GlaxoWellcome

June 14, 2000

Mr. Thomas H. Perez
Advisors and Consultant Staff
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-21
5630 Fishers Lane
Rockville, MD 20857

Re: NDA 21-107; LOTRONEX® (alosetron hydrochloride) Tablets
General Correspondence: Advisory Committee Meeting

Dear Mr. Perez:

Reference is made to our NDA referenced above and to our upcoming Advisory Committee Meeting on June 27, 2000 to discuss risk management of post-marketing adverse events associated with Lotronex Tablets.

Enclosed please find 40 copies of the meeting package as discussed. If you need further assistance, please give me a call at (919) 483-3073.

Sincerely,

Robert J Baumgartner for

Mark A. Baumgartner, R.Ph.
Director
Regulatory Affairs

Attachment: Advisory Committee Meeting package (40 copies)

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Document Number: RM2000/00271/00

Briefing Document: FDA Advisory Committee Meeting on LOTRONEX (Risk Management)

Date of Report: 12 June 2000

Sponsor Signatory:
(and Medical Officer)

Allen W Mangel, MD, PhD
International Product Development Leader and Director,
Gastroenterology Clinical Development
Glaxo Wellcome Inc.

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1. INTRODUCTION

This briefing document is intended to orient the Advisory Committee Members to information pertinent to discussions on risk management and post-marketing adverse events associated with LOTRONEX that will be discussed at the meeting of the FDA Gastrointestinal Drugs Advisory Committee Meeting scheduled for June 27, 2000.

A New Drug Application (NDA) was submitted for LOTRONEX® (alosetron hydrochloride) Tablets on June 29, 1999. On November 16, 1999, the application was reviewed by the FDA Gastrointestinal Drugs Advisory Committee. The committee voted unanimously for approval. On February 9, 2000 the FDA approved Glaxo Wellcome's NDA (21-107) for LOTRONEX for the treatment of irritable bowel syndrome (IBS) in women whose predominant bowel symptom is diarrhea. During the period since approval through June 1, 2000, it is estimated that a total of 130,000 prescriptions have been dispensed in the United States.

The NDA relied primarily on two identically-designed Phase III studies (S3BA3001 and S3BA3002), with support from two Phase II dose-ranging trials (S3BP12 and S3BA2001), to provide substantial evidence of safety and effectiveness of alosetron for the proposed indication. Data from the Phase II program revealed that efficacy was preferentially observed in females, as compared to males, and that 1mg BID is the optimal clinical dose. Studies to further explore possible physiologic mechanisms responsible for the observed differential gender effect have been initiated and an additional, large dose-ranging efficacy study in males is also underway. In addition to the controlled efficacy/safety studies described above, the Phase III program also included a 12-month, long-term safety trial (S3BA3003). This study was initiated in both genders in order to establish the safety of long term alosetron therapy in women and men. With the exception of study S3BP12, data from the controlled trials have been collected primarily at US sites. The clinical pharmacology studies were conducted primarily outside of the United States.

Glaxo Wellcome believes that LOTRONEX represents a significant improvement for the treatment of females with the diarrhea predominant form of IBS. The drug has been shown to have clinically meaningful efficacy in improving the most bothersome IBS symptoms by providing relief of IBS pain and discomfort, decreasing days with urgency, decreasing stool frequency, and producing firmer stools. Data submitted with the NDA provided evidence of a favorable benefit/risk profile for LOTRONEX in women with diarrhea-predominant IBS.

The clinical development program for LOTRONEX remains active since approval of the NDA with ongoing studies targeted to expand the current scientific and medical knowledge of the product. Studies are planned or ongoing in the following areas:

- Studies intended to better assess safety/efficacy with long-term use.
- Studies intended to assess safety/efficacy in IBS populations other than those covered by the approved labeling including: other IBS subtypes (alternators), males, and pediatrics (females and males).

- Studies intended to assess safety/efficacy in other gastrointestinal disorders e.g. Non-Ulcer Dyspepsia (NUD).
- Trials intended to gain a better understanding of how the product can be used to maximize benefits and minimize adverse side effects (e.g., constipation management)

As part of an ongoing process, Glaxo Wellcome has conducted a thorough review of the adverse event reports from clinical trials, as well as voluntary, spontaneous reports received since the drug has been marketed. Since approval of the NDA, Glaxo Wellcome has submitted to FDA reports of ischemic colitis and complications of constipation derived from both ongoing clinical trials and spontaneous reports. These new adverse event reports have been the subject of several interactions between representatives of FDA and Glaxo Wellcome.

Glaxo Wellcome and the Agency are presently working cooperatively toward labeling modifications for LOTRONEX. Glaxo Wellcome is committed to product labeling that indicates which patients are appropriate for treatment, identifies the product's potential adverse side effects, and explains how the product should be used to maximize benefits and minimize adverse side effects. In addition, Glaxo Wellcome and FDA have held several discussions regarding development of an appropriate risk management plan for LOTRONEX. On May 26, 2000, FDA requested that Glaxo Wellcome present to the Advisory Committee an update of new information regarding the benefits/risks of the product and an overview of its risk management plan. Glaxo Wellcome is committed to a program of responsible stewardship to enhance the safe use of its products. In that spirit, it is hoped that the meeting on June 27 will yield meaningful discussion regarding risk management.

Included with this briefing document is a concise review of the safety and efficacy data at the time of approval and new information that has become available since the drug was introduced for marketing.

The risk management program is described in Section 5 of the briefing document. The risk management plan includes three components: 1) risk definition, an extensive program of research-based activities to better understand the safe use of LOTRONEX; 2) risk communication, examples of which are provided in Section 5 and will be presented in greater detail at the June 27 meeting of the Advisory Committee; and 3) program monitoring, to assure that as new signals emerge, Glaxo Wellcome can take appropriate steps to adjust the risk management program.

2. OVERVIEW OF SAFETY DATABASES

In this briefing document, safety data are reported from both the clinical trials database and from postmarketing spontaneous reports. At the time of approval, approximately 3000 male and female subjects had received alosetron. In our Phase II and III IBS program, 1,263 patients received BID doses of alosetron for up to twelve weeks in duration (studies S3B-P12, S3B2001, S3B3001, and S3B3002). In a long-term safety study, 640 IBS patients received 1 mg alosetron BID for period up to 12 months in duration. In ongoing studies, approximately 1,250 patients had received treatment with alosetron. Four reports of transient ischemic colitis had been submitted and were included in the application review at the time of approval. In all 4 cases, the events all resolved without sequelae. No serious adverse events or complications related to constipation were reported at the time of approval.

At the Agency's request, Glaxo Wellcome has provided a concise overview of the safety data obtained since the time of approval. For preparation of this briefing document and, likewise, the Advisory Committee Meeting on June 27, 2000, the FDA and Glaxo Wellcome agreed to a database cutoff of June 1, 2000. This date applies to information regarding the number of reports of ischemic colitis and constipation as well as determination of the denominators for clinical trials patients as well as post-marketing spontaneous reports to Glaxo Wellcome of other relevant safety information and estimates of exposure for clinical trials and marketing experience.

On June 6, 2000 representatives of the FDA Division of Gastrointestinal Drugs and Coagulation Drug Products and the Office of Drug Evaluation III reviewed individual case reports that include a description of ischemic colitis and cases involving sequelae of constipation. At the conclusion of that discussion it was understood that:

1. FDA and Glaxo Wellcome agreed to a diagnosis of ischemic colitis in 3 cases reported post-approval from clinical trials. As of June 1, 2000, a total of 6852 male and female subjects had received alosetron in repeat dose studies.
2. There have been a total of 5 cases derived from the voluntary, spontaneous reporting system for which FDA and Glaxo Wellcome agree to a diagnosis of ischemic colitis. It is estimated that as of June 1, 2000, a total of 130,000 prescriptions had been dispensed.
3. Post-approval, there have been two cases derived from the clinical trials database that involved hospitalization associated with complications of constipation. One case required surgical intervention.
4. As of June 1, 2000, there have been a total of 4 cases derived from the voluntary, spontaneous reporting system that have involved hospitalization associated with constipation. Of these, two cases required surgical intervention.

This information is summarized on the following page.

Table 1

Date	Ischemic Colitis		Serious Constipation	
	Clin Trials	Spontaneous	Clin Trials	Spontaneous
February 9, 2000 (Approval) (n=3000)	4	NA	0	NA
June 1, 2000 (n=6852)	7 (4 original plus 3)	5	2	4

At the time of approval the rate of ischemic colitis in the clinical trials database was estimated by Glaxo Wellcome as 4/3000 or 1:750. This estimated incidence contrasts to an estimated incidence of 1/300 described by FDA during the Agency presentation at the November 16, 1999 GI Drugs Advisory Committee Meeting. This difference resulted from FDA's selection of a denominator; i.e., the estimated rate considered only the studies in which reports occurred and did not take into account other completed and ongoing trials in which there had been no reports of ischemic colitis (e.g. other IBS trials, studies in other GI disorders, and multiple-dose clinical pharmacology studies). As of June 1, 2000 the estimated rate of ischemic colitis derived from the clinical trials database by Glaxo Wellcome was estimated as 7/6852 or 1:979. An incidence rate from marketing experience cannot be reliably determined.

At the conclusion of the June 6, 2000 teleconference between FDA and Glaxo Wellcome, it was agreed that the relative frequency and severity of cases of ischemic colitis reported post-approval is comparable to reports prior to approval. It was also agreed that there have been rare post-approval reports of patients who have experienced complications of constipation that are severe and had not been observed prior to approval.

3. LOTRONEX CLINICAL DEVELOPMENT

Irritable bowel syndrome (IBS) is one of the most common gastrointestinal disorders. The hallmark features of IBS are chronic, recurrent abdominal pain that is associated with alterations in bowel function. The bowel changes may manifest predominantly as diarrhea, predominantly as constipation or as an alternation between the two (1). IBS is considered a functional bowel disorder in which no endoscopic, radiographic or laboratory findings have been identified (1). Thus, the diagnosis of IBS is based upon a collection of symptoms following an exclusionary work-up for organic disease. The Rome Criteria represent a diagnostic criteria for IBS (2); however, the Rome Criteria are mainly used in clinical trials and have little role in standard medical practice.

Because of the chronic, recurrent nature of the symptoms of IBS, IBS has been shown to have a large negative impact on patient's quality of life (QOL) (3). As illustrated in Figure 1 below, when disease burdens are compared, the QOL burden for IBS has a similar magnitude to that observed in patients with chronic depression.

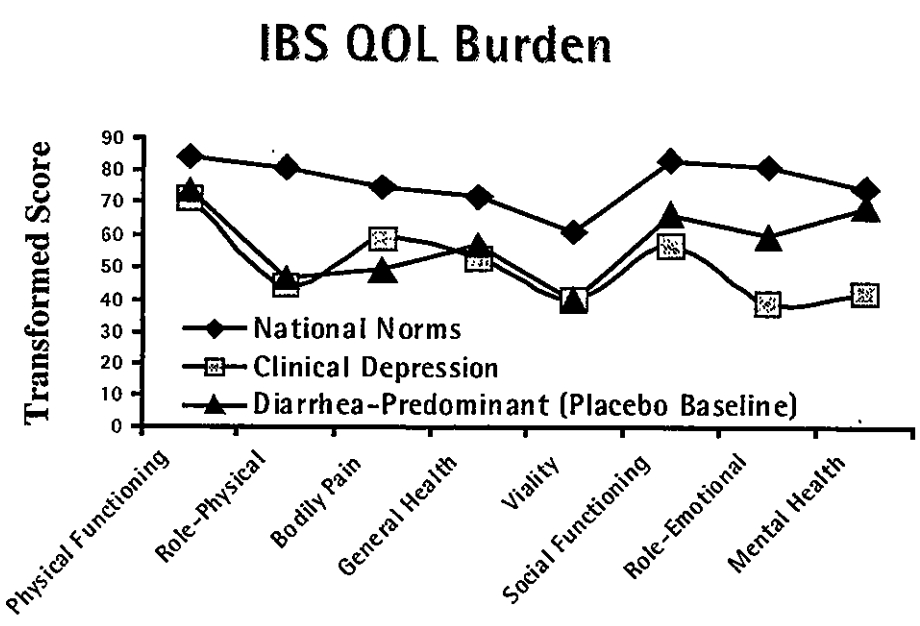


Figure 1

Although IBS does not lead to life threatening sequelae, the consequence of IBS is large, affecting many aspects of patients' everyday lives.

Alosetron is a potent and selective $5HT_3$ receptor antagonist and $5HT_3$ receptors have been shown to play important roles in the motor and visceral-sensory activity of the gastrointestinal tract (4). Thus, a rational basis exists for the efficacy of alosetron in the treatment of IBS.

Based on earlier results in phase II studies (5,6), only women were studied in the phase III program. In phase III, benefit with alosetron was most obvious in the diarrhea-predominant IBS subtype. Since IBS is a female predominant condition with 70-75% of sufferers being women (7), diarrhea-predominant women with IBS represent an important population. A large male dose-ranging study is also ongoing at the present time to more fully explore the safety profile and the potential for benefit in males.

Alosetron fulfills a large unmet medical need for females with diarrhea-predominant IBS, representing the first new agent approved for the treatment of IBS in decades. The feedback that Glaxo Wellcome has received is that many patients' lives have been positively changed following treatment with alosetron.

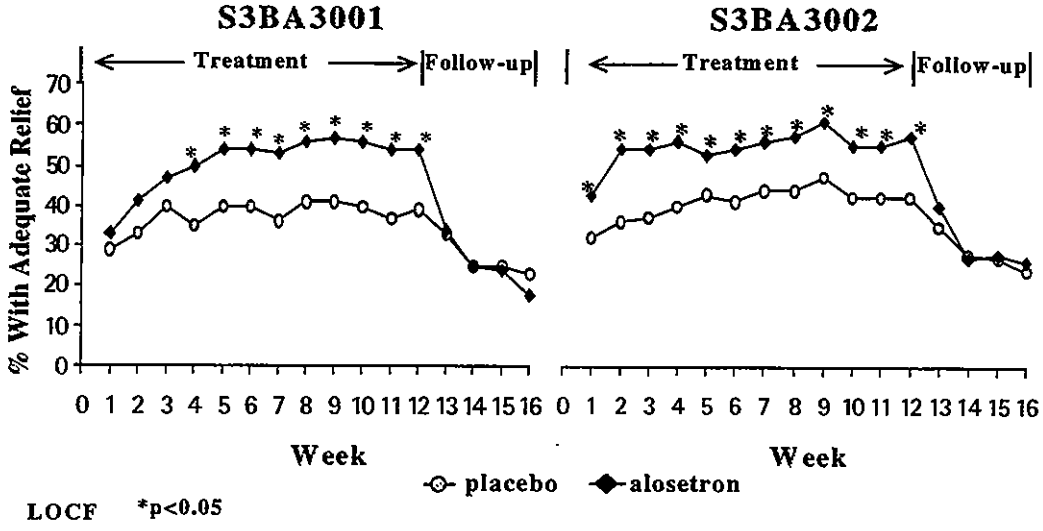
3.1. Review of Efficacy at Time of Approval

Phase III Program: Two identically designed phase III studies which enrolled nonconstipated (diarrhea-predominant and alternating patients), female IBS patients were simultaneously conducted (S3BA3001 and S3BA3002). Each study enrolled over 600 female patients, randomly assigned in a ratio of 1:1 to either treatment with alosetron (1 mg BID) or placebo. The study consisted of a 2 week screening period, 12 weeks of treatment, and a 4 week follow-up phase with no treatment. Data were collected using a novel electronic, touch-tone telephone based system. Patients called in daily to a central computer, and answered a series of automated questions by pressing appropriate keys on the touch-tone pad. Once responses were entered, the data were locked and secured.

Patients were asked daily questions about urgency to defecate, stool frequency and consistency, severity of abdominal pain or discomfort, sense of incomplete evacuation, and bloating. Once every 7 days patients were asked, "IN THE PAST 7 DAYS HAVE YOU HAD ADEQUATE RELIEF OF YOUR IRRITABLE BOWEL SYNDROME PAIN AND DISCOMFORT?" (adequate relief, hereafter). Responses to this question represented the primary efficacy measure for analysis. For women with diarrhea-predominant IBS, a significantly greater proportion of patients treated with alosetron reported adequate relief compared to placebo.

ADEQUATE RELIEF: Shown in Figure 2 are the percentages of diarrhea predominant patients in S3BA3001 and S3BA3002 reporting weekly adequate relief of their IBS pain and discomfort. In each study, significantly more subjects receiving alosetron had adequate relief compared to that seen with placebo. In S3BA3001, significantly more women reported adequate relief by the end of the fourth week of treatment with alosetron than those receiving placebo. Once achieved, significant benefit persisted throughout the remainder of the 12-week treatment period. Following discontinuation of treatment, benefit rapidly dissipated. A similar pattern was noted in S3BA3002, however, an earlier onset of activity was observed. These results provide independent replication, demonstrating consistent and convincing efficacy of alosetron in the treatment of female, diarrhea-predominant IBS patients (Figure 3).

"In the Past Seven Days Have You Had Adequate Relief of Your Irritable Bowel Syndrome Pain and Discomfort?"
(Female Diarrhea-Predominant)



LOCF *p<0.05

Figure 2

"In the Past Seven Days Have You Had Adequate Relief of Your Irritable Bowel Syndrome Pain and Discomfort?"
(Female Diarrhea-Predominant)

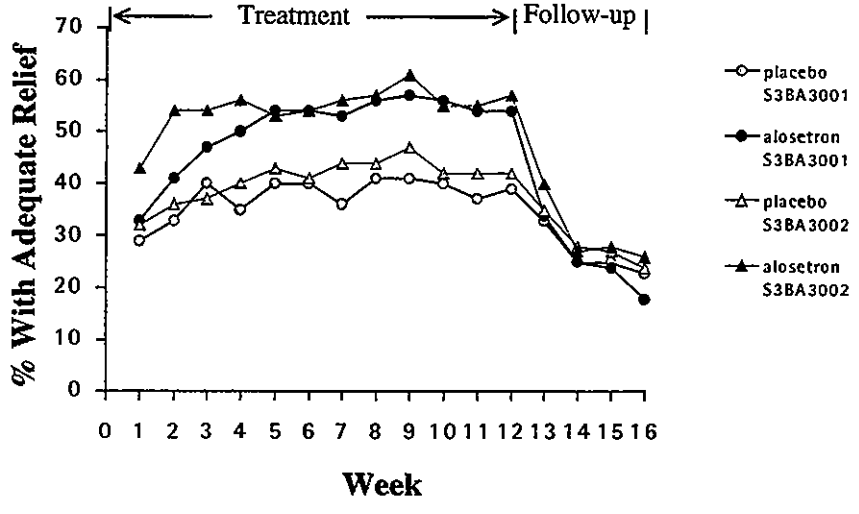


Figure 3

SECONDARY ENDPOINTS: In addition to greater percentages of patients reporting adequate relief of IBS pain and discomfort, alosetron also provided significant improvement in urgency (Figure 4), stool consistency (Figure 5) and stool frequency (Figure 6). For each symptom, significant improvement occurred within the first week of treatment, persisted throughout all 12 weeks of treatment and rapidly dissipated with cessation of therapy.

