)	UK	NDA
S3BB1002 NN2001/ 00059/00 Wingate	Rand, SC, DB, PC, CO	-Alosetron 4mg BID -Placebo	7-1/2 days	8 9	23-50 (34)	67/33 (0/78/22)	Completed (10/11/96)	UK	sNDA
S3BB1007 GM1997/ 00310/00 Smout	Rand, SC, DB, PC, CO, RD	-Alosetron 4mg BID -Placebo	7 days	30 29	24-51 (38)	53/47 (0/97/3)	Completed (7/31/96)	Netherlands	NDA
S3BA1006 (NN2000/000 99/00) Chey	Rand, SC, DB, PC, CO	-Alosetron 1mg BID -Placebo	14 days	20 22	19-78 (47)	32/68 (5/90/5)	Completed (09/07/98)	US	sNDA
S3BA2003 (RM1998/008 19/00) Katz	Rand, SC, DB, CO, PC, RD	-Alosetron 4mg BID -Placebo	7 days	20 20	21-63 (32)	80/20 (5/65/30)	Completed (06/04/97)	US	NDA

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TABLE OF CLINICAL TRIALS

Protocol (report #) # Invest. Public.*	Study Design	Treatment Dose(s)	Duration of Drug Treatment	Number for Each Treatment (enrolled)	Age Range in Years (mean)	%M/F (B/W/O)	Status (Date of First Dose)	Country Code	When Submitted*
Pharmacodynamics: Effects on Visceral Sensitivity									
G91-019 (GMH/91/051) Read	Rand, SC, DB, PC, CO	-Alosetron 1mg -Alosetron 4mg -Placebo	SD	7 7 7	23-55 (36)	12/88 (0/75/25)	Completed (09/15/92)	UK	NDA
C93-059 (FNL/94/ 004) Delvaux Aliment Pharmacol Ther. 1998; 12: 849-855	Rand, SC, DB, PC, Par, RD	-Alosetron 0.25mg BID -Alosetron 4mg BID -Placebo	6-1/2 days	8 11 6	26-64 (47)	52/48	Completed (03/12/94)	France	NDA
S3B-H04 (GGN/93/013) Bruley des Varannes, Galmiche	Rand, SC, DB, PC, CO	-Alosetron 1mg BID -Placebo	6-1/2 days	15 13	20-28 (23)	100/0 (6/88/6)	Completed (04/09/93)	France	NDA
S3B-H08 (FNL/94/ 005) Galmiche	Rand, SC, DB, PC, CO, RD	-Alosetron 1mg BID -Placebo	6-1/2 days	15 17	19-56 (31)	44/56 (0/100/0)	Completed (04/25/94)	France	NDA
S3BB1003 (GM1998/001 96/00) Mayer	Rand, SC, DB, PC, Par	-Alosetron 0.1mg BID -Alosetron 4mg BID -Placebo	6-1/2 days	5 5 4	26-59 (40)	69/31 (0/95/5)	Completed (05/10/96)	US	NDA
S3BB1006 (GM1999/000 98/00) Jacyna	Rand, SC, DB, PC, CO, RD	-Alosetron 4mg BID -Placebo	6.5 days	2 2	39-52 (45)	100/0 (50/50/0)	Completed (05/07/96)	UK	NDA
S3B10945 NN2001/ 00060/00 Simren	DB, RD, PC, CO	-Alosetron 1mg BID -Placebo	15 Days 15 Days	23 23	21-60 (40)	0/100 (0/100/0)	Completed (05/30/00)	Sweden	sNDA
Pharmacodynamics: Effects on Gastrointestinal Bloating									

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TABLE OF CLINICAL TRIALS

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S3BB1009 (GM1999/000 49/00) Whorwell	Rand, SC, DB, PC, CO, RD	-Alosetron 1mg BID -Placebo	14 days	12 13	27-65 (49)	0/100 (0/100/0)	Completed (11/13/97)	UK	NDA
Pharmacodynamics: Effects on Absorption									
S3B-H01 (GGN/93/010) Farthing Aliment Pharmacol Ther 1997;11: 1109-1114	Rand, SC, DB, CO, PC	-Alosetron 4mg -Placebo	SD	14 12	20-35 (23)	100/0 (0/94/6)	Completed (06/10/92)	UK	NDA
S3B-H02 (GGN/93/011) Farthing Aliment Pharmacol Ther 1997;11: 1109-1114	Rand, SC, DB, CO, PC	-Alosetron 4mg -Placebo	SD	10 9	20-34 (24)	100/0 (0/100/0)	Completed (01/14/93)	UK	NDA