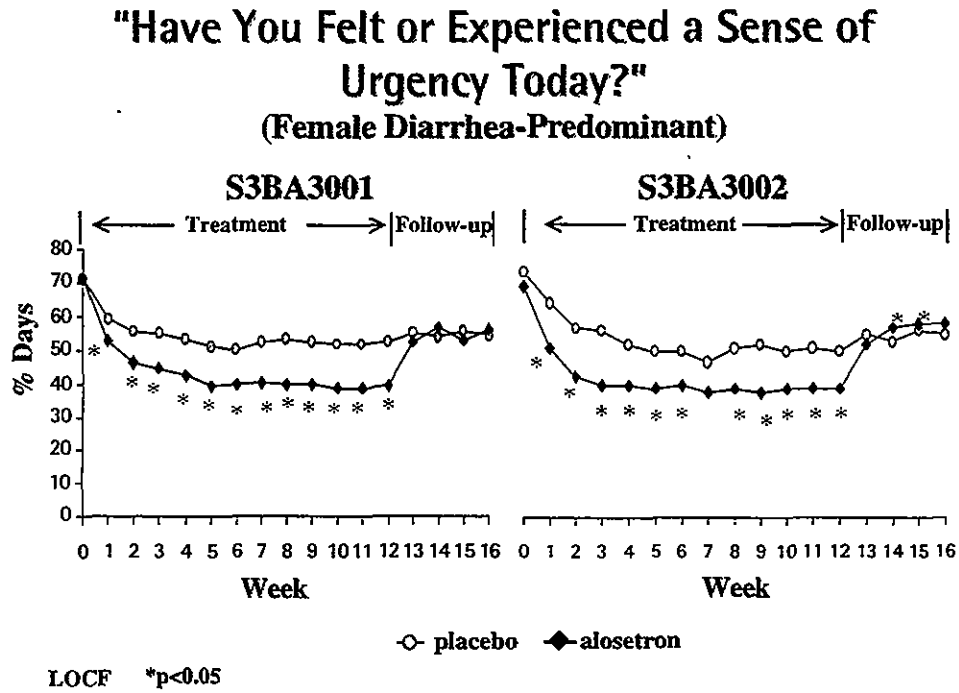
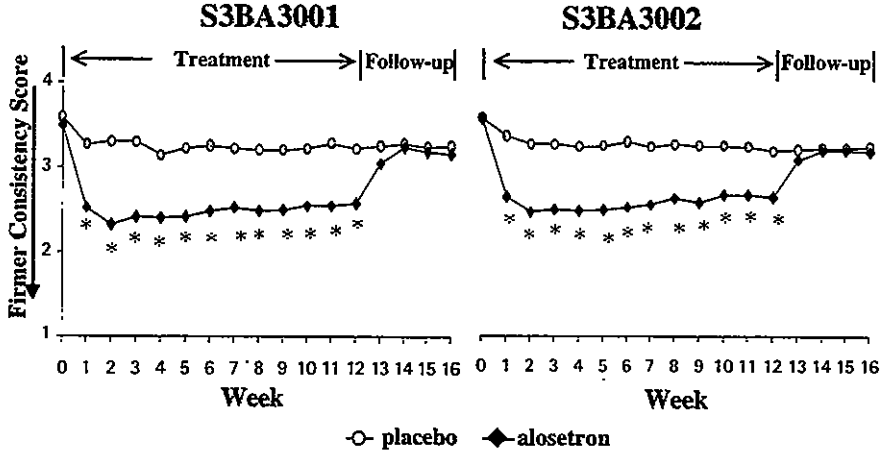


Figure 4

"Please Rate the Consistency Of Your Stool Today"

(Female Diarrhea-Predominant)

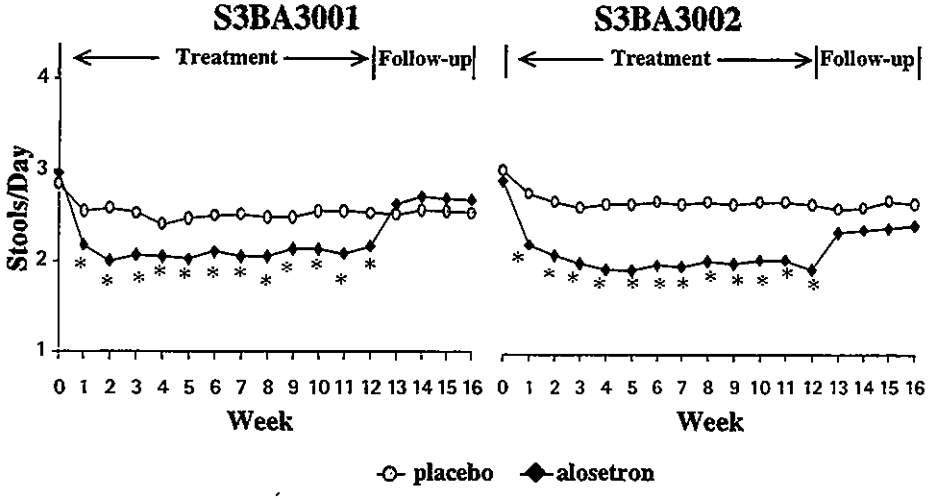


LOCF *p<0.05

Figure 5

"Please Enter the Number of Times You Have Passed Stool Today"

(Female Diarrhea-Predominant)



LOCF * p<0.05

Figure 6

3.1.1. Efficacy Conclusion at Time of Approval

IBS is multidimensional in nature, and alosetron provides multidimensional improvement in female, diarrhea-predominant IBS patients. Alosetron represents the first agent proven in two large, placebo controlled studies to improve multiple symptoms of IBS (i.e., provides adequate relief of IBS pain and discomfort, decreasing days with urgency, decreasing stool frequency and producing firmer stools).

3.2. Review of Safety at Time of Approval

ADVERSE EVENTS: Shown in Table 2 are the most common adverse events reported in the Phase II and Phase III safety/efficacy trials (also referred to hereafter as the repeat dose alosetron studies)

Table 2
MOST COMMON ADVERSE EVENTS
(Phase II/III 12 week studies)

Event	Placebo (n=834)	(Alosetron BID) 0.1mg (n=115)	0.5 mg (n=116)	1 mg (n=702)	2 mg (n=187)	4 mg (n=75)	8 mg (n=60)
Any Event	63%	50%	54%	73%	60%	72%	74%
Gastrointestinal							
• Constipation	5%	3%	13%	27%	20%	20%	29%
• Nausea	6%	3%	7%	7%	7%	9%	3%
• Abdominal discomfort and pain	3%	7%	9%	5%	6%	8%	7%
Neurology							
• Headache	12%	14%	11%	9%	10%	7%	13%

Constipation: Constipation was the only adverse event that occurred commonly (>5% of patients) and at a substantially greater rate during treatment with alosetron as compared to placebo. During treatment with alosetron, if constipation occurred it was generally reported during the first month of treatment, had a median duration of 6 days and most cases were coded as mild or moderate by the study physicians (Table 3). 75% of patients who reported an episode of constipation did not report a second event. As bowel functions are considered relevant endpoints in IBS studies, laxatives were not permitted during the phase III studies and 10% of alosetron-treated patients in these studies withdrew secondary to constipation.

In addition to a specific patient complaint of constipation, an adverse event was also recorded in the Phase III studies if the patient experienced the absence of stool for four consecutive days. If patients went four consecutive days without a bowel movement, then study medication was interrupted for up to four days and constipation was recorded as an adverse event. If bowel movements resumed during study drug interruption, then patients resumed treatment, otherwise they were withdrawn from the study. In the phase III program, 9% of the patients for whom constipation was reported as an adverse event had four consecutive days without a bowel movement. Following interruption of treatment, 88% of the affected patients resumed bowel movements within the 4-day

period and were able to reinitiate treatment with LOTRONEX. No complications related to constipation were reported.

Table 3
CONSTIPATION
(First Episode in Phase II/III 12 week studies)

Parameter	Placebo BID (n=834)	Alosetron 1 mg BID (n=702)
Time to onset (Days-median)	20.5	10.0
Duration (Days-median)	5.0	6.0
Severity		
• Mild	31%	21%
• Moderate	49%	44%
• Severe	21%	35%

S3BP12, S3BA2001, S3BA3001, S3BA3002

DEATHS AND SERIOUS ADVERSE EVENTS: Serious adverse events reported at the time of alosetron approval in the phase II and III program are given in Table 4. All events resolved without sequelae with the exception of the patient with breast cancer whose status remained unchanged.

Table 4
SAEs in Completed 12 Week Repeat Dose Studies in Patients with IBS (S3BP12, S3BA2001, S3BA3001, S3BA3002)*

Placebo (n=834)	Alosetron (N=1255)
Cardiovascular	
Anginal episode (S3BA3001, 04384) Unstable angina (S3BA3001, 05625)	Worsening coronary artery disease (S3BA2001, 02480) Angina (S3BA2001, 00778)
Drug Interaction Overdose & Trauma	
Low back strain (S3BA3002, 07932) Post-polypectomy bleeding (S3BA3002, 06703)	Complications due to operative hematoma of the uterus (S3BP12, 0783) R hip fracture/syncope (S3BA3002, 06333)
Ear Nose & Throat	
	Acute tonsillitis (S3BA2001, 00768) Upper respiratory infection (S3BA3002, 06641)
Endocrine & Metabolic	
Dehydration/diarrhea/vomiting (S3BA3002, 07100)	
Gastrointestinal	
Non-specific esophagitis/ cellulitis R groin, at femoral catheterization site (S3BA3001, 04989) Partial bowel obstruction (S3BA3002, 06585) Bleeding gastric ulcer (S3BA3002, 06462)	**Flare up of IBS (S3BP12, 0910) **Perianal abscess/ **fever (S3BP12, 0786) Diverticulitis (S3BA2001, 02443; S3BA2001, 02063) Ischemic colitis*** (S3BA2001, 02829; S3BA3002, 07195) **Severe segmental colitis (S3BA3001, 15687) Viral gastroenteritis (S3BA3001, 04163; S3BA3001, 04190) **Constipation (S3BA3002, 07002) Chronic/unspecified peptic ulcer with hemorrhage (S3BA3002, 07104) Abdominal pain/ gastritis/ duodenitis (S3BA3002, 07228)
Hepatobiliary & Pancreas	
	Acute pancreatitis (S3BA3001, 04445)
Respiratory	
Asthma attack (S3BA3001, 04960)	Exacerbation of asthma (S3BA3001, 06041) Pulmonary edema (S3BA3001, 04595) Acute bronchitis/vertigo (S3BA3002, 06451) Pneumonia (S3BA3002, 07900)
Musculoskeletal	
	Ischiatiform pain, herniated disc (S3BP12, 0117) Degeneration of R ankle joint (S3BA3002, 07809)
Neurology	
Probable R Bell palsy/ tension headache (S3BP12, 0219)	
Non-site specific	
**Atypical chest pain (S3BA3001, 05759) Chest pain, mid-sternal (S3BA3002, 07937)	Salmonella - infection (S3BP12, 0817) Chest pain (S3BA2001, 02396) Chest pain of unknown etiology (S3BA3001, 05079)
Reproduction	
Ovarian cyst (S3BA2001, 02503) Ruptured R ovarian cyst (S3BA2001, 02670)	Ovarian cyst laparotomy (S3BP12, 0140) Breast cancer (S3BP12, 01080)
Skin	
	**Urticaria (S3BP12, 0777)
Urology	
	Kidney stone (S3BP12, 01035)

* Entries are SAE (Study no., Subject no.) ** SAE(s) attributed to study drug by the investigator
*** Severe segmental colitis was also considered to be ischemic colitis. A 4th case was reported in an ongoing study.

Two deaths were reported in the one year safety study (Study S3BA3003; described below under LONG-TERM SAFETY). Both deaths occurred in patients who had pre-existing cardiac risk factors and were judged by the investigators as not related to alosetron.

- Patient 11950 was a 50 year old obese white female smoker with a history of hypertension and preceding chest pain who developed a cardiac dysrhythmia and died following 180 days of treatment with alosetron 1 mg BID. Preliminary autopsy findings revealed severe atherosclerotic disease with biventricular dilatation.
- Patient 10209 was a 54 year old white male with a history of hypertension who died following 252 days of treatment with alosetron 1 mg BID. The patient presented to the emergency room with sudden onset of dull mid-clavicular pain following an episode of indigestion, shortness of breath and nausea. ECG was normal and the patient was discharged. The following day the patient underwent a cardiac arrest. No autopsy was performed.

LABORATORY VALUES: Laboratory values overall were not affected by treatment with alosetron. A review of liver function tests at time of approval revealed similar rates of placebo and alosetron-treated subjects who had elevations in ALT of ≥3x normal. In one patient (S3BA3001, 04595), a reversible increase in ALT to greater than three times normal levels, with increased AST, alkaline phosphatase, and bilirubin was observed. Following 4 weeks of alosetron treatment, the subject presented with rectal bleeding (~3/30/98) and Crohn's disease was diagnosed. The patient stopped alosetron on 4/20/98 and on 4/22/98 AST, alkaline phosphatase and bilirubin had normalized. ALT was normal on 5/1/98. The respective values are shown below:

Table 5

Parameter	Pretreatment 2/10/98	Week 4 3/20/98	Week8 4/17/98	4/22/98*	Post-Treatment 5/1/98
ALT (6-34)	21	65	131	75 (0-50)	29
AST (9-34)	26	52	111	38 (0-45)	10
ALK Phos (31-110)	103	198	174	156 (25-165)	90
Bili (0.2-1.2)	0.5	0.4	2.1	1.1 (0.1-1.2)	0.7

* Alosetron stopped 4/20/98; laboratory analysis on 4/22/98 performed at outside lab with different range of normal values.

ISCHEMIC COLITIS: As described in Section 2, prior to approval of the NDA, four cases of ischemic colitis had been reported in the clinical development program in which approximately 3000 male and female subjects had been exposed to alosetron in ongoing and completed studies (rate approximately 1:750). All four patients had brief hospitalizations and the events resolved without sequelae. All reports of ischemic colitis occurred in 12 week studies; there were no reports of ischemic colitis in alosetron treated subjects in long-term studies in which patients received continuous alosetron treatment for up to one year. Given below are narratives for the four reported cases:

- Subject 2829 is a 33 year old female who received alosetron 2 mg BID to treat diarrhea-predominant IBS. Concurrently she received an estradiol patch, famotidine

and Tums. Patient is currently a smoker. Two days after initiating therapy with alosetron she experienced severe, cramping abdominal pain and heme positive diarrhea. Alosetron was stopped and 2 days later she was admitted to the hospital with diffuse abdominal tenderness and diarrhea. A colonoscopy revealed erythema, edema and scattered erosions at 40-80 cm. Biopsies revealed no evidence of ischemic colitis.

Hospitalized: 4 days; Constipation: no; Diverticuli: no.

- Subject 15687 is a 41 year old female who received alosetron 1 mg BID to treat IBS. Concomitant medication included 3-4 grams of aspirin per day. 54 days after initiating study treatment she developed rectal bleeding and abdominal pain. Alosetron was discontinued and she was admitted to the hospital. Colonoscopy revealed severe segmental colitis with irregular ulcerations with skip areas consistent with Crohn's disease, ischemic colitis, or self-limiting colitis from the mid-transverse to the proximal sigmoid colon. Biopsies were read as consistent with ischemic colitis.

  Hospitalized : 3 days; Constipation: no; Diverticuli: no

- Subject 7195 is a 48 year old female with a longstanding history of hypertension, Cushing's syndrome, hysterectomy, cholecystectomy, and constipation who received alosetron 1 mg BID. Twenty three days after initiating alosetron she experienced abdominal cramping, nausea, vomiting, rectal bleeding, fever, leukocytosis and constipation. The patient was hospitalized and colonoscopy revealed mucosal sloughing, ulceration and inflammation from 30-60 cm. Biopsies were read as consistent with ischemic colitis.

  Hospitalized: 1 day; Constipation: yes; Diverticuli: no.

- Subject 34069 is a 61 year old postmenopausal female who received alosetron 1 mg BID for 7 days for the treatment of IBS. Patient was also receiving amitriptyline and raloxifene. The patient developed severe abdominal pain on day 8 and alosetron was discontinued. An abdominal CT revealed mural thickening of the entire transverse and descending colon, as well as the distal ascending colon at the hepatic flexure. Findings were compatible with some form of colitis-infectious or inflammatory colitis considered most likely. Admission labs were notable for leukocytosis. The patient received 3 days of antibiotics. On day 6 a colonoscopy was performed revealing patchy areas of erythema/edema adjacent to more pale areas, diverticuli and large hemorrhoids were noted. Biopsies were interpreted as consistent with ischemic colitis. She was discharged the next day to home.

  Hospitalized: 6 days; Constipation: no; Diverticuli: sigmoid

To better understand the possible development of ischemic colitis during treatment with alosetron, Glaxo Wellcome had taken these steps as of the time of approval:

- Reviewed toxicology studies in which animals had received high dose alosetron for up to two years duration. In these studies no suggestion of colonic or small intestinal lesions was found (Attachment 1).

- Evaluated the ability of alosetron to directly constrict blood vessels. No spasmogenic activity was noted in dog mesenteric arteries as assessed by changes in spontaneous tone or neurogenically mediated contractions (Attachment 2).
- Reviewed cases of rectal bleeding in the clinical development program for the potential of mis/undiagnosed ischemic colitis. There was no evidence that ischemic colitis was mis/undiagnosed as rectal bleeding (Attachment 3).

Additionally, the effect of alosetron on colonic mucosal microcirculation in rats had been evaluated. Alosetron had no effect on mesenteric blood flow (Attachment 4).

Post-approval, additional studies are being planned and conducted (see below).

LONG-TERM SAFETY

In addition to the Phase II and III safety/efficacy trials, the NDA also contained data from a long-term safety trial (S3B3003) conducted in to comply with the ICH guideline. By prior agreement with the Agency, a report containing data for at least 300 patients treated continuously for 6 months was submitted as part of the NDA on June 29, 1999 (first interim report). A second report was included in the NDA safety update on September 24, 1999 (second interim report) which was intended to provide data for at least 100 patients treated continuously for 12 months.

The first interim analysis included data from 728 patients (553 received alosetron, 175 placebo). Of these, 330 received 1 mg alosetron and 119 received placebo twice daily for at least 6 months. The second interim analysis included data from all 850 patients who received study medication. Of these, 560/850 patients received study drug for at least 6 months (415 alosetron and 145 placebo) of whom, 257 had received study drug continuously for 1 year (187 alosetron and 70 placebo).

The most common treatment-emergent adverse events reported at the time of the NDA Safety Update involved the gastrointestinal and neurological body systems. A summary of the events for these body systems is provided in Table 6 below.

Table 6
Most Common Treatment-Emergent AEs in Alosetron Long-Term Safety Study (S3BA3003) at time of NDA Safety Update: GI and Neurology

Body System	Adverse Event	% of Patients Reporting Adverse Event	
		Placebo (N=210)	Alosetron 1mg bid (N=640)
Any Body System	Any Event	75	80
Gastrointestinal	Constipation	5	31
	Diarrhea	9	8
	Abdominal discomfort and pain	6	9
	Nausea	5	8
	Gastrointestinal discomfort and pain	4	7
Neurology	Headaches	6	9

A similar pattern and frequency of adverse events were noted with 12 month dosing of alosetron as was seen in the 12 week Phase II and III studies. Constipation was the only adverse event occurring notably more frequently in alosetron-treated subjects. In the alosetron group, 31% (201/640) of patients reported constipation compared with 5% (10/210) of patients in the placebo group.

In addition to study S3BA3003, at the time of approval there was a large, placebo-controlled, Phase III study ongoing that was intended to obtain safety and efficacy data for continuous treatment through 48 weeks (S3BA30006). Since the data remained blinded, safety information from this trial did not contribute to the NDA approval. Results from this trial are presently under analysis with availability targeted for July 2000.

3.2.1. Safety Conclusion at Time of Approval

At the time of approval, more than 3000 volunteers and patients had participated in 52 completed and 15 ongoing studies. The primary safety data were provided from two 12-week Phase II trials conducted in women and men with IBS; two 12-week Phase III trials conducted in women with IBS; and a 12-month, long-term safety study conducted in women and men.

Of the 640 patients randomized to alosetron treatment in the long-term safety study, 415 (65%) received alosetron 1mg bid for at least 6 months (314 females and 101 males) including 187/640 (29%) who received 1mg bid alosetron for at least 1 year (117 females and 70 males).

Data from the studies provided in the NDA support the following conclusions.

- Constipation was the most frequently observed adverse event in both the 12-week repeat-dose studies and long-term safety study. Constipation occurred in 27% of alosetron-treated patients in the 12-week repeat dose studies (5% on placebo) and 31% following up to 12-months of treatment with alosetron (4% on placebo). The comparable incidence of constipation between patients treated for 12 weeks and those treated for up to 12 months indicates that constipation does not become more frequent with an extended duration of alosetron dosing.
- The incidence of serious adverse events was similar in alosetron- and placebo-treated patients (4% and 5%, respectively).
- No greater propensity for AEs was observed when examined by age, gender, race or female hormone use.

In the alosetron clinical development program there were four reports of acute, transient ischemic colitis without sequelae. Review of all events of unexplained rectal bleeding revealed no evidence of undiagnosed events of ischemic colitis.

3.3. Update on Efficacy and Safety

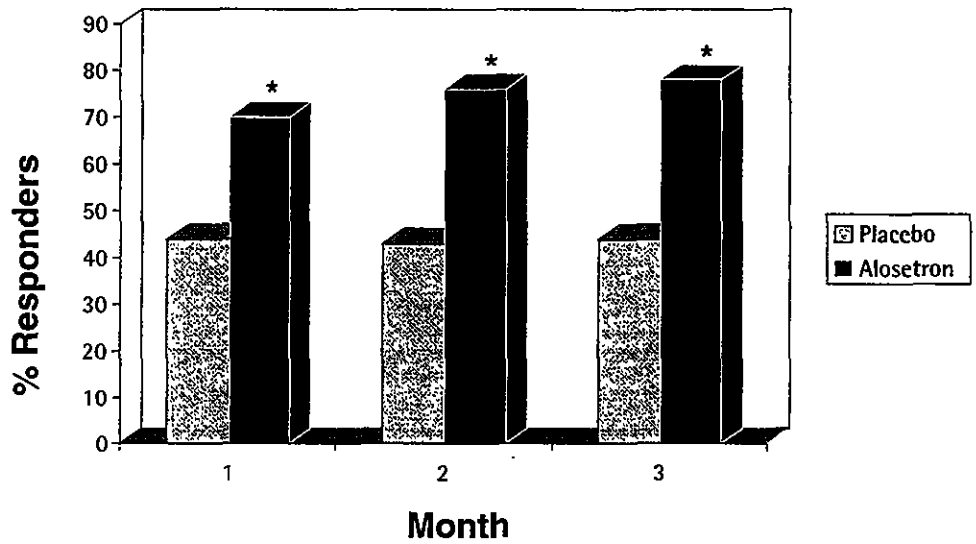
3.3.1. Update on Efficacy

The clinical development program for alosetron remains active since approval of the NDA on February 9, 2000. Subsequent to approval, Glaxo Wellcome has recently completed a randomized, double-blind, placebo controlled, trial designed to evaluate control of bowel urgency (S3B30011). In addition, Glaxo Wellcome has completed two large active comparator trials to support non-US registrations (S3BB3001 and S3BB3002). Since these studies have been recently completed, FDA has not yet had the opportunity to review the data.

IBS is a multidimensional disorder and alosetron produces multidimensional improvement. The data above shows that alosetron provides adequate relief of pain and discomfort and improves days with urgency, stool consistency and frequency. To appreciate the overall benefit of alosetron across the multiple endpoints, we incorporated a global improvement index in study S3B30011. The study randomized 801 diarrhea-predominant females to 12 weeks treatment with placebo or alosetron 1mg BID (1:2 randomization scheme).

The IBS Global Improvement Scale consisted of the following question: "Compared to the way you usually felt during the 3 months before you entered the study, are your **IBS symptoms** over the past 4 weeks: substantially worse, moderately worse, slightly worse, no change, slightly improved, moderately improved, or substantially improved." A global improvement responder was prospectively defined as patients who reported substantial or moderate improvement on the 7-point IBS Global Improvement Scale. Alosetron produced robust benefit on the global improvement scale (Figure 7). At each monthly interval, significant and substantial (25-30%) benefit was seen with alosetron treatment as compared to that seen with placebo.

Global Improvement Responder



* p<0.001

Figure 7

Results are also available from two additional large (>600 patients) IBS studies in women comparing 12-weeks of alosetron treatment to two of the most commonly used IBS agents in Europe: mebeverine (an antispasmotic agent) and trimebutine (an opioid-like agent). In both studies, a greater proportion of women treated with alosetron reported adequate relief compared to either mebeverine (S3BB3001) or trimebutine (S3BB3002). Shown in Figure 8 are the weekly adequate relief responses with alosetron, mebeverine and trimebutine in the diarrhea-predominant female patients.

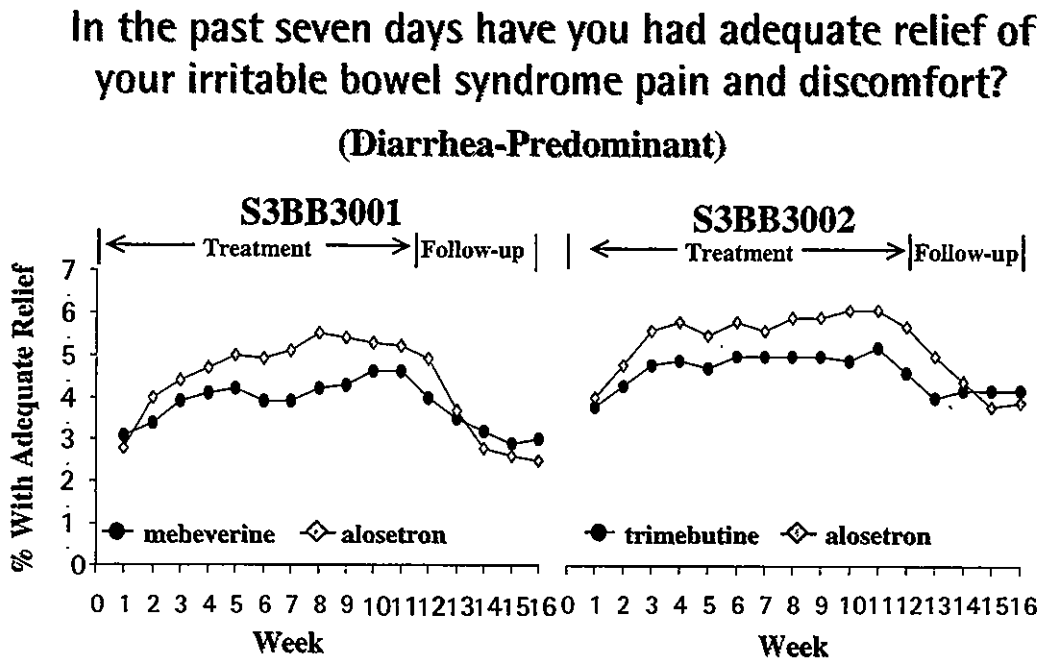


Figure 8

3.3.2. Efficacy Conclusion

Additional data since the time of approval of alosetron confirm consistent and reproducible treatment effects in female, diarrhea-predominant IBS patients.

3.3.3. Update on Safety

Shown in Table 7 are the most frequently reported adverse events for the integrated alosetron safety database for all completed repeat dose phase II and III studies in the core alosetron clinical program. Included are results from completed studies in IBS patients and other functional bowel diseases. Constipation remains as the only adverse event that was reported as a common adverse event (>5% of patients) and that occurred at a substantially higher rate on alosetron than on placebo.

Since the November 16,1999 GI Drugs Advisory Committee Meeting, the 12 month safety study with male and female IBS patients (S3BA3003) has been completed. The final report for study S3BA3003 was submitted on January 17, 2000. The final report provided data for 558/850 patients who received study drug for at least 6 months (414 alosetron and 144 placebo) of whom, 439 patients received study drug for 1 year (323 alosetron and 116 placebo). Although for some patients the duration of exposure had increased, there were no patients described in the final report who had not previously been included in the second interim report.

The most commonly reported adverse events noted in the completed 12 month study are given in Table 8. A similar pattern and frequency of adverse events were noted with 12 month dosing of alosetron as was seen in the 12 week studies. Similar to the 12 week studies, most reports of constipation were of mild or moderate severity, were single episodes of about 8 days duration, and occurred a median of 13 days after initiating treatment.

Table 7
ADVERSE EVENTS
(Phase II/III 12-Week Studies)

Event	Placebo (n=1225)	(Alosetron BID) 0.1mg (n=115)	0.5 mg (n=193)	1 mg (n=2135)	2 mg (n=275)	4 mg (n=88)	8 mg (n=68)
Any Event	63%	50%	60%	70%	64%	66%	74%
Gastrointestinal							
• Constipation	8%	3%	26%	28%	28%	22%	29%
• Nausea	5%	3%	5%	7%	7%	8%	3%
• Abdominal discomfort and pain	4%	7%	6%	6%	5%	7%	7%
Neurology							
• Headache	10%	14%	10%	9%	9%	6%	13%

Table 8
MOST COMMON ADVERSE EVENTS
12 Month Study

Event	Placebo (n=210)	Alosetron BID 1 mg (n=640)
Any Event	76%	83%
Gastrointestinal		
• Constipation	5%	32%
• Nausea	7%	8%
• Abdominal discomfort and pain	7%	10%
Neurology		
• Headache	8%	10%

Study S3BA3003

LABORATORY VALUES: In the clinical development program, subsequent to approval of alosetron, 0.9% of placebo-treated patients and 0.4% of alosetron-treated patients showed ≥3x elevation in ALT. In the 12 month safety study, 1% of placebo treated patients and 0.3% of alosetron treated patients exhibited a 3 fold or greater elevation in ALT. For placebo-treated patients peak elevations ranged from 3.4-9.6 fold normal and between 3.5-4.3 fold normal in alosetron treated patients.

In the spontaneous reporting database, two patients were reported to show increased liver function tests. The MEDWATCH reports of the two patients are provided in Attachment 5 and summarized below.

- A0119607A: A 75 year old female with a history of multiple drug allergies, intractable nausea and vomiting, small bowel obstructions, chronic bronchiectasis, aortic insufficiency, mitral regurgitation and IBS. The patient had a 3-4 week history

of fluid retention edema, a recent exacerbation of COPD and had recently begun alosetron. Following the second dose she reported to her physician's office with pitting edema up to her waist, bloody diarrhea, hypotension, cool blue toes and shortness of breath. Patient was concurrently taking torasemide, ciprofloxacin, guaiphenesin, famotidine, salcatonin and recently discontinued mirtazapine. She was hospitalized and treated with IV fluids and dopamine. During hospitalization she developed acute renal failure and her chest X-ray suggested congestive heart failure. Hepatic ultrasound showed a hyperechoic liver and some ascites. This was reported as consistent with fatty changes or cirrhosis. LFTs during hospitalization were elevated to ALT 891, AST 260, alkaline phosphatase was 59. All medications were stopped and after a total of 7 days in the hospital she was discharged with a presumed diagnosis of acute hepatitis with severe hepatotoxic reaction.

- A0120634A: A 80 year old female received alosetron for IBS. 5 weeks after initiating alosetron she had an elevated SGOT/SGPT and alkaline phosphatase to 299, 210, and 155, respectively. She was hospitalized and alosetron was discontinued. A CT scan showed mild dilatation of intrahepatic ducts. Three days later her LFTs had normalized.

ISCHEMIC COLITIS: At the time alosetron was approved, there were 4 reports of ischemic colitis out of the approximately 3000 male and female subjects who had received alosetron (RATE 1:750). In the clinical development program to date, there is a cumulative total of 7 reports of ischemic colitis (4 original plus 3 new reports) out of approximately 6852 male and female subjects exposed to alosetron in completed and ongoing studies (rate=1:979; rate for females=1:805). Of the three new events, two of the patients were not hospitalized, and the other patient had a brief hospitalization. No patient exhibited sequelae. In the 12 month safety study there has been one report of ischemic colitis in a placebo treated patient. Narratives for the 3 new cases are given below and a summary of all cases in the clinical development program is presented in Table 9.

- Subject 78134 is a 20 year old female with a history of kidney stones who received alosetron 1 mg BID to treat her IBS. Concurrently she received levonorgestrel/ ethinyl estradiol as an oral contraceptive and she also is a smoker. Three days (4 doses) after initiating therapy with alosetron she developed nausea, vomiting, and severe crampy abdominal pain. On examination she was reported to have diffuse tenderness of her abdomen on palpation. She was admitted to the hospital and on the next day developed rectal bleeding. Colonoscopy was performed and revealed erythema with loss of vasculature and a few shallow ulcers at the splenic flexure to descending colon. Biopsy was read as consistent with ischemic colitis. The events resolved and the patient was discharged.

  Hospitalization: 3 days; Constipation: no; Diverticuli: no

- Subject 72823 is a 64 year old female who was treated with alosetron 1 mg BID for IBS. Concurrently she received thyroxine, zolpidem, lansoprazole, alprazolam, estradiol and prasterone. One day after initiating study drug she reported constipation and subsequently developed abdominal pain and bloody diarrhea. The

next morning she presented to her physician's office. A flexible sigmoidoscopy was attempted but aborted and alosetron was discontinued. Four days later a colonoscopy was performed and reported to show ulceration and inflammation proximal to the splenic flexure with areas of a nonspecific colitis in the descending colon. Biopsies were read as consistent with, but not specific for, ischemic colitis.

Hospitalization: 0 days-managed as an outpatient; Constipation: yes; Diverticuli: no

- Subject 72824 is a 57 year old female with a history of severe reflux disease who received alosetron 1 mg BID for the treatment of IBS. Concurrently she received conjugated estrogens, atenolol, lansoprazole and clonazepam. Four days after initiating alosetron, the subject developed abdominal cramps, diarrhea, and rectal bleeding. Alosetron was discontinued and 6 days later a colonoscopy revealed nonspecific colitis in the descending and sigmoid colon. Biopsies were read as consistent with ischemic colitis. The patient's symptoms had resolved at that time.

  Hospitalization: 0 days-managed as outpatient; Constipation: no; Diverticuli: no

Table 9
ISCHEMIC COLITIS REPORTS
(Clinical Development)

Subject #	Age	Treatment Days	Hospitalization	Constipation/ Hard Stools	Hormones
2829	33	2	4 days	-	OCP
15687	41	54	3 days	-	-
7195	48	23	1 day	+	-
34069	61	7	6 days	-	-
78134	20	2	3 days	-	OCP
72823	64	2	Not hospitalized	+	HRT
72824	57	4	Not hospitalized	-	HRT

Bold indicates new cases since approval.
OCP=oral contraceptive pills HRT=hormone replacement therapy

Since approval of alosetron and as of the June 1, 2000 cutoff date, there have been approximately 130,000 alosetron prescriptions dispensed. In the post-marketing, spontaneous reporting database there have been 5 reports of ischemic colitis. A summary of these cases is presented below and in Table 10, with the MEDWATCH reports in Attachment 5.

- A0119468A: A 50 year old female with pre-existing constipation and prior history of hospitalization for abdominal pain and rectal bleeding was prescribed alosetron. After 2-3 weeks of therapy she developed increasing constipation, abdominal pain and rectal bleeding. Colonoscopy was performed revealing ulceration suggestive of ischemic colitis. Biopsy was read as consistent with ischemic colitis.

  Hospitalized: 0 days-managed as an outpatient; Constipation: yes; Diverticuli: no

- A0117893A: A 55 year old male received 5 day therapy with alosetron for IBS. On day 5 he developed constipation and stopped alosetron. Later that night he experienced severe cramping abdominal pain and bloody diarrhea. Two days later,

during a previously scheduled screening colonoscopy, ulceration, friability, erythema and granularity were noted in the region of the splenic flexure. Biopsies were read as consistent with pseudomembranous colitis of possible ischemic or infectious etiology.

Hospitalized: 0 days-managed as an outpatient; Constipation: yes; Diverticuli: no

- A0120828: A 53 year old female with a history of diverticular disease received treatment with alosetron 1 mg BID for diarrhea-predominant IBS. Two days after initiation she was hospitalized with rectal bleeding. She did not report abdominal pain. CT scan was suggestive of ischemic colitis in the splenic flexure . Colonoscopy and biopsy were reported as consistent with ischemic colitis and the patient was discharged to home.

  Hospitalization: 2-3 days; Constipation: no; Diverticuli: yes

- A0120834: A 46 year old female received alosetron to treat diarrhea-predominant IBS. After a few weeks of therapy she developed constipation. After approximately 6 ½ weeks of treatment she developed crampy lower abdominal pain and rectal bleeding. She was hospitalized and colonoscopy revealed ulceration and erythema in the descending colon. Biopsy was read as consistent with ischemic colitis.

  Hospitalization: 1 day; Constipation: yes; Diverticuli: no

- A0121411A: A 51 year old female with a history of depression, diverticulosis and migraine headache. Patient returned from a trip to Mexico with a diarrhea-like illness characterized by pain and diarrhea. She was admitted to the hospital for diverticulitis. During hospitalization colonoscopy was performed which was reported as normal. She continued to experience diarrhea and was diagnosed with IBS. She was discharged on alosetron. Two weeks later she developed pain and bloody diarrhea. She was hospitalized and colonoscopy revealed segmental colitis from 50cm to the splenic flexure. Biopsy read as consistent with ischemic colitis.