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TABLE OF CLINICAL TRIALS

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Pharmacodynamics: Interaction Studies									
GHP:89:17 (GMH/91/025) Freedman	Rand, SC, DB, PC, CO	-Alosetron 0.01mg IV + Scopolamine 0.4mg IM -Alosetron 0.25mg IV + Scopolamine 0.4mg IM -Scopolamine 0.4mg IM -Placebo IV	SD	20	18-38 (26)	100/0 (5/95/0)	Completed (01/22/90)	UK	NDA
				20					
				20					
				20					
GHP:89:37 (GMH/90/009) Millson	Rand, SC, DB, CO, PC	-Alosetron 0.5mg IV + Scopolamine 0.4mg IM -Scopolamine 0.4mg IM -Placebo IV	SD	5	20-39 (28)	100/0	Completed (09/20/89)	UK	NDA
				5					
				5					
C92-006 (GCP/92/006) Cowen Behav Pharmacol 1996; 6: 216- 227	Rand, SC, DB, PC, CO	-Alosetron 2mg + Amphetamine 20mg -Alosetron 2mg -Amphetamine 20mg -Placebo	SD	26	20-41 (28)	100/0 (0/100/0)	Completed (09/28/92)	UK	NDA
				26					
				26					
				25					
S3BA1003 (NN1999/000 89/00) Warrington	Rand, SC, OL, CO, PC, RD	-Alosetron 1mg BID -Mebeverine 135 mg TID + Alosetron 1mg BID	1 week	14	21-38 (29)	0/100 (0/100/0)	Completed (04/17/99)	UK	sNDA
				14					

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sNDA = December 7, 2002

TABLE OF CLINICAL TRIALS

Protocol (report #) # Invest. Public.*	Study Design	Treatment Dose(s)	Duration of Drug Treatment	Number for Each Treatment (enrolled)	Age Range in Years (mean)	%M/F (B/W/O)	Status (Date of First Dose)	Country Code	When Submitted*
Pharmacodynamics: Effects on Intra gastric Acidity									
C92-019 (GCP/92/019) Sohail	Rand, SC, DB, CO, PC	-Alosetron 4mg -Placebo	SD	6 6	18-40 (28)	0/100 (0/100/0)	Completed (05/20/92)	UK	NDA
Pharmacodynamics: Cardiovascular Effects									
GHP:90:05 (GMH/90/012) Millson	Rand, SC, DB, CO	-Alosetron 16mg oral solution -Placebo	SD	1 1	22 (22)	100/0	Completed (02/22/90)	UK	NDA
S3B10932 (NN1999/000 59/00) P. Leese	Rand, SC, DB, CO, PC, RD	-Alosetron 1mg BID -Alosetron 2mg BID -Alosetron 4mg BID -Placebo	4 days	20 20 20 20	21-49 (32)	0/100 (0/95/5)	Completed (07/20/99)	US	sNDA
Pharmacodynamics: Effects on Serotonin Synthesis Rate									
S3B10901 (NN1999/000 93/00) Boivin & Diksic	Part A: Rand, DB, CO, PC, RD Part B: NA	Part A: -Alosetron 1mg -Placebo Part B: No drug	Part A: 2 weeks 2 weeks Part B: NA	Part A 14 14 12	Part A:18-60 (41) Part B:32-62 (48)	47/53 (6/94/0)	Completed (03/19/99)	Canada	sNDA
Pharmacodynamics: Effects on Brain Activation									
S3BA2002 (RM1999/004 94/00) Mayer	Rand, SC, DB, PC, Par, RD	-Alosetron 1mg BID -Alosetron 2mg BID -Alosetron 4mg BID -Placebo -None	3 weeks	16 5 3 23 7	21-59 (39)	52/48 (11/83/6)	Completed (05/20/97)	US	sNDA
CONTROLLED STUDIES OF USES OTHER THAN THOSE CLAIMED IN THE APPLICATION									
Treatment of IBS Anxiety									
S3B30004 (RM/2000/000 1/00) 4 Inv	Rand, MC, DB, Par, PC, RD	-Alosetron 1mg BID -Placebo	8 weeks	32 28	19-73 (46)	0/100 (15/80/5)	Completed (07/31/98)	US	sNDA