  Hospitalized: 3 days; Constipation: no; Diverticuli: no

Table 10
ISCHEMIC COLITIS REPORTS
(Post-Marketing Spontaneous Reports)

Subject #	Age	Treatment (Days)	Hospitalization	Constipation	Hormones
A0117893A	55 (male)	5	Not hospitalized	+	NA
A0119468A	50	14	Not hospitalized	+	-
A0120828A	53	2	2-3 days	-	-
A0120834A	46	46	1 day	+	+
A0121411A	51	3	3 days	-	-

It is very important to Glaxo Wellcome to completely understand the possible mechanisms of development of ischemic colitis during treatment with alosetron. The following activities are ongoing or will be initiated soon:

- Using PET scanning, colonic blood flow will be measured in humans before and during treatment with alosetron.
- The effect of alosetron on clotting factors is being evaluated alone and in combination with oral contraceptives.
- The effect of alosetron on cell integrity is being evaluated in a cultured human endothelial cell line.

CONCLUSION - ISCHEMIC COLITIS: In summary, the cumulative safety database from clinical trials has been derived from approximately 7000 subjects treated with alosetron. From clinical trials, there have been a total of 7 reports for which FDA and Glaxo Wellcome agree to a diagnosis of ischemic colitis (4 prior to approval, 3 post-approval). Of these, 5 had brief hospitalizations with no sequelae, the other 2 patients were not hospitalized and managed on an outpatient basis. Since approval of the NDA, Glaxo Wellcome estimates that a total of approximately 130,000 prescriptions have been dispensed. There have been a total of 5 cases derived from the voluntary, spontaneous reporting system for which FDA and Glaxo Wellcome agree to a diagnosis of ischemic colitis. Of these, 3 patients were briefly hospitalized and 2 were managed as outpatients. No patient exhibited sequelae. It has been agreed by FDA that the relative incidence and severity of cases reported as ischemic colitis are comparable to reports prior to approval.

Glaxo Wellcome believes that the cases of ischemic colitis reported to date in patients following treatment with alosetron, are more consistent with transient acute ischemic colitis rather than severe forms of ischemic colitis that may involve complications such as necrosis, perforation, and death. Generally, in transient acute ischemic colitis, patients have self-limiting disease and most are conservatively managed. The incidence of acute transient ischemic colitis in the general population is unknown, primarily because patients with milder disease may not seek care, symptoms may resolve before studies are performed and/or the condition may be misdiagnosed, often as inflammatory bowel disease. In most cases, symptoms rapidly resolve during which healing of the colonic mucosa can be observed. Whether severe ischemic colitis may, in the future, be associated with treatment with LOTRONEX is presently unknown, as it has not been reported to date.

CONSTIPATION: Since the time of approval of alosetron, there have been two cases in the clinical development program and four cases in the post-marketing spontaneous database of serious constipation requiring hospitalization. Narratives for the two clinical cases are given below.

- Subject 03773 is a 54 year old female who received alosetron 1 mg BID for treatment of IBS. One week after initiating treatment the patient developed worsening constipation and abdominal pain. The patient was hospitalized for disimpaction. The patient had been previously hospitalized for constipation and disimpaction prior to initiating alosetron therapy.
- Subject 67694 is a 56 year old female with a history of hypertension, peptic ulcer disease, and IBS who developed constipation 27 days after initiation of alosetron 1 mg BID. It is notable that prior to enrollment into the study that a colonoscopy was terminated at 40 cm due to large volume, solid stool. The patient reported being

awakened from sleep with crampy abdominal pain. Subsequently, she developed emesis. The patient felt increasingly constipated, used Fleets enemas and Milk of Magnesia without relief and went to the emergency room. In the emergency room a nasogastric tube was inserted with a litre of red, heme positive drainage removed. In the ER she was noted to be hypotensive, but not orthostatic, with an elevated white blood count. The patient was admitted and an unenhanced CT scan revealed nonspecific transmural thickening of a loop of proximal small bowel as well as the left colon. An upper endoscopy was performed which was normal. Colonoscopy was performed but aborted at 15 cm due to stool. The mucosa was normal up to 15 cm. During hospitalization the patient's status deteriorated and she went to the operating room for exploration. At surgery she was noted to have dense abdominal adhesions from the omentum to the anterior abdominal wall; the transverse colon was densely adhesed and massively dilated along with the right and left colon. There were patchy areas of necrosis without obvious perforation but perforation was believed to be pending. There was ascites in the abdomen and purulent material in the pelvis. The patient underwent a total colectomy with Brook ileostomy. The sequence of events was that the patient developed an obstruction due to stool, toxic megacolon, and secondary colonic ischemia. The patient had a complicated hospital course, recovered and was discharged to home.

Four serious events related to constipation have been reported in the post-marketing spontaneous database through June 1, 2000 (estimated 130,000 dispensings of LOTRONEX). Descriptions of these cases are given below. MEDWATCH reports are provided in Attachment 5.

- A0117392A: A 50 year old female receiving alosetron for treatment of IBS. The patient experienced no bowel movement for 4 days . She presented to the emergency room with abdominal pain and alosetron was discontinued. She was admitted for treatment of stool impaction and a small bowel obstruction. She received supportive care including enemas, the obstruction resolved and she was discharged to home after 23 hours.
- A0120067A: A female patient in her 70s received one week treatment with alosetron for IBS. Concomitant medication included hydrocodone. She developed sudden pelvic pain and went to the emergency room. CT scan revealed a mass outside of the bowel. She went to the operating room for repair of a sigmoid colon perforation with abscess. She was treated with antibiotics and discharged to home after two weeks.
- A0118883A: An adult female received alosetron for treatment of IBS. She was noted to be taking darvocet concurrently. After 2 days of therapy she developed constipation. Alosetron was discontinued. Two days later she presented to her physician with complaints of constipation and was noted to have abdominal tenderness and distension. CT scan was read as consistent with diverticulitis. She was admitted for management of diverticulitis and discharged in good condition 2 days later on clear liquids. Two weeks later (i.e., approximately 18 days after stopping alosetron) she returned to her physician for a follow-up visit. She was distended and constipated. She was readmitted to rule-out diverticulitis. X-rays showed previous contrast in colon and colon full of stool. She was treated with

enemas. The next day she felt sick and went to the operating room for exploratory laparoscopy. The reporter states no abscess, ischemia, phlegmon or diverticuli were observed. A temporary loop colostomy was performed. Over the next four days the patient passed stool, decompressed and was discharged.

- A0117431A: A 48 year old female with a history of idiopathic constipation received alosetron for treatment of IBS. Following 7-10 days of treatment she developed constipation which was not responsive to outpatient management. She was admitted for obstipation resulting in obstruction. Alosetron was discontinued. Colonoscopy was performed and showed a 1.5 cm stercoral ulcer in the distal transverse colon.

A summary of the serious constipation cases is given in Table 11.

Table 11
Serious Constipation

	Clinical Trials	Spontaneous Reports
Hospitalized	2	4
Surgery	1	2

Additionally, in the spontaneous reporting database, two patients required disimpaction as outpatients. These cases did not meet the regulatory definition of a serious adverse event. Narratives are below.

- A0117776A: A 32 year old female patient received alosetron. After 12 days of use she developed fecal impaction. An enema was given but was not successful and she was digitally disimpacted. Alosetron was discontinued and restarted at a lower dose without events.
- A0117244A: A 77 year old female developed constipation after several days of alosetron treatment. Alosetron was continued and the symptoms persisted. Subsequently she developed sour stomach followed by five episodes of diarrhea which the patient attributed to her diet. The patient noted that the constipation worsened, as she had 3 days with no stool. She treated herself with a Fleet enema but believed impaction prevented insertion of the tip. She lubricated the tip and successfully administered the enema and evacuated. The patient discontinued alosetron.

CONCLUSION – CONSTIPATION: Since the time of approval, rare cases of severe complications of constipation have been reported. Based on new information received regarding constipation, Glaxo Wellcome believes that the product labeling for physicians and patients should be changed to enhance the information about possible health consequences associated with constipation that have been observed in rare cases. Glaxo Wellcome feels that the labeling should be revised to include information regarding special care to be exercised by the practitioner for safe and effective use as it relates to occurrence of constipation and to better identify patients who may be at increased risk of experiencing severe complications of constipation and who should therefore not use the drug.

OTHER SERIOUS EVENTS: Given in Attachment 5 are the MEDWATCH reports for serious events in the post-marketing spontaneous database which are not included in the cases of ischemic colitis, constipation or altered liver function tests. In aggregate, there have been 21 serious reports including 4 of constipation, 5 of ischemic colitis, and 2 with elevated liver functions. Of the remaining 10 reports there is no evidence of a consistent pattern to the type of adverse events, diagnoses or laboratory findings.

4. UPDATE ON ACTIONS FOR RISK MANAGEMENT

The present section will review activities which are ongoing/completed or soon to be initiated:

- Glaxo Wellcome will promptly provide to FDA all reports that involve a description of ischemic colitis. Pursuant to FDA's request, Glaxo Wellcome will provide the Agency with all spontaneous reports of ischemic colitis as expedited 15-Day Reports and will include copies of the requested source documents when they are available, until directed otherwise. These reports will be submitted to FDA in accordance with 21 CFR 314.80(c). In addition to the defined reporting requirements, a desk copy of the report will also be submitted to the FDA Division or Gastrointestinal and Coagulation Drug Products (HFD-180). Further, cases of ischemic colitis derived from clinical trials that meet the criteria described under 21 CFR 312.32 will be handled in accordance with the procedures defined for IND Safety Reports. Regardless of whether the criteria for an IND Safety Report have been fulfilled, at FDA request, all cases of ischemic colitis, along with available source documents, will be provided promptly to the FDA Division or Gastrointestinal and Coagulation Drug Products (HFD-180).

- Label changes are being discussed with the FDA to incorporate new information since the NDA was approved and to incorporate essential information for the safe and effective use of the product.
- The Glaxo Wellcome salesforce is currently undergoing additional training to emphasize appropriate patient selection, patient education, and appropriate recognition of adverse events.
- Mechanistic studies are ongoing to help elucidate possible mechanisms of colitis.
- Specifics of a large constipation management study are being discussed with the FDA.
- Studies evaluating safety and efficacy are ongoing in males and alternators to ensure no additional risks are present in these populations. A dose-ranging phase II study has also been completed in patients with NUD.

In Section 5 the risk management plan is outlined in detail.

5. RISK MANAGEMENT PROGRAM

Glaxo Wellcome is committed to a program of responsible product stewardship for LOTRONEX to assure that appropriate patients receive the medicine, that adverse events are avoided, or managed successfully, to the fullest extent possible, and that Glaxo Wellcome continues to actively monitor and understand the safety of LOTRONEX in general use.

As any new medicine is introduced into general medical practices, new information is learned relating to safety and utilization that cannot be obtained during the carefully controlled pre-clinical and clinical trial experience prior to drug approval. New information includes identification of new safety events as well as information on how the product is used and perceived. That new information is used to refine the research and educational programs that are designed to assure that the benefits of therapy are maximized and risks are minimized. Early experience with LOTRONEX post-approval indicates that many patients who have sought medical consultation for their IBS are achieving significant benefit from therapy. That experience also indicates that constipation, a common side effect of alosetron can lead to serious sequelae on rare occasions. Complications can be diminished if patients at risk of serious complications of constipation are not prescribed alosetron, and if constipation is actively managed when it occurs during treatment. In addition, infrequent reports of acute ischemic colitis have occurred during alosetron treatment. Patients should be aware that if they experience a sudden worsening of abdominal pain and/or rectal bleeding, they should stop the medication and consult their physician. Taking these steps should help maintain the overall positive benefit-risk ratio for alosetron in general use.

Glaxo Wellcome has developed a program to actively reduce risks and optimize the benefits of LOTRONEX therapy. The program includes three key components:

1) Definition of Risk: A clinical and epidemiologic research program is under development to deepen our knowledge of the safety profile of alosetron through analyzing the frequency of ischemic colitis and severe constipation and their risk factors in both patients and in the general population. This program will also include mechanistic studies to better understand possible links between alosetron and ischemic colitis, studies on dose optimization, and studies to more fully optimize constipation management allowing development of additional clinical recommendations to optimize the safe use of LOTRONEX. The evaluation of spontaneously reported adverse experiences, enhanced through additional data gathering on all serious cases, remains a key tool in understanding the safety of LOTRONEX.

2) Communication of Risk: A strong, integrated communication program targeted to prescribers, pharmacists, and patients is under development. This program will emphasize three key messages: the importance of patient selection (e.g., only adult female IBS patients whose predominant bowel symptom is diarrhea, and that patients with a history of chronic or severe constipation or who are currently constipated should not be prescribed LOTRONEX), what actions to take when patients become constipated on LOTRONEX, and what actions to take if patients experience a worsening of

abdominal pain and/or rectal bleeding. A variety of communications vehicles will be used, and will be tested for understanding in the intended target groups.

3) Monitoring Effectiveness: An important component of our risk management involves monitoring to ensure our messages are accurately and adequately communicated. This monitoring will help detect signals that may suggest when additional activities should be undertaken.

The components of each of these programs are described further.

5.1. Definition of Risk

The first step in Glaxo Wellcome's Risk Management plan is to develop a scientific foundation to more fully understand the risk of ischemic colitis and complications of constipation that may occur with administration of LOTRONEX. In addition to the information detailed above, a number of research endeavors are being undertaken or planned to further define these conditions. This includes investigations into possible etiologic factors leading to the potential development of ischemic colitis, patient characteristics or confounders that might elevate the risk for ischemic colitis or severe constipation, as well as the epidemiology of severe constipation and its sequelae or ischemic colitis among patients receiving LOTRONEX. This information will direct educational efforts to identify the appropriate patients for which LOTRONEX should be used, as well as appropriate use of the drug in these patients.

5.1.1. Mechanistic Studies

These studies are being conducted in order to further evaluate possible mechanisms by which ischemic colitis arises in association with the use of LOTRONEX.

- **Assessment of Alosetron on Cultured Endothelial Cell Integrity:**

  This in vitro test will assess the effect of alosetron on cultured human endothelial cell integrity. Secretion of collagen IV and the glycoproteins fibronectin and laminin will be assessed by immunohistochemistry as indicators of extracellular matrix production. Apoptosis will be assessed morphologically by light and transmission electron microscopy.

- **Assessment of LOTRONEX on Human Mesenteric Blood Flow by PET Scanning:**

  This study will assess mesenteric blood flow in humans before and during alosetron administration by using a positron emission tomographic (PET) scanning technique.

- **Assessment of Concomitant Administration of LOTRONEX and Oral Contraceptives on Thrombosis:**

  This open-label study will evaluate the effect of alosetron on coagulation parameters. Furthermore, effects of co-administration of LOTRONEX and an oral contraceptive on coagulation factors will be determined.

5.1.2. Epidemiology Studies

An extensive program of epidemiologic research has been initiated to generate population-based data to quantify the occurrence of ischemic colitis and severe constipation and its sequelae in alosetron users and to evaluate risk factors for those events. The studies fall into two categories: 1) studies specifically evaluating ischemic colitis and severe constipation in populations that include LOTRONEX users, and 2) studies designed to improve our understanding of the background incidence and risk factors for these events.

The program of epidemiologic research has been initiated in diverse patient populations, using multiple data sources, including an UK medical records database and several US automated medical data sources that include claims and can be supplemented with medical record abstraction.

The evaluation of ischemic colitis (IC) presents several methodologic challenges. This is due to the sometimes transient nature of the disease, the relatively short time frame in which IC can be reliably diagnosed, the overlap in clinical presentation between ischemic colitis (IC) and other diseases, and, in research that utilizes the ICD (International Classification of Diseases) coding scheme for case ascertainment, the non-specificity of codes used for IC. Taken together, these issues have limited the prior study of IC at the population level. There are no existing population-based estimates of the frequency of ischemic colitis. Ongoing efforts include:

- **Phase IV epidemiology study of the incidence of, and risk factors for, ischemic colitis and severe constipation and its sequelae in 10,000 patients treated with LOTRONEX (United HealthCare)**

  The Phase IV epidemiology protocol that has previously been submitted to the Agency is being expanded and modified to evaluate the incidence of, and risk factors for, ischemic colitis and the incidence of, and risk factors for, severe constipation and its sequelae in 10,000 patients prescribed LOTRONEX in patients with IBS and in the general population.

  The study will utilize the United Healthcare Research Database (UHC). UHC is the second largest health care company in the US 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 7 million members since 1990 who have medical and prescription coverage.

  The study includes 3 phases: 1) the development of algorithms for the use of claims data to identify individuals with IBS, colitis, ischemic colitis and severe constipation in order to ensure accurate and complete case ascertainment 2) an observational cohort study of the incidence of, and risk factors for, ischemic colitis and severe constipation and its sequelae in 10,000 patients prescribed LOTRONEX and 3) further characterization of the occurrence of ischemic colitis and severe constipation and its sequelae in patients with IBS who do not receive LOTRONEX and in the general population.

Glaxo Wellcome intends to submit the final protocol to the Agency within 1 month of receiving comment on the draft protocol from the Agency. Initiation of the study will occur within 3 months of approval of the final protocol by the Agency.

Alec Walker, MD, DrPH, Professor and Chairman of Epidemiology, Harvard School of Public Health, is serving as primary consultant to Glaxo Wellcome on the Phase IV Study.

Interim reports will be provided to the FDA every six months. It is estimated that it will take 2-3 years to complete the study.

- **Case-control study of Ischemic Colitis Events in LOTRONEX users, possibly including pharmacogenetic analysis**

  A case-control study of ischemic colitis will be performed to identify risk factors for ischemic colitis in patients exposed to LOTRONEX. The cases will consist of patients from Glaxo Wellcome-sponsored clinical trials of LOTRONEX. By comparing to controls who have used LOTRONEX and who have not developed ischemic colitis, we hope to identify comorbidities, co-medications, symptoms and/or possible genetic risk factors that can be useful to identify patients who may be at heightened risk for ischemic colitis among LOTRONEX users. Data collection on cases that have already been accumulated will commence in the year 2000, along with the addition of any new cases needed subsequently to meet the objectives of the study.

- **Descriptive and Case-Control Studies in the General Practice Research Database (GPRD) of Severe Constipation and Ischemic Colitis**

  Glaxo Wellcome has initiated a descriptive study of the occurrence and natural history of ischemic colitis in the general GPRD population and of ischemic colitis in IBS patients in the database. The GPRD is a UK primary healthcare database containing computerized information entered by General Practitioners. Over 400 General Practitioners have been contributing medical history data since 1987 on over 6 million patients. The database contains extensive longitudinal follow-up on patients, including information such as patient characteristics, clinical diagnoses, prescribed drugs, notations of referrals to consultants and hospitalizations.

  In this study, patients with a diagnosis of ischemic colitis and patients with a diagnosis of irritable colon have been identified from the database and their recorded medical histories are being explored. Of particular interest is the incidence of ischemic colitis in IBS patients compared to the background incidence of the condition in the general database population. Further consideration is given to age at diagnosis, past and current comorbidities and medications, and whether the patient was hospitalized. An external research organization in the UK is in the process of abstracting further medical records of selected available cases from the General Practices to verify diagnoses and obtain additional relevant information. The target date for completion of the medical records abstraction is Summer 2000.

  The Boston Collaborative Drug Surveillance Program (Drs. Hershel and Susan Jick) will conduct a case-control study of ischemic colitis in the GPRD to assist in the evaluation of risk factors for ischemic colitis. Cases are all persons in the database with a confirmed diagnosis of ischemic colitis. There will be 4 controls per case,

matched by age, gender, general practice and length of recorded follow-up data. The date of ischemic colitis diagnosis for the cases will also be the index date for the matched controls. Risk factors to be analyzed include ischemic heart disease, IBS, constipation, diabetes, estrogen use and use of NSAIDs. Further available medical records of selected cases and controls will be abstracted from General Practices for verification of diagnoses and for obtaining further medical information. The target date for initiation of this study is Summer 2000.

Glaxo Wellcome has initiated a descriptive study of the occurrence and natural history of severe constipation and its sequelae in the GPRD population. Patients with a diagnosis of constipation, impaction, bowel obstruction or perforation or with a diagnosis of toxic megacolon will be identified from the database and their medical histories will be explored. The incidence rate of each of these conditions will be calculated for the general GPRD population. Factors such as age at diagnosis, past and current comorbidities and medications and whether the patient was hospitalized for the condition will also be analyzed. Further available medical information on selected cases will be obtained from the General Practices in order to verify diagnoses and gain additional insight into these conditions. Pending the initial results of the descriptive work described above, a more in-depth case-control study in the GPRD may be undertaken to assist in the evaluation of risk factors for severe constipation and its sequelae.

- **Study of Ischemic Colitis Using Tennessee Medicaid**

  A study of ischemic colitis is being negotiated with experts at Vanderbilt University using Tennessee Medicaid. Tennessee Medicaid is an optimal datasource in the US because of the size of the database (approximately 1.4 million individuals enrolled in the Tennessee Medicaid waiver program, TennCare), the ability to access medical records of hospitalized patients to verify diagnoses, and the large percentage of female patients in the database.

  Potential IC cases will be identified through review of hospitalizations with the code "acute vascular insufficiency of the intestine" (ICD-9 code 557.0) from the computerized medical records. Available medical records will be abstracted for verification of diagnoses using an *a priori* case definition based on available evidence associated with an inpatient admission for IC. Availability of computerized pharmacy records provides an opportunity to study the risk of IC associated with known and suspected colitis-inducing medications, such as NSAIDs and estrogen-containing preparations. A case-control study design will be employed to examine the effects of these medications, as well as other known and putative risk factors including ischemic heart disease and its risk factors, IBS, constipation, and diabetes on the incidence of IC. The target date for initiation of this study is Summer 2000.

  Collaborating investigators at Vanderbilt University are Walter E. Smalley, Jr., MD, MPH, Associate Professor of Medicine, Preventive Medicine, and Surgery in the Division of Gastroenterology, and Wayne Ray, PhD, Professor of Preventive Medicine.

- **Study of ischemic colitis using information from the Mayo Clinic**

A study of IC is being planned in which data would be obtained through the Rochester Epidemiology Project. This population was selected because of the extensive longitudinal follow-up data available on the population of Olmstead County. Computerized records and outpatient and inpatient medical records are available for review to verify diagnoses and ascertain risk factor information. IC will be identified through an automated search of the central diagnostic index to identify all codes related to IC. Diagnoses related to inpatient and outpatient medical contacts, emergency room visits, as well as death certificates and autopsy results of all individuals are contained in a central diagnostic index. Available medical records of all potential IC cases will be abstracted, according to a protocol, by a trained abstractionist. An *a priori* case definition based on available (clinical, radiographic, endoscopic, and histological) evidence will be developed and cases will be classified based on these criteria. A case-control study to evaluate risk factors for IC will be undertaken if such a study appears feasible based on the results of the descriptive study.

The lead investigator in this study is Edward V. Loftus, MD, Assistant Professor of Medicine in the Division of Gastroenterology and Hepatology. The protocol is under development, and it is anticipated that this research will be initiated in Fall 2000.

5.1.3. Clinical Studies

An essential part of any Risk/Management program is to provide prescribers with information on the appropriate safe use of the drug. This includes appropriate patient selection criteria and dose regimen, as well as safety and efficacy information in disease states for which the drug may be used. In order to generate information on the safe and effective use of the drug in disease states for which LOTRONEX might be considered for use, clinical trials are on-going or planned. These studies will contribute to a better understanding of constipation and ischemic colitis associated with LOTRONEX in various populations of patients.

- A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Study of Alosetron in Female Subjects with Alternating Diarrhea/Constipation Irritable Bowel Syndrome.

  This on-going clinical trial is being conducted in 600 patients to evaluate the safety and efficacy of alosetron in the treatment of female IBS patients who exhibit alternating bowel patterns.

- A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of Alosetron in Male IBS Subjects.

  This on-going Phase II clinical trial is being conducted in 600 male, diarrhea-predominant IBS patients to determine the lowest alosetron dose that is safe and effective in treating this population of patients. Doses being studied are 0.5 mg, 1.0 mg, 2.0, and 4 mg BID.

- A successful dose-ranging phase II study of alosetron in the treatment of Non-Ulcer Dyspepsia (NUD) is complete. Data and phase III design will be discussed with the FDA.

- Additional dose-ranging, safety and efficacy studies are planned for the following patient populations:
  - Chronic pelvic pain
  - Non-cardiac chest pain
  - Dumping syndrome
  - Post-cholecystectomy pain and diarrhea
  - Patients with ileostomy
  - Patients with microscopic colitis

5.1.4. Information on Optimal Dose

Based on the two dose-ranging studies in IBS patients (S3BP12 and S3BA2001), alosetron 1 mg BID was determined to be the most effective dose. This dose was chosen for the pivotal Phase III studies and subsequently is the registered dose. Data from the small number of subjects that received 0.5 mg BID in the IBS dose-ranging study indicated that the incidence of constipation (13%) was lower than that experienced by patients receiving 1 mg BID in the Phase II and III studies (27%). Since the risk of constipation may be lower at a dose less than the currently registered 1.0 mg BID alosetron dose, we plan on conducting studies to determine if some patients might receive benefit from a lesser dose.

- **A Randomized, Placebo-Controlled, Double-Blind, Dose Optimization Study in Female, Diarrhea-Predominant IBS Subjects**

  We plan to conduct a randomized, controlled, dose optimization study in female IBS patients whose predominant bowel pattern is diarrhea. In this study, subjects will initially be started at ½ the approved 1.0 mg BID alosetron dose or placebo. If the subject does not receive adequate relief of their abdominal pain and discomfort by the end of four weeks of therapy, their dose will be doubled to 1.0 mg BID alosetron. Comparisons of efficacy and safety at each dose level will be conducted.

- **A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of Alosetron in Male IBS Subjects.**

  This on-going clinical trial is being conducted in 600 male IBS patients to determine the lowest effective alosetron dose that is safe and effective in treating this population of patients. Doses being studied are 0.5 mg, 1.0 mg, and 2.0 mg alosetron BID.

5.1.5. Information on Limiting Risk by Treating Constipation

Data from the IBS development studies indicate that in a significant percentage of patients developing mild to moderate constipation while receiving LOTRONEX the constipation is transient and only occurs once during therapy. Additionally, if the patient continues on therapy they receive the same benefit as those who do not become constipated. Therefore, if the patient's constipation is managed appropriately, they may

receive the benefit of continued LOTRONEX therapy. The following study is designed to optimize constipation management regimens on the severity and duration of constipation in patients taking LOTRONEX.

- A 12-Week, Randomized, Double-Blind, Placebo-Controlled Study to Compare Methods of Constipation Management in Female Diarrhea Predominant IBS Subjects Treated with Open-Label Alosetron.

  This placebo-controlled study will examine the effect of managing constipation during alosetron treatment. Several strategies will be employed including, decreasing the dose of alosetron to 1.0 mg QD, concomitant treatment with a laxative, or interruption of alosetron therapy. Constipation duration and severity for each management regimen will be determined and compared.

5.2. Communication of Risk

Our risk management program is threefold: definition of risk, communication of risk, and monitoring effectiveness of our messages. The communication component of the program is designed to deliver clear and effective messages about appropriate patient selection, management of constipation, and early recognition and management of serious adverse events including ischemic colitis. The communication component will be directed on an ongoing basis to healthcare providers including physicians, nurses, physician assistants, and pharmacists as well as patients using a variety of vehicles that are described in the communication plan. As new information is learned about the safety and efficacy of alosetron as well as the effectiveness of the communication program, the program will be modified accordingly.

Because labeling revisions have not as yet been agreed, the messages included in the plan below are representative of the types of information that might be communicated, and are not indicative of specific messages that have been agreed with the FDA. The components of the plan are discussed below.

The materials for the communication program are currently being refined and are not available for inclusion in this document, although we have included several concepts. The program will be presented at the meeting June 27th.

5.2.1. Communication Program

Based on the current label, we believe there are 3 concept messages that need to be communicated clearly and consistently. These message will be expanded/modified to include appropriate context, once final labeling is agreed with the FDA.

5.2.1.1. Strategic Messages

- Select the appropriate patient
- Manage constipation
- Recognize early signs and symptoms of constipation and possible ischemic colitis and take appropriate action.

5.2.1.2. Target Audiences

- Physicians and their office staff (nurse practitioners and physicians assistants)
- Hospital and retail pharmacists
- Patients prescribed LOTRONEX (including advocacy organizations)

5.2.1.3. Communication Vehicles

"Dear Healthcare Practitioner" Letter

A "Dear Healthcare Practitioner" letter describing changes to the prescribing information for LOTRONEX will be sent to approximately 300,00 physicians (primary care, internal medicine, gastroenterologists, and ob/gyn), 60,000 pharmacists, and 120,000 nurse practitioners and physicians assistants. All healthcare professionals who have received information on LOTRONEX since the launch of the product will be included in this distribution. The letter will be mailed within three weeks of agreement with FDA on its contents.

Appropriate Use Program

A specific and unique communication program dedicated to the appropriate use of LOTRONEX is under development (Appendix A-1, A-2, & A-3 in Attachment 6 for a depiction). This program will be designed to convey the key information contained in the revised physician and patient package inserts and will include a comprehensive set of materials to be distributed to physicians and their office staff, patients, and pharmacists.

This program will help healthcare practitioners understand critical information about LOTRONEX and provide multiple vehicles for communicating this information to the patient.

The following elements are being developed:

<u>Information for Patients</u>

- Physicians will distribute "patient starter kits" (Appendix A-1 in Attachment 6) to patients during their office visit. These kits will contain various materials designed to reinforce appropriate use of LOTRONEX and what to do if a serious side effect occurs. The following messages are representative of the types of information that will be communicated to patients. As indicated previously, these messages may need to be modified for consistency with final product labeling.

IMPORTANT INFORMATION

LOTRONEX *is* ...

- Only for women.
- Only for you if your most frequent bowel symptom is diarrhea.

LOTRONEX *is NOT for you if...*

- You are constipated most of the time.
- You are currently constipated.
- You have had a serious intestinal problem in the past.

For your safety...

- The most common side effect is constipation. In rare cases, constipation resulted in a serious intestinal problem. Call your doctor if you become constipated.
- If you experience a new or sudden worsening of abdominal pain or if you see blood in the stool, this may be a sign of a serious intestinal problem. Stop taking LOTRONEX and call your doctor right away.

* Fewer than three bowel movements per week

Due to production lead times, the starter kits would be distributed in two phases:

Phase I Patient Starter Kit:

The current sample package (Appendix A-1, Phase 1, Figure 1 in Attachment 6) will be reconfigured to include:

- A prominently placed sticker drawing attention to important information located inside the package
- An "Important Information" card (Appendix A-1, Phase 1, Figure 3 in Attachment 6)
- A separate patient package insert (Appendix A-1, Phase 1, Figure 2 in Attachment 6)
- Full Prescribing information (Appendix A-1, Phase 1, Figure 2 in Attachment 6)

The reconfigured sample package will be distributed with a patient brochure (Appendix A-1, Phase 2, Figure 5 in Attachment 6).

The current sample package also provides a 1-800# and a website on the outside of the carton. Patients accessing these sites would again be exposed to the "important information" and offered follow-up information. The follow-up information includes a three wave mailing (Appendix A-1 in Attachment 6), and a newsletter, both of which reinforce the "Important Information" messages. These subsequent reminders to patients who register will reinforce the actions patients are asked to follow when they are prescribed LOTRONEX.

Phase II Patient Starter Kit:

An expanded "kit" that contains items for use by the patient will be developed, (Appendix A-1, Phase 2, Figure 4 in Attachment 6). While the carton design is yet to be determined, "Important Information" will be displayed in a prominent location on the outside of the carton. The kit will contain the following elements:

- Patient brochure (Appendix A-1, Phase 2, Figure 5 in Attachment 6);
- Symptom diary to help patients monitor their symptoms (Appendix A-1, Phase 2, Figure 7 in Attachment 6). The "Important Information" messages will be included in the diary;
- Sample package with the sticker and physician and patient inserts as previously described (Appendix A-1, Phase 2, Figure 1 in Attachment 6);
- A business reply card (Appendix A-1, Phase 2, Figure 8 in Attachment 6) offering the three wave mailing (Appendix A-1, Figure 8 in Attachment 6) and the newsletter;
- A refrigerator magnet (Appendix A-1, Phase 2, Figure 6 in Attachment 6) containing the 1-800# and website.

Information for Physicians and Their Office Staff:

- A letter introducing the program (Appendix A-2, Figure 9 in Attachment 6).
- An "Appropriate Patient Selection" card (Appendix A-2, Figure 10 in Attachment 6), containing a simple checklist, will serve as an easy guide for office staff to use to determine which patients, based on history of constipation, are not appropriate candidates for LOTRONEX. This card is intended to be inserted into a patient's file by the nurse as a reminder to the physician during patient's visit.
- A Physician Booklet (Appendix A-2, Figure 11 in Attachment 6) will provide information on IBS and appropriate use of LOTRONEX for the prescriber.
- A "Commonly Asked Questions and Answers" card (Appendix A-2, Figure 12 in Attachment 6) for patients that will be distributed to physician/clinic office staff to help them with patient questions and concerns;
- A Rolodex card and magnet with an 1-800# for professionals (Appendix A-2, Figure 13 in Attachment 6);

Information for Hospital and Retail Pharmacists:

- A letter introducing the program to pharmacists (Appendix A-3, Figure 14 in Attachment 6);
- Patient brochures (Appendix A-1, Phase 2, Figure 5 in Attachment 6), (per the patient starter kits) and patient package inserts (Appendix A-3, Figure 15 in Attachment 6) will be distributed to pharmacies by GW sales representatives. These materials will also be available by calling an 1-800# that is provided to pharmacies;

- Prescription bottle stickers (Appendix A-3, Figure 16 in Attachment 6) will be distributed to pharmacists. These stickers are intended to be affixed to prescription bottles for LOTRONEX.
- Computer System Flags - we will contact PBMs and major chain stores to include flags in their computer systems to remind the pharmacist of key safety information concerning LOTRONEX.

Print and Web-based Materials

All print/web-site materials will be revised to increase the prominence of the appropriate use messages (Appendix A-4 in Attachment 6). These materials will be used in presentations by the Glaxo Wellcome salesforce, our Customer Response Center, Clinical Research, Medical Information Department, Speaker Bureau, and advertising and promotions vendors who fulfill patient and health care practitioner requests for information. Examples would include:

- Sales brochures and visual aids
- Prescribing information (package insert)
- Patient education brochures
- Panels for display at the exhibit stand during conventions
- Print advertising

Healthcare Practitioner Educational Programs

We are committed to ensuring that all specialists who consult for us as speakers are knowledgeable regarding the changes to the prescribing information for LOTRONEX. All previously trained speaker/consultants will be issued new slide sets and trained via face to face meetings. We will insist on an understanding of the revised labeling as a condition for continued speaking engagements. This may take the form of pre and post training knowledge surveys. We will also ensure that all promotional/educational programs for which Glaxo Wellcome has sponsored the speaker will include the key label changes.

Salesforce Training

All Glaxo Wellcome representatives responsible for conveying information on LOTRONEX will be trained on the key messages in face-to-face meetings. All printed and web-based training materials will be updated to emphasize the key messages. All representatives will be competency tested to ensure the messages have been clearly communicated and their knowledge of the changes to the prescribing information is held to an appropriate standard.

Packaging

The package insert will be redesigned such that each stock and sample package will contain separate healthcare practitioner and patient package inserts. An ongoing supply

of patient package inserts will be provided to pharmacists (Appendix A-3, Figure 15 in Attachment 6) for use when less than a full bottle of LOTRONEX is dispensed.

5.3. Monitoring

An important component of our risk management program involves monitoring to ensure our messages are accurately and adequately communicated. Details of plans for testing communication materials and tracking awareness and source of knowledge are presented below.

5.3.1. Development Testing of Communication Materials

Development of clear, comprehensible messages will be done via qualitative research with physicians, patients and pharmacists. The one-on-one, in-person interviews will be conducted at centralized third-party research facilities in three geographically representative cities. An experienced, professional third-party moderator will conduct the interviews.

A sample of 50 physicians, 50 IBS patients and 50 pharmacists will be interviewed as participants for this research. The physicians will be appropriately distributed by specialty, e.g., approximately 30 primary care physicians and approximately 20 gastroenterologists. The respondents will be screened via telephone to ensure that they meet selection criteria, such as correct specialty, actively seeing IBS patients in an office setting, and at least two years experience in practice.

There will be five rounds of this research. Each round will take place in a given city and include approximately 10 physicians, 10 patients and 10 pharmacists to be interviewed. Each interview will be approximately 30–45 minutes in length. The research will begin by testing first drafts of the communication messages, separately for physicians, patients and pharmacists. Throughout the research process, messages will be modified in an iterative fashion, in order to maximize clarity of message communication.

The interviews will proceed according to a discussion guide developed jointly by Glaxo Wellcome market research personnel and the third-party research consultant. Consistent standard market research practices will be employed.

5.3.2. Tracking Awareness and Source of Knowledge

Awareness of key messages and source of knowledge will be measured through quantitative research with both physicians and pharmacists. A structured questionnaire will be administered via telephone with respondents by a third-party market research company.

The first wave of the study will be conducted prior to the distribution of the communication materials with the second wave approximately two months following the implementation of the communication program. A total of four waves will be conducted, prior to distribution of material and subsequently at three-month intervals following the initial distribution.

For each wave of the tracking study, 375 respondents will be surveyed. The sample will consist of 150 primary care physicians, 75 gastroenterologists and 150 pharmacists. Respondents will be chosen randomly and be representative across the geography of the U.S. The respondents will be screened via telephone to ensure that they meet selection criteria, such as correct specialty, actively seeing IBS patients and at least two years experience in practice.

The telephone interviews will follow a structured questionnaire designed jointly by Glaxo Wellcome market research personnel and the third-party research consultant. Questions will be primarily closed-ended, with a few open-ended questions for which verbatim responses will be captured and recorded. Standard market research practices will be employed. The interviews will be approximately 10–15 minutes in length.

Results of this quantitative study will be projectable to the larger populations of physicians and pharmacists from which the samples are drawn. The methodology will remain consistent from wave to wave, allowing data to be trended and significant changes to be identified.