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SNDA = December 7, 2002

TABLE OF CLINICAL TRIALS

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Treatment of Non-Cardiac Chest Pain									
S3B20012 (RM2000/003 66/00) Katz	Rand, SC, DB, CO, PC, RD	-Alosetron 1mg BID -Placebo	14 days	4 5	37-62 (50)	0/100 (0/100/0)	Completed (01/02/99)	US	sNDA
Treatment of Dumping Syndrome									
S3B20013 (RM2000/003 67/00) Chey	Rand, SC, DB, Par, PC, RD	-Alosetron 1mg BID -Placebo	3 weeks	9 10	36-79 (57)	42/58 (0/100/0)	Completed (09/01/98)	US	sNDA
Treatment of Non-ulcer Dyspepsia									
S3B20015 (RM2000/001 76/00) 87 Inv Aliment Pharmacol Ther 2001; 15: 525-537	Rand, MC, DB, Par, PC, RD	-Alosetron 0.5mg BID -Alosetron 1mg BID -Alosetron 2mg BID -Placebo	12 weeks	77 79 83 81	19-83 (45)	31/69 (6/85/9)	Completed (4/12/99)	US, Spain, Canada, S. Africa, Norway	sNDA
OTHER STUDIES AND INFORMATION STUDIES COMPLETED BUT SAFETY DATA IS NOT INTEGRATED									
Pharmacokinetics: Single-Dose									
S3BB1010 (PM1999/000 01/00) Decourt, Deray	OL, MC	-Alosetron 1mg	SD	24	23-84 (53)	37/63 (16/84/0)	Completed (01/14/98)	France	NDA
AS-01 (JJD/94/ 001) Murasaki	Rand, SC, OL, PC, CO	-Alosetron 0.5mg -Alosetron 1mg -Alosetron 2mg -Alosetron 4mg -Placebo	SD	3 6 6 6 6	24-38 (30)	100/0 (0/0/100)	Completed (06/92)	Japan	NDA

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TABLE OF CLINICAL TRIALS

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S3B10942 (QN2000/000 47/01) Johnson	OL, SD	-Alosetron 1mg	SD	25	F 18-45 (28-2) M 18-40 (24.5)	52/48 (0/0/100)	Completed (12/15/99)	Korea	sNDA
Pharmacokinetics: Repeat-Dose									
AS-02 (JJD/94/ 002) Murasaki	Rand, Single blind, SC, RD	-Alosetron 1mg BID -Placebo	7 days	6 2	26-30 (27)	100/0 (0/0/100)	Completed (09/92)	Japan	NDA
Pharmacodynamics: Interaction Studies									
AS-03 (JJD/94/ 003) Murasaki	Rand, SC, OL, CO	-Alosetron 1mg -Alosetron 1mg + food	SD	8 8	20-26 (22)	100/0 (0/0/100)	Completed (07/92)	Japan	NDA
Treatment of Carcinoid Diarrhea									
S3BMDIND Camilleri Gut 1998; 42(5): 628-34.	Rand, SC, DB, Par, RD	-Alosetron 0.1mg BID -Alosetron 0.5mg BID -Alosetron 2mg BID	3 weeks	8 9 9	37-81 (67)	62/38	Completed (09/23/94)	US	NDA
S3BMDEX Camilleri Gut 1998; 42(5): 628-34.	OL, compass- ionate Use	-Alosetron 2mg BID	1 year	9	55-81	44/56	Completed (03/20/95)	US	NDA

Inv: Investigators, Public: Publication citation, Rand: Randomized, Str: Stratified, SC: Single-Center, MC: Multiple-Center, DB: Double-Blind, OL: Open-Label, Par: Parallel, CO: Crossover, PC: Placebo-Controlled, SD: Single-Dose, RD: Repeat-Dose

* Only full publications are listed (abstracts are not described).

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