5.3.3. Monitoring Prescribing Patterns and Drug Utilization

The objective of this study is to monitor prescribing patterns by evaluating computerized pharmacy and medical records in a large managed care organization.

The objectives of this study are to monitor dispensings of LOTRONEX, to characterize the patient population over time, by patient demographics and history of constipation severe enough to seek medical attention, and to identify some indicators of severity of IBS, in patients receiving LOTRONEX. This monitoring program will be conducted in collaboration with Epidemiology Research Institute and United Healthcare.

5.4. Conclusions and Next Steps

Glaxo Wellcome is committed to an active program to optimize the safe use of alosetron. We believe the benefits of therapy in the appropriate female patients with diarrhea-predominant irritable bowel syndrome greatly outweigh the known risks, and that the risks with alosetron can be appropriately managed. We are committed to a program of clear communication with healthcare professionals and patients. We are also committed to diligent monitoring of the safety of LOTRONEX, through continued surveillance and epidemiologic studies, and to advancing the scientific knowledge to improve patient management.

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GlaxoWellcome

Memorandum

From	Dr CR Pick Mr JC Klapwyk	Date	15 October 1999
		Reference	
To	Roger Secker		

Review of intestinal changes in the preclinical studies with alosetron

As requested, a review of the preclinical studies performed with alosetron has been undertaken to ascertain whether there is any evidence for alosetron having an adverse effect on the intestinal tract of animals.

The review revealed that macroscopic and microscopic changes in the large and small intestine of animals were rare, and none of the changes reported were suggestive of any treatment-related adverse effect.

During its preclinical development programme, alosetron has been administered daily to rats dogs and mice by the oral route in repeat dose studies of one month to two years in duration. In all of these studies the small and large intestines have been subjected to macroscopic examination, and routine representative samples of these organs have been examined microscopically, together with any area showing a macroscopic change.

The pathology reports from the following major studies have been reviewed, and any findings recorded for the small or large intestine have been scrutinised.

Study	Species	Study type	Number of treated animals	Duration
R11832	Rat	Repeat dose	60	1 month
R12458	Rat	Oncogenicity	360	2 years
M12401	Mouse	Oncogenicity	360	2 years
D11825	Dog	Repeat dose	18	1 month
D11865	Dog	Repeat dose	25	6 month
D12561	Dog	Repeat dose	28	12 month

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Macroscopic and microscopic changes in the large and small intestine have been rare, and none of the changes seen were suggestive of a treatment-related adverse effect.
In particular:

- No changes suggestive of ischaemic damage were seen in any study.
- The few instances of vascular or necrotic changes were confined to the lifetime studies in rodents, and were not suggestive of any treatment-related effect.

The results are summarised in the tables which follow.

CR Pick
Pathologist

JC Klapwyk
Pathologist

Study R11832 one month oral toxicity study in RH rats

Gross examination of small (duodenum, jejunum & ileum) and large intestine (colon only)

Sex	Males				Females			
Group	1	2	3	4	1	2	3	4
Dose (mg/kg/day)	0	1	8	64	0	1	8	64
Animals examined	10	10	10	10	10	10	10	10
Small intestine NAD	10	10	10	10	10	10	10	10
Large intestine NAD	10	10	10	10	10	10	10	10

Microscopic examination of small (duodenum, jejunum & ileum) and large intestine (colon only)

Sex	Males				Females			
Group	1	2	3	4	1	2	3	4
Dose (mg/kg/day)	0	1	8	64	0	1	8	64
Animals examined	10	10	10	10	10	10	10	10
Duodenum no abnormality detected -	10			10	10			10
Jejunum no abnormality detected -	10			10	10			10
Ileum no abnormality detected -	10			10	9			10
lymphoid hyperplasia -					1			
Colon no abnormality detected -	10			9	10			10
oedema -				1				

Study R12458 oral (dietary) oncogenicity study in rats

Gross examination of small and large intestine

Sex	Males				Females			
Group	1	2	3	4	1	2	3	4
Dose (mg/kg/day)	0	1	6.5	40	0	1	6.5	40
Animals examined	120	60	60	60	120	60	60	60
Duodenum								
distended	0	0	0	0	0	0	0	1
abnormal content	3	0	0	1	2	0	0	2
thickened wall	0	0	1	0	0	0	0	0
mass(es)	0	1	0	0	2	1	0	0
adhesions	0	0	1	0	0	0	0	0
Jejunum								
adhesions	1	0	1	0	1	0	0	0
abnormal content	4	0	0	1	2	0	4	2
distended	0	0	0	0	0	0	0	1
mass(es)	1	0	1	1	1	0	0	0
Ileum								
distended	2	0	0	0	0	0	0	1
abnormal content	2	0	0	1	1	1	3	2
mass(es)	0	0	0	0	0	0	0	1
Caecum								
distended	1	0	0	1	0	0	0	0
appears large	1	0	0	0	0	0	0	0
abnormal content	8	3	0	1	2	1	4	2
thickened wall	0	4	1	1	0	1	1	2
wall dark	0	1	0	0	0	0	0	0
area/s of change	0	1	0	0	0	0	0	0
mass(es)	1	0	0	0	0	0	0	0
Colon								
distended	2	2	2	1	0	0	0	0
abnormal content	1	1	0	1	0	0	0	0
Rectum								
distended	2	1	3	0	0	0	0	0
abnormal content	0	1	0	0	0	0	0	0

Study R12458 oral (dietary) oncogenicity study in rats

Microscopic examination of small (duodenum, jejunum & ileum) and large intestine(caecum, colon & rectum)

Sex	Males				Females			
Group	1	2	3	4	1	2	3	4
Dose (mg/kg/day)	0	1	6.5	40	0	1	6.5	40
Animals examined	120	60	60	60	120	60	60	60
Duodenum	n=119							
leiomyoma -	0	0	0	0	1	1	0	0
sarcoma -	0	1	0	0	0	0	0	0
submucosal chronic inflammation -	0	0	0	0	0	0	1	0
Jejunum		n = 59			n = 119			
carcinoma	0	0	0	1	0	0	0	0
adenoma	1	0	0	0	0	0	0	0
leiomyosarcoma	0	0	0	0	1	0	0	0
Ileum								
ulcer(s)	0	0	0	0	0	0	0	1
villous stunting	0	0	0	0	0	0	0	1
dilated	0	0	0	0	0	0	0	1
Caecum								
sarcoma -	1	0	0	0	0	0	0	0
submucosal oedema -	0	0	0	0	1	0	0	0
mucosal acute inflammation -	0	0	0	1	0	0	0	0
ulcer(s) -	0	1	0	0	0	0	0	0
submucosal chronic inflammation -	0	0	0	0	0	0	1	0
arteritis -	0	0	0	0	1	0	0	0
Colon								
dilated -	1	1	0	1	0	0	0	0
submucosal granuloma(s) -	1	0	0	0	0	0	0	0
Rectum								
submucosal acute inflammation -	1	0	0	0	0	0	0	0
dilated -	0	1	1	0	0	0	0	0

Study M12401 oral (drinking water) oncogenicity study in B6C3F1 mice

Gross examination of small (duodenum, jejunum & ileum) and large intestine(caecum, colon & rectum)

Sex	Males					Females				
Group	1	2	3	4	5	1	2	3	4	5
Dose (mg/kg/day)	0	0	1	5.5	30	0	0	1	5.5	30
Animals examined	60	60	60	60	60	60	60	60	60	60
Small intestines										
mass(es) or nodule(s) -		1	1	3		2	1			1
raised area or swelling -						1			1	
enlargement -		1	1							1
gaseous liquefied contents -									1	
fluid-filled -						1				1
Peyer's patches prominent -						1				
possible fat adhesion in upper jejunum -							1			
pale swellings -	1									
Large intestines										
anal area swollen							1		1	
anal prolapse							1			
red discharge from anus							1			
black spots on the surface							1			
fluid or liquefied contents						1			1	1
caecal contents dark								1		

Study M12401 oral (drinking water) oncogenicity study in B6C3F1 mice

Microscopic examination of small (duodenum, jejunum & ileum) and large intestine(caecum, colon & rectum)

Sex	Males					Females				
Group	1	2	3	4	5	1	2	3	4	5
Dose (mg/kg/day)	0	0	1	5.5	30	0	0	1	5.5	30
Small intestines										
Animals examined	(54)	(58)	(59)	(59)	(59)	(59)	(59)	(56)	(60)	(60)
no abnormality detected -	31	33	36	35	39	33	20	34	33	36
adenocarcinoma -							1			
deposit of lymphoreticular tumour -	1	2	4	2		6	6	5	4	5
serosal metastasis from primary in liver -			1							
GALT hyperplasia -	19	23	17	18	18	14	29	14	22	16
acute inflammatory cell infiltrate -			1	1			1			
lamina propria mixed inflammatory cell infiltrate -					1					1
ulceration -						1				
mucosal necrosis -							1			
lamina propria haemorrhage -								1		
glandular distension -	1		1	1	1					
crypt abscess -	3					2		1		
vascular amyloid -						1		1		
ectopic pancreas in duodenal submucosa -				1						
pancreatic tissue in lamina propria -							1			
Large intestines										
Animals examined	(58)	(60)	(59)	(60)	(60)	(60)	(60)	(59)	(60)	(60)
no abnormality detected -	43	42	48	48	53	41	45	41	50	50
adenocarcinoma -									1	
deposit of lymphoreticular tumour -	1	2		1		1	3	2		4
metastasis from primary in liver -					1					
GALT hyperplasia -	11	15	11	10	3	11	10	8	4	4
mucous cell hyperplasia -		1								
submucosal oedema -						2		3	3	2
erosion(s) -					1		1		1	
vascular amyloid -						1		1		
lymphoid infiltration or foci -						1			1	
inflammatory cell infiltrate -					1				1	
prolapse -							1			
large dilated squamous lined spaces -							1			
blood in lumen -								1		

Study D11825 35 day oral toxicity study in the dog

Gross examination: as standard autopsy procedure, the entire intestine from duodenum to rectum was opened and the mucosal surface examined

Sex	Males				Females			
Group	1	2	3	4	1	2	3	4
Dose (mg/kg/day)	0	1	5.5	30	0	1	5.5	30
Animals examined	3	3	3	3	3	3	3	3
Small intestine NAD	3	3	3	3	3	3	3	3
Large intestine NAD	3	3	3	3	3	3	3	3

Microscopic examination of small intestine (duodenum jejunum ileum) and colon

Sex	Males				Females			
Group	1	2	3	4	1	2	3	4
Dose (mg/kg/day)	0	1	5.5	30	0	1	5.5	30
Animals examined	3	3	3	3	3	3	3	3
Small intestine NAD	3	3	3	3	3	3	3	3
Colon NAD congestion	3	3	3	2 1	3	3	3	3

Study D11865 six month oral toxicity study in the dog

Gross examination: as standard autopsy procedure, the entire intestine from duodenum to rectum was opened and the mucosal surface examined

Sex	Males				Females			
Group	1	2	3	4	1	2	3	4
Dose (mg/kg/day)	0	1	5.5	25	0	1	5.5	25
Animals examined	4	4	4	4 (c)	4	4	4	5 (a) (b)
Small intestine NAD Abnormal colour	4	4	4	4	4	4	4	4 1(b)
Ileo-caecal junc NAD Abnormal colour	4	2 2	4	4	4	4	4	4 1(b)
Large intestine NAD Abnormal colour	4	4	4	4	4	4	4	4 1(b)

a) Intercurrent death on day 8
b) Intercurrent death on day 58
c) Intercurrent death on day 69

Microscopic examination of small intestine (duodenum jejunum ileum) and colon

Sex	Males				Females			
Group	1	2	3	4	1	2	3	4
Dose (mg/kg/day)	0	1	5.5	25	0	1	5.5	25
Animals examined	4	4	4	4 (c)	4	4	4	5 (a) (b)
Small intestine NAD Autolysis (duod) Diverticulum (ile)	4	4	4	4	4	3 1	4	4 1(b)
Ileo-caecal junc congestion haemorrhage		1 1						
Colon NAD congestion	4	4	4	4 1(c)	4	4	4	4 1(a)

a) Intercurrent death on day 8
b) Intercurrent death on day 58
c) Intercurrent death on day 69

Study D12561 12 month oral toxicity study in the dog

Gross examination as standard autopsy procedure, the entire intestine from duodenum to rectum was opened and the mucosal surface examined

Sex	Males				Females			
Group	1	2	3	4	1	2	3	4
Dose (mg/kg/day)	0	1	5	25	0	1	5	25
Animals examined	6	4	4	6	6	4	4	6
Small intestine NAD Few ascarids	6	4	4	6	6	4	4	4 2
Large intestine NAD	6	4	4	6	6	4	4	6

Microscopic examination of small intestine (duodenum jejunum ileum) and colon

Sex	Males				Females			
Group	1	2	3	4	1	2	3	4
Dose (mg/kg/day)	0	1	5	25	0	1	5	25
Animals examined	6	4	4	6	6	4	4	6
Small intestine NAD	6	4	4	6	6	4	4	6
Colon NAD Submucosal granuloma	5 1	4	4	6	6	4	4	6

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October 15, 1999

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International Director,
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North Carolina 27709
(FAX 919-483-8614)

Dear Dr. Mangel:

Please find our report on the effects of alosetron on mesenteric arterial contraction enclosed. We performed these studies to ask the following questions: i) does alosetron affect basal tone of mesenteric arteries? (concentration-response data were performed to answer this question). ii) Does alosetron affect nerve-mediated contractions? (we tested nerve-mediated contractions before and after alosetron application). We found that this compound (up to 10^{-6} M) did not have vasoactive effects.

Thank you for supporting this investigation.

Sincerely,

Kenton M. Sanders

Kenton M. Sanders, Ph.D.
Professor and Chairman

(702)784-6908

FAX (702)784-6903

Effect of Alosetron on Mesenteric Artery Tone

Purpose: To evaluate whether Alosetron is a vasoconstrictor of mesenteric arterial smooth muscle.

Methods: Guinea-pigs were killed by inhalation of CO_2 followed by esangulation. Dogs were killed with an overdose of phenobarbitol following sedation with ketamine. The inferior mesenteric artery of each species with associated mesentery and fat were removed.

Ring preparations (3 mm long) of guinea-pig artery were dissected free of fat and connective tissue and mounted in organ baths by inserting two stainless steel triangle mounts into the lumen. The bottom triangle was attached to a stable hook while the top triangle was attached to a strain gauge (Grass FT03C). Dog vessels were prepared in a similar manner (as ring segments) or in some cases as spiral strips cut with a fine iris scissors. In the case of spiral strips one end was attached to a stable mount and the other to a tension transducer wire with suture. Care was taken during dissection to maintain the endothelial lining of blood vessels. In some vessels the presence of endothelium was confirmed by observing the relaxation produced by 10^{-6} M acetylcholine in the presence of a histamine analogue. Changes in the smooth muscle tone were recorded on a chart recorder and also acquired and analyzed on line by a Biopac system (MP100) and Acknowledge 2.3.4 software.

Vessels were submerged in isolated tissue baths. The bath contained Krebs solution of following composition (mM): 118.5 NaCl; 4.2 KCl; 1.2 $MgCl_2$; 23.8 $NaHCO_3$; 1.2 KH_2PO_4; 11.0 dextrose; 1.8 $CaCl_2$, aerated with 95% O_2/5% CO_2 and maintained at 37°C. A resting force of 0.4 g was applied to the guinea-pig arteries and 0.7 g to the canine arteries. This was found to stretch vessels to near the optimum length for tension development. In all experiments tissues were initially equilibrated for 1 hour followed by at least 3 exposures (3 minute per exposure) every 15 minutes to KCl (70 mM) in order to establish viability and equilibrate the tissue.

Nerves were stimulated for a period of 1 minute with platinum stimulating electrodes placed on either side of the vessel at a distance of 2-3 mm from the tissue. Stimulation parameters were initially adjusted for optimum reproducibility of response. Frequency used were either 15 or 20 Hz, voltage was held constant (12 V) and pulse duration was adjusted between 0.1 and 0.3 ms. All of these stimulus parameters give rise to tetrodotoxin sensitive neural responses. Once optimum conditions were established, these parameters were maintained for the remainder of the experiment.

Effects of cumulative addition of Alosetron. Alosetron was added cumulatively (10^{-9} - 10^{-6} M) to vessels 8-10 minutes after a control neural response. Each concentration of Alosetron was tested for 2 minutes. Ten minutes after washing out the highest concentration of Alosetron nerve stimulation was again tested.

Effect of Alosetron on the response to nerve stimulation. Additional experiments were undertaken to determine whether Alosetron had significant effects upon the response to nerve stimulation. For these experiments stable neural responses were first established. After 2 responses to nerve stimulation (control 1 and control 2) Alosetron (10^{-7}M) was added. Following ten minutes exposure to Alosetron nerve stimulation was again tested in the presence of Alosetron. Following wash out of

Alosetron another control nerve response was obtained (Control 3). Next 10^{-6}M Alosetron was added for 10 minutes and the response to nerve stimulation again tested in the presence of Alosetron. Following nerve stimulation Alosetron was washed out for 10 minutes and a final response to nerve stimulation determined.

Results:

Fourteen vessels from 5 guinea-pigs and 13 vessels from 2 dogs were tested. All vessels contracted in response to addition of 70 mM KCl. In all 27 vessels there was no contraction observed with Alosetron (22 tested with 10^{-6} M Alosetron).

Effect of cumulative addition of Alosetron. In 5 guinea-pig vessels and 5 dog vessels stable reproducible neural responses were established and the concentration-dependent effects of Alosetron tested. There was no change in tone observed for any concentration of Alosetron tested in all blood vessels. In addition there was no significant difference ($p<0.05$) in the response to nerve stimulation after cumulative addition of Alosetron was completed. Figure1 shows an example of one experiment undertaken in dog and one in guinea-pig. Figure 2 shows the cumulative data comparing nerve stimulation amplitude before and after the concentration-response relationship for Alosetron was obtained. Table I includes the normalized data for these experiments.

Effect of Alosetron on the response to nerve stimulation. Neither 10^{-7}M Alosetron nor 10^{-6}M Alosetron produced a significant change in the response to nerve stimulation in either dog or guinea-pig nor did addition of alosetron produce any change in resting tone. Figure 3 shows the cumulative data comparing nerve stimulation amplitude before and after addition of 10^{-7}M Alosetron to dog (n=7) or guinea-pig (n=6). Figure 4 shows the cumulative data before and after addition of 10^{-6}M Alosetron to dog (n=7) or guinea-pig (n=9). There was a tendency for neural responses of the guinea-pig to decline approximately 18% during 1 hr experiments (see Figure 3) but there was no significant difference in the response to nerve stimulation in the presence of 10^{-7}M Alosetron when compared to the control responses obtained before or after addition of Alosetron. Tables II and III plot the normalized data for the effects of Alosetron on responses to nerve stimulation.

Conclusion:

The drug Alosetron is without effect on either resting tone or the response to nerve stimulation in the guinea-pig and dog inferior mesenteric arteries.

Lack of effect of alosetron on resting tone of the dog and guinea-pig inferior mesenteric artery

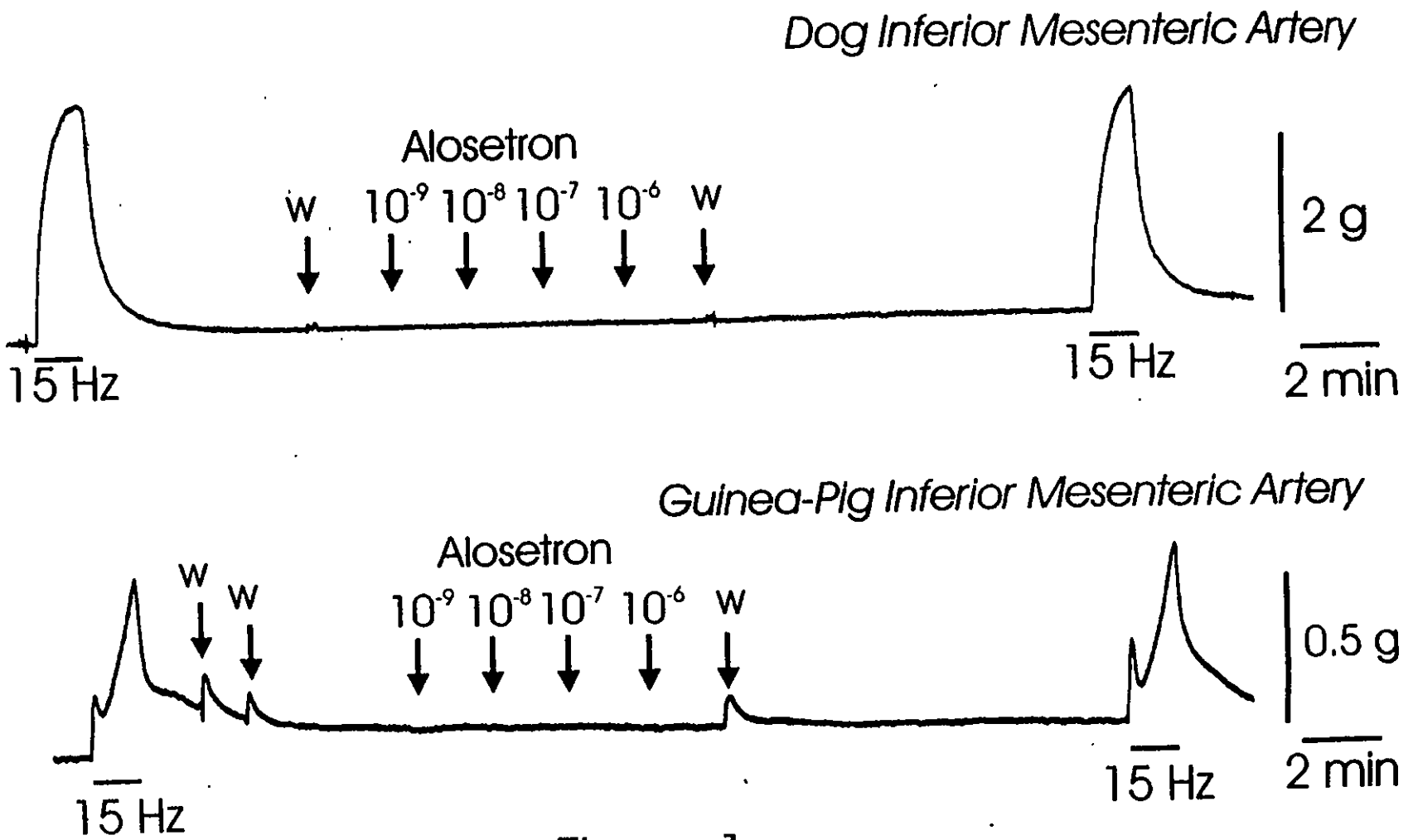
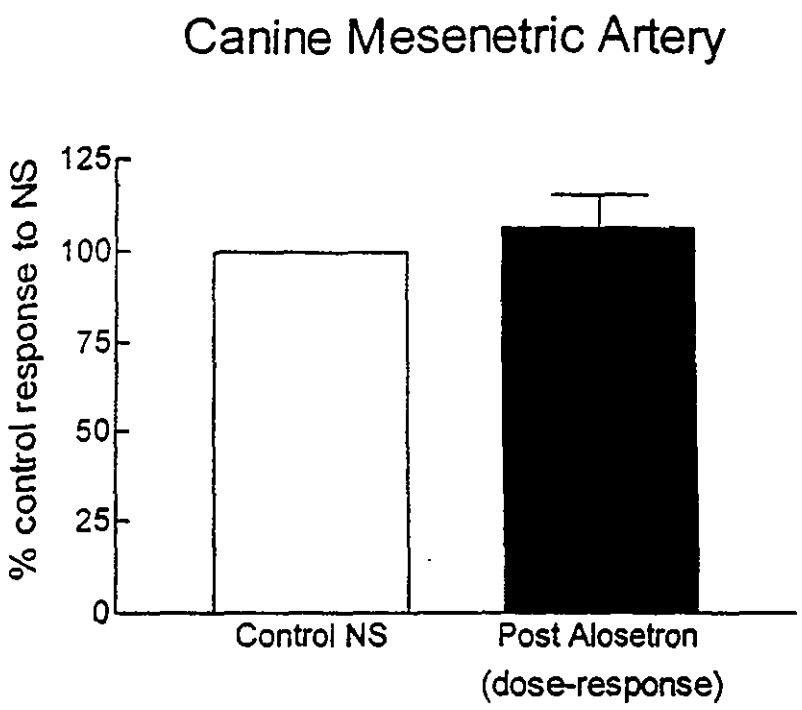


Figure 1

A.


Canine Mesenetric Artery
% control response to NS
125
100
75
50
25
0
Control NS
Post Alosetron
(dose-response)

B.

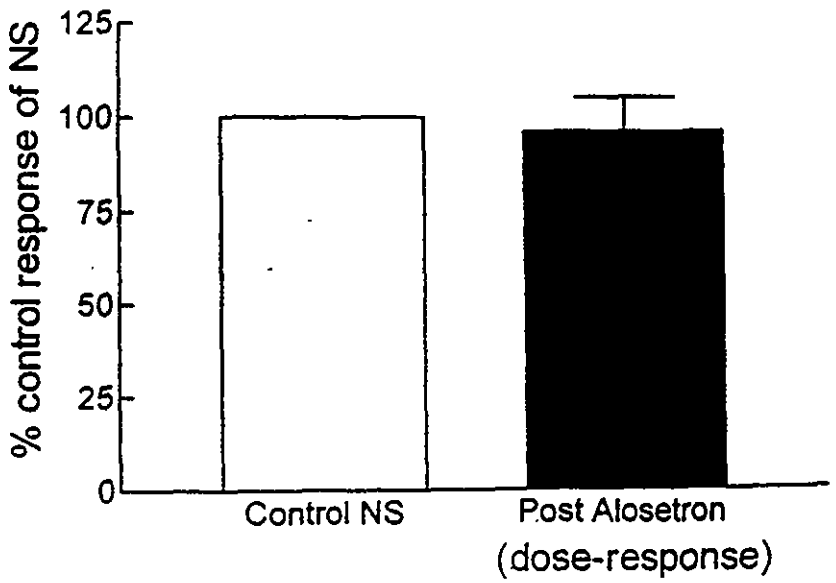
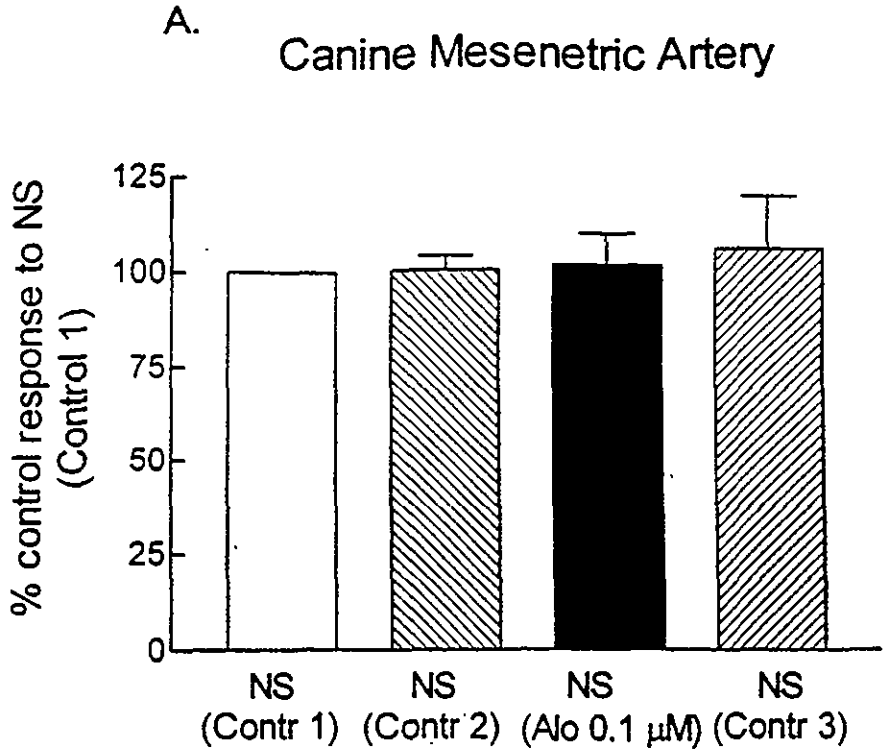

Guinea-Pig Mesenteric Artery
% control response of NS
125
100
75
50
25
0
Control NS
Post Alosetron
(dose-response)

Figure 2.

A.


Canine Mesenetric Artery
% control response to NS (Control 1)
125
100
75
50
25
0
NS (Contr 1)
NS (Contr 2)
NS (Alo 0.1 μM)
NS (Contr 3)

B.

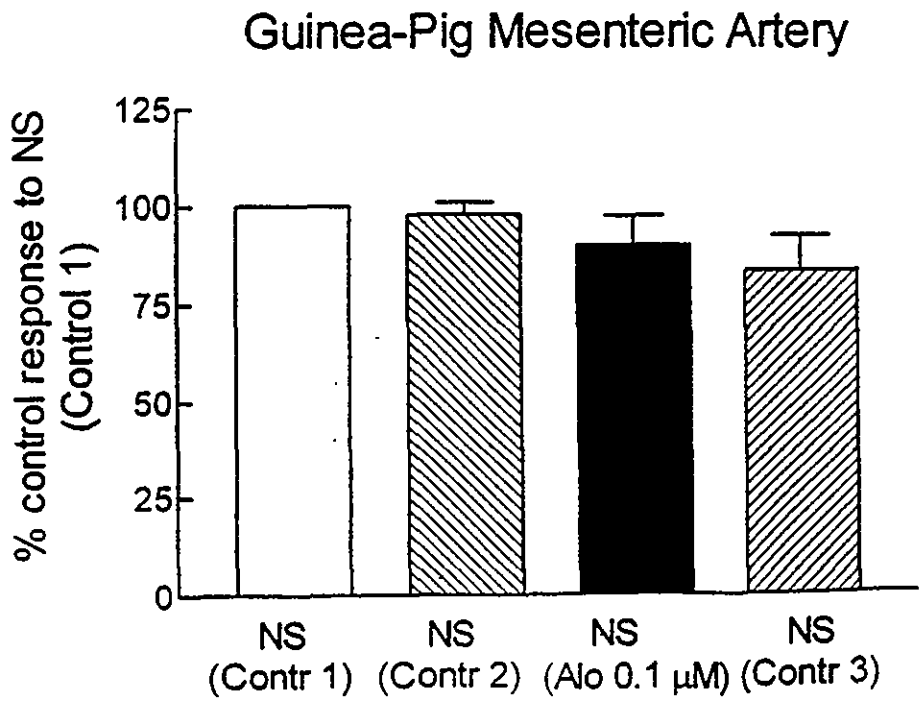
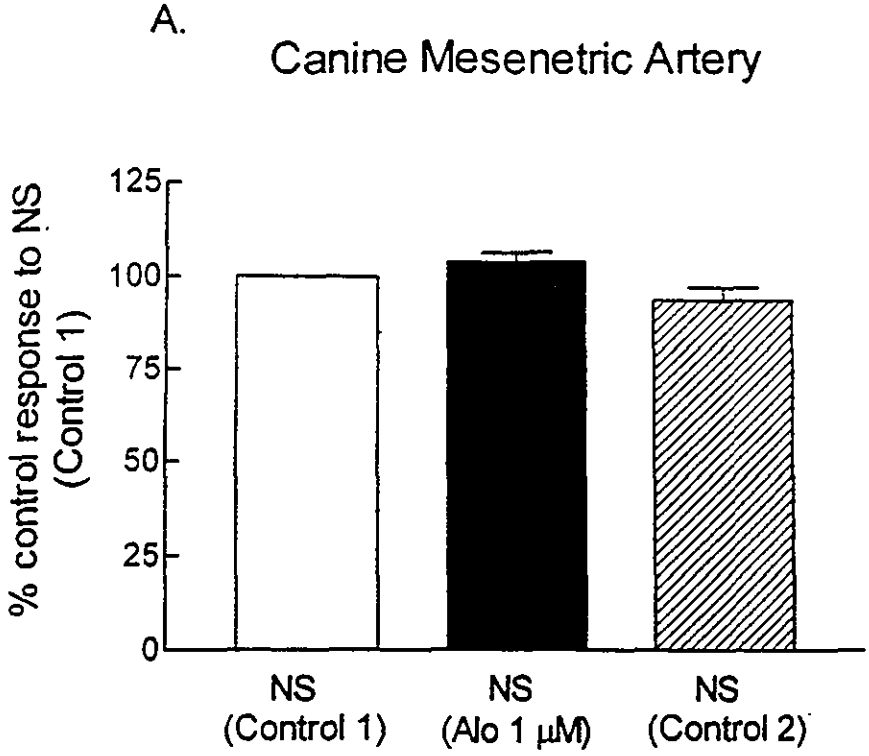

Guinea-Pig Mesenteric Artery
% control response to NS (Control 1)
125
100
75
50
25
0
NS (Contr 1)
NS (Contr 2)
NS (Alo 0.1 μM)
NS (Contr 3)

Figure 3.

A.


Canine Mesenetric Artery
% control response to NS (Control 1)
125
100
75
50
25
0
NS (Control 1)
NS (Alo 1 μM)
NS (Control 2)

B.

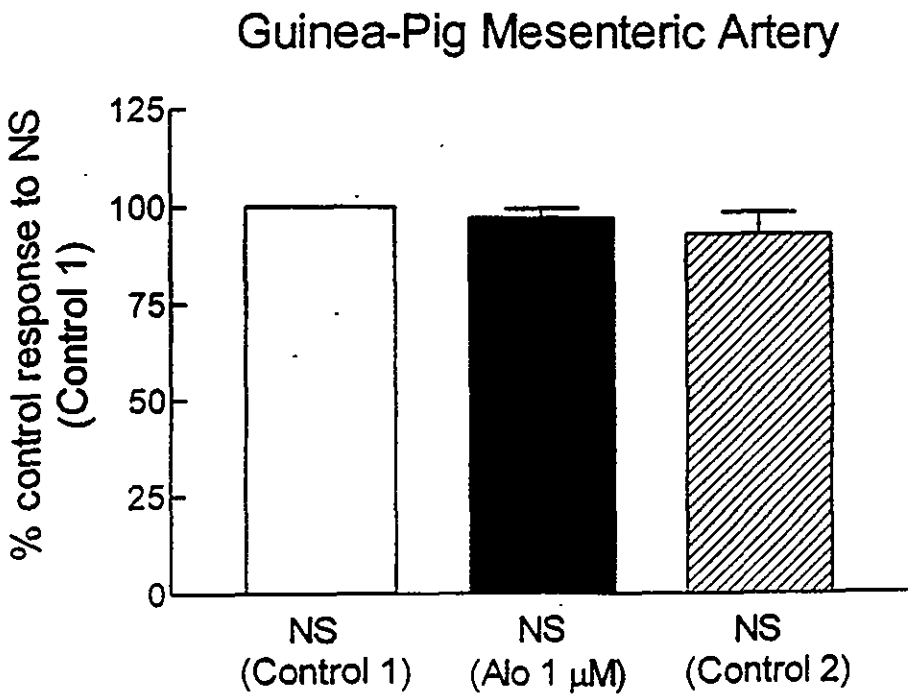

Guinea-Pig Mesenteric Artery
% control response to NS (Control 1)
125
100
75
50
25
0
NS (Control 1)
NS (Alo 1 μM)
NS (Control 2)

Figure 4.

	Canine Mesenteric Artery		
	Date	*100%*	*%of control*
		(Control NS)	(After cumulative treatment with Alosetron)
	10/11/99	100	98.8
	10/11/99	100	91.9
	10/11/99	100	124
	10/12/99	100	123
	10/13/99	100	96
	Mean	100.00	106.74
	SEM	0.00	6.93
	n	5	5
	Guinea-Pig Mesenteric Artery		
	Date	*100%*	*%of control*
		(Control NS)	(After cumulative treatment with Alosetron)
	10/11/99	100	102
	10/12/99	100	93
	10/12/99	100	94
	10/12/99	100	92
	10/13/99	100	100
	Mean	100.00	96.20
	SEM	0.00	2.01
	n	5	5

Table 1.
Comparison of the contractile responses to electrical field stimulation before (control NS) and after cumulative application of Alosetron (10^{-9} M-10^{-6} M) in canine and guinea-pig mesenteric artery segments.

Alosetron 0.1 uM					
Canine Mesenteric Artery					
Date	Control 1	Control 2	Alosetron 0.1 uM	Control 3 (post Alosetron)	
	100%	% of control 1	% of control 1	% of control 1	
10/12/99	100	102.5	104.5		
10/12/99	100	93.5	93.5		
10/14/99	100	87.5	81.25	81.25	
10/14/99	100	100	83.3		
10/13/99	100	119	147	147	
10/13/99	100	105.2	105.2	100	
10/13/99	100	100	100	98.2	
Mean	100.00	101.10	102.11	106.61	
SEM	0.00	3.73	8.31	14.11	
n	7	7	7	4	
Guinea-Pig Mesenteric Artery					
	Control 1	Control 2	Alosetron 0.1 uM	Control 3 (post Alosetron)	
	100%	% of control 1	% of control 1	% of control 1	
10/13/99	100	100	95	95	
10/13/99	100	109	109	100	
10/13/99	100	92.1	57.8	43.4	
10/13/99	100	100	100	100	
10/14/99	100	86.9	78.2	73.9	
10/14/99	100	100	100	89.5	
Mean	100.00	98.00	90.00	83.63	
SEM	0.00	3.11	7.66	8.97	
n	6	6	6	6	

Table 2.
Comparison of the contractile responses to electrical field stimulation in absence (control 1, control 2) and in presence of Alosetron (10^{-7} M) in canine and guinea-pig mesenteric artery segments. Control 3 obtained after washout of Alosetron.

Alosetron 1 uM			
Canine Mesenteric Artery			
Date	Control NS-1	Alosetron 1 uM	Control NS -2 (Post Alosetron)
	100%	(% of control 1)	(% of control 1)
10/11/99	100	107.5	95
10/11/99	100	117.9	
10/13/99	100	100	
10/14/99	100	100	84.6
10/13/99	100	103.2	101.6
10/13/99	100	100	
10/13/99	100	100	94.5
Mean	100.00	104.09	93.93
SEM	0.00	2.54	3.50
n	7	7	4
Guinea-Pig Mesenteric Artery			
Date	Control NS-1	Alosetron 1 uM	Control NS -2 (Post Alosetron)
	100%	(% of control 1)	(% of control 1)
10/11/99	100	103.1	
10/13/99	100	92.9	94.7
10/13/99	100	100	109
10/13/99	100	84.8	67
10/13/99	100	100	100
10/14/99	100	91.6	
10/14/99	100	105.8	94
10/14/99	100	100	94.1
Mean	100.00	97.28	93.13
SEM	0.00	2.45	5.73
n	8	8	6

Table 3.
Comparison of the contractile responses to electrical field stimulation in absence (control 1) and in presence of Alosetron (10^{-6} M) in canine and guinea-pig mesenteric artery segments. Control 2 obtained after washout of Alosetron.

Assessment of Patients with Unexplained Rectal Bleeding

During discussions at the October 6, 1999 90-day conference, FDA requested that GlaxoWellcome evaluate all adverse events of unexplained rectal bleeding, to ascertain if any of these could represent cases of unrecognized ischemic colitis. To accomplish this goal, the safety database of S3BP12,S3BA2001, S3BA3001, S3BA3002, and S3BA3003 was searched for the following adverse events: GI hemorrhage, rectal hemorrhage, blood in stool, bloody diarrhea, positive fecal occult blood, excretion of blood per rectum, exacerbation of excretion of blood per rectum, rectal bleeding with bowel movement, rectal bleeding due to rectal/anal fissure, bloody mucus in stool, recurrent rectal hemorrhage, rectal bleeding with menses, perianal hemorrhage, abnormal colonoscopy findings, colitis, collagenous colitis, coloproctitis, ischemic colitis, and hemorrhoidal bleeding. In the alosetron development program for IBS, treatment randomization schemes provided an approximate 1.9:1 ratio of alosetron to placebo treatment in S3B-P12, S3BA2001, S3BA3001, S3BA3002, and S3BA3003. This search yielded 60 subjects with adverse events, divided as follows:

Adverse Events of Rectal Bleeding or Colitis in S3BP12, S3BA2001, S3BA3001, S3BA3002, and S3BA3003

	Placebo (n=18/1044)	Alosetron (n=42/1903)
Rectal bleeding or rectal bleed/blood or increased rectal bleeding or hematochezia or scant rectal bleeding or blood per rectum or bloody diarrhea or rectal blood	11	29 (20 occurring w/o constipation; 9 occurring w/ constipation)
Blood with stools or blood in stool or bloody mucus stools or bloody stool	5	5
Ischemic colitis		3 Subj# 2829–S3BA2001 Subj# 15687-S3BA3001 Subj# 7195-S3BA3002
Bleeding hemorrhoids	1 Subj#10080-S3BA3003	3 Subj#796-S3BA2001 Subj# 4881-S3BA3001 Subj# 6017-S3BA3001
Rectal tear with bleeding		1 Subj# 11937-S3BA3003
Hemoccult positive stool	1 Subj# 10151-S3BA3003	1 Subj# 10418-S3BA3003

Only adverse events in the first two categories (rectal bleeding or blood with stools) represented unexplained events of rectal bleeding. Events of bleeding hemorrhoids or rectal tear with bleeding are not further discussed, as an explanation has been provided. Events of Hemoccult positive stool are not included, as ischemic colitis is typically accompanied with hematochezia. The events identified as ischemic colitis have been evaluated by an external expert, Lawrence

Brandt, M.D. (Appendix 3); the conclusion of this expert was that there is "no pathophysiologic evidence that suggests that alosetron might precipitate colon ischemia".

The events of rectal bleeding were evaluated by treatment, revealing 29 subjects in the alosetron-treatment group and 11 subjects receiving placebo (see attached table). In addition, events of "blood with stools" occurred in 5 alosetron-treated and 5 placebo-treated subjects

Ischemic colitis is most frequently accompanied by rectal bleeding (>87%), abdominal pain (>80%), and diarrhea (50%) (Matsumoto et al, Gastroenterology & Hepatology 1994; 9:572-5). To discern any possible association with ischemic colitis, the occurrence of adverse events of abdominal pain and/or diarrhea within 7 days of the unexplained rectal bleed or blood with stool were examined. In addition, as alosetron is associated with constipation, which could potentially be associated with events of rectal fissures or hemorrhoidal bleeding, adverse events of constipation occurring within 7 days of the rectal bleed were also captured. The table on the proceeding page reveals events of unexplained rectal bleeding or blood in stools in both treatment groups.

Among alosetron-treated subjects, 24/1903 (1.3%) subjects exhibited rectal bleeding or blood in stools occurring in the absence of constipation and 10 subjects had events occurring in conjunction with constipation. Of the 24 subjects without constipation at the time of the rectal bleeding, the majority of rectal bleeding events were rated as mild (n=15) and the remainder as moderate (n=9), with the exception of one severe bleed, occurring in a subject diagnosed with Crohn's disease during the study. Among all alosetron-treated subjects with these bleeding events, nine subjects exhibited concomitant abdominal pain and five subjects exhibited diarrhea; of these, two subjects exhibited concomitant abdominal pain and diarrhea. There appeared no dose response relationship to alosetron treatment, with events occurring in those receiving alosetron 0.1 to 4-mg po BID and no events in those treated with alosetron 8-mg po BID. Of the 24 subjects receiving alosetron who did not report constipation, concomitant medications in 10 subjects included: nonsteroidal antiinflammatory agents (n=4), estrogen (n=5), mesalamine (n=1), and digoxin (n=1).

Of alosetron-treated subjects who did not report constipation and exhibited rectal bleeding or blood with stool, in conjunction with either abdominal pain or diarrhea (n=14), additional information on the event was requested from the investigators, to include: clinic notes, endoscopy reports and/or biopsies (including anoscopy, flex. sigmoidoscopy, or colonoscopy) performed within one month of the rectal bleeding event, stool cultures (including Clostridium difficile & enterotoxigenic E. coli), ova & parasites obtained at the time of the event, any X-rays or imaging reports obtained at the time of the event, and preceding or subsequent history of rectal bleeding and source (if known). These queries yielded substantive additional information for 8 alosetron-treated subjects (subjects with asterisks in attached Table), including both subjects with abdominal pain and diarrhea occurring with rectal bleeding. For these 8 subjects, this additional information revealed: internal hemorrhoids (n=5), rectal ulcer in conjunction with internal hemorrhoids and a colonic polyp (n=1), "blood around a diverticulum" in conjunction with small internal hemorrhoids and a colonic polyp (n=1), and diverticulosis and hemorrhoids (n=1)." No evidence of ischemic colitis was noted in any follow up information.

Of alosetron-treated subjects who developed constipation and exhibited rectal bleeding or blood with stool, abdominal pain occurred within the preceding week in 4 subjects. Additional information on the event was requested from the investigators, and yielded substantive information in 2 subjects, revealing the presence of internal hemorrhoids. No evidence of ischemic colitis was noted in this group.

Among placebo-treated subjects, 16/1044 (1.5%) exhibited rectal bleeding or blood in stools. In the placebo group, associated abdominal pain was noted in 2 subjects and diarrhea in 3 subjects. No subjects in the placebo group exhibited concomitant abdominal pain and diarrhea. Of the 16 subjects receiving placebo who exhibited these bleeding events, concomitant medications in 9 subjects included: nonsteroidal antiinflammatory agents (n=7), estrogen (n=5), and digoxin (n=1).

In summary, a similar very low incidence of rectal bleeding or blood in stools adverse events was noted in alosetron and placebo-treated subjects. Hemorrhoids was the most common etiology of rectal bleeding in both treatment groups. These events were infrequently associated with abdominal pain and/or diarrhea. The majority of events were mild. Concomitant use of nonsteroidal antiinflammatory agents, known to enhance GI bleeding, may have contributed to some of these rectal bleeding events.

Incidence of Rectal Bleeding Adverse Events: Placebo - Treated

#	Subj #	Study #	Event	Sev. grade	# evts	Days To Onset	Dur (d)	Const.	Abd. pain	Diarr	Study Drug	Demog	Other info (procedures, etc)
1	00587	S3BP12	Blood with Stools	1	1	40	5	0	0	0	Placebo	28 yo WF	
2	04099	S3BA3001	Blood in stools	1	1	21	9	0	0	0	Placebo	43 yo Asian F	Meds: ibuprofen, estrogen
3	04761	S3BA3001	Blood in stool	2	1	56	1	0	0	0	Placebo	21 yo WF	Withdrew secondary to AE
4	05122	S3BA3001	Scant rectal Bleeding	1	1	12	2	0	0	1	Placebo	40 yo WF	
5	05516	S3BA3001	Rectal bleeding	1	1	69	1	0	0	0	Placebo	28 yo WF	
6	05204	S3BA3001	Rectal bleeding	1	1	23	22	0	0	0	Placebo	53 yo WF	Meds: aspirin
7	06353	S3BA3002	Rectal bleeding	1	1	41	1	0	1	0	Placebo	21 yo WF	Con. Meds included colon'y prep 5 days after rectal bleed
8	08046	S3BA3002	Blood in stool	1-2	4	15,18 31,35	2	0	0	0	Placebo	30 yo WF	Meds: ibuprofen, estrogen
9	08767	S3BA3002	Blood in stool	1	1	118	?	0	0	0	Placebo	57 yo WF	
10	10229	S3BA3003	Hematochezia	1	1	226	18	0	0	0	Placebo	64 yo WF	Meds: digoxin, aspirin
11	08450	S3BA3003	Rectal bleeding With menses	1	1	144	?	0	1	0	Placebo	23 yo WF	Meds: naproxen sodium, estradiol
12	10480	S3BA3003	Intermittent Rectal bleeding	1	1	178	6	0	0	0	Placebo	82 yo WF	Meds: ibuprofen
13	08440	S3BA3003	Rectal bleeding	1	1	35	8	0	0	0	Placebo	51 yo WF	Meds: estrogen PMHx: h/o hemorrhoids
14	08245	S3BA3003	Bloody diarrhea	2	1	299	12	0	0	1	Placebo	26 yo WF	Meds: estrogen
15	08528	S3BA3003	Rectal bleeding	1	1	161	4	0	0	0	Placebo	51 yo BF	Meds: aspirin
16	10496	S3BA3003	Rectal bleeding	1	1	120	4	0	0	0	Placebo	39 yo WF	

Incidence of Rectal Bleeding Adverse Events: Alosetron – Treated Patients (Phase II)

#	Subj #	Study #	Event	Sev. grade	# evts	Days To Onset	Dur (d)	Const.	Abd. pain	Diarr	Study Drug	Demog	Other info (procedures, etc)
1	00378	S3BP12	Rectal bleeding	2	1	66	<1	0	0	0	Alos 0.1 Mg BID	61 yo WF	Rectal bleeding preceded study drug treatment and resolved at Week 12 visit; hard stool reported with rectal bleeding AE
2	00257*	S3BP12	Rectal bleeding	2	1	11	2	0	0	1	Alos 0.1 BID	41 yo WF	F/u info: "the patient had a diagnosis of hemorrhoids and a h/o hemorrhoids at the study start"; "the rectal bleeding was.. resolved at the time of the study end"
3	00241	S3BP12	Rectal bleeding	1	2	6 12	1	0	1	0	Alos 0.1 BID	25 yo WF	
4	02788*	S3BA2001	Rectal blood	2	1	15	21	0	1	1	Alos 4 mg BID	28 yo WM	F/u info: 2 weeks prior to study, subject had a rectal bleed with flex. sig. Revealing int. hemorrhoids for which a trial of injection sclerotherapy was recommended
5	02837	S3BA2001	Rectal bleeding	1	1	21	1	1	0	0	Alos 4 mg BID	44 yo WF	Withdrew secondary to AE
6	02633*	S3BA2001	Rectal bleeding	3	1	50	3	1	1	0	Alos 2 mg BID	37 yo WM	No f/u info. available – site now disbanded

*Additional info. obtained from principal investigator

Incidence of Rectal Bleeding Adverse Events: Alosetron – Treated Patients (Phase III)

#	Subj #	Study #	Event	Sev. grade	# evts	Days To Onset	Dur (d)	Const.	Abd. pain	Diarr	Study Drug	Demog	Other info (procedures, etc)
7	04148 *	S3BA3001	Bloody, mucous Stool	1	1	10	4	0	1	0	Alos 1 mg Bid	46 yo WF	Meds: estrogen F/u info: Patient noted "very small infreq. Stools, abd'l pain, mucus and blood x 3 Days; had normal BM on following day. No Further evaluation performed (flex. sig. 1 mo. earlier revealed only mild rectal erythema
8	04287 *	S3BA3001	Rectal bleeding	2	1	54	1	0	1	0	Alos 1 mg BID	79 yo WF	Hemorrhoids noted 1 day after rectal bleed as AE. Meds: digoxin F/u info: anoscopy and sigmoidoscopy performed one day following rectal bleed revealed Grade II+ internal hemorrhoids with " a nasty purplish ecchymotic area" and occasional uncomplicated diverticulum.
9	04595	S3BA3001	Rectal bleeding	3	1	32	3	0	0	0	Alos 1 mg BID	33 yo WF	Subject underwent colonoscopy and was diagnosed with Crohn's disease as the etiology of the rectal bleed 6 d after the bleed
10	05473 *	S3BA3001	Rectal bleeding	1	1	24	12	0	1	0	Alos 1 mg BID	50 yo WF	Meds: Ibuprofen F/u Info: 1 day after straining at stool, subject noted stool, "then diarrhea, then mucus and blood on toilet tissue" On the subsequent day, the subject noted "speck of blood" with a "bit of diarrhea", so underwent flex sig. which revealed int.hemorrhoids (which was stated as the diagnosis of the rectal bleed)
11	04969 *	S3BA3001	Rectal bleeding	1	1	42	10	0	1	0	Alos 1 mg BID	69 yo WF	F/u Info. Flex. sig. performed after bleeding (report to be sent) PE revealed BRB on rectal exam. Stool C&S (including E.coli 0157:h7) neg. O&P neg., Giardia neg. Hgb 11.9 No h/o rectal bleeding recurrence subsequently.
12	04809	S3BA3001	Rectal bleeding	2	1	11	3	0	0	0	Alos 1 mg BID	55 yo WF	Meds: estrogen
13	04811	S3BA3001	Rectal bleeding	1	1	64	19	0	0	0	Alos 1 mg BID	38 yo WF	Hard stool reported with rectal bleeding AE

Incidence of Rectal Bleeding Adverse Events: Alosetron – Treated Patients (Phase III)

	Subj #	Study #	Event	Sev. grade	# evts	Days To Onset	Dur (d)	Const.	Abd. pain	Diarr	Study Drug	Demog	Other info (procedures, etc)
14	05882	S3BA3001	Rectal bleeding	1	1	15	85	0	0	0	Alos 1 mg BID	38 yo WF	AE occurred with hard stool & decreased stool frequency Meds: aspirin, naproxen sodium
15	07707	S3BA3002	Increased Rectal bleeding	1	1	24	1	0	0	0	Alos 1 mg BID	51 yo WF	AE of increased rectal bleeding reported 2 days prior to study drug treatment
16	07309	S3BA3002	Rectal bleeding	1	1	10	?	0	0	0	Alos 1 mg BID	27 yo WF	
17	12016 *	S3BA3003	Rectal bleeding	1	1	159	12	0	0	1	Alos 1 mg BID	38 yo WF	F/u info: colon'y (on day of report of bright red blood per rectum, abd'l pain, diarrhea) revealed diverticulosis, hemorrhoids. PE unremarkable. Stool O&P neg.
18	12116	S3BA3003	Blood in stool	1	1	31	12	0	0	0	Alos 1 mg BID	47 yo WF	Internal hemorrhoids noted 1 mo. after blood in stool AE. Meds: estrogen
19	08419	S3BA3003	Bloody stool	1	1	16	4	0	0	0	Alos 1 mg BID	40 yo WF	Hemorrhoids listed as AE on date of Bloody stool AE
20	08425	S3BA3003	Blood in stool	1	1	289	2	0	0	0	Alos 1 mg BID	52 yo WM	
21	08664	S3BA3003	Rectal bleeding	2	1	15	6	0	1	0	Alos 1 mg BID	59 yo WM	Hard stool reported with rectal bleeding AE
22	08160	S3BA3003	Rectal bleeding	2	1	5	5	0	0	0	Alos 1 mg BID	44 yo WM	PMHx: polyps, diverticulosis
23	10160 *	S3BA3003	Hematoche zia	2	1	335	2	0	1	0	Alos 1 mg BID	52 yo WM	Meds: mesalamine, aspirin F/u info: 2 episodes of red blood with passage of stool; eval. in ER: Flex sig: revealed normal mucosa, but "a small source of fresh blood was seen on a friable hemorrhoid". Hgb normal.
24	11970	S3BA3003	Rectal bleeding	1	1	55	33	0	0	0	Alos 1 mg BID	56 yo WF	Meds: estrogen
25	10211 *	S3BA3003	Rectal bleeding	1	1	92	4	0	0	1	Alos 1 mg BID	74 yo WF	Meds: aspirin F/u info: 4 days after rectal bleed, colon'y revealed "erythema and minimal old blood around a diverticulum, but no active bleeding", "small internal hemorrhoids", 1.2 cm benign polyp in the mid transverse colon. ASA discontinued.

Incidence of Rectal Bleeding Adverse Events: Alosetron – Treated Patients (Phase III)

#	Subj #	Study #	Event	Sev. grade	# evts	Days To Onset	Dur (d)	Const.	Abd. pain	Diarr	Study Drug	Demog	Other info (procedures, etc)
26	10206 *	S3BA3003	Blood per rectum	2	1	142	2	0	1	1	Alos 1 mg BID	49 yo WF	Meds: estrogen F/u info: colon'y 24 d after rectal bleed revealed a solitary 0.5 cm rectal ulcer, internal hemorrhoids, and a colonic polyp at 10-15 cm (not biopsied secondary to poor prep) Pathol. Of rectal ulcer: acute ulcerative proctitis with epithelial inflammatory and reparative atypia; negative for malignancy
27	04968	S3BA3001	Rectal bleeding	1	1	62	20	1	0	0	Alos 1 mg BID	73 yo WF	Meds: estrogen
28	04868	S3BA3001	Rectal bleeding	1	1	14	1	1	0	0	Alos 1 mg BID	43 yo WF	Withdrew secondary to AE Meds: nabumetone
29	04857 *	S3BA3001	Rectal bleed	3	1	11	5	1	1	0	Alos 1 mg BID	50 yo WF	F/u info: Anoscopy (6 days after bleed) Revealed a hemorrhoid which "recently bled" Meds: estrogen
30	10227	S3BA3003	Rectal bleeding	1	1	350	4	1	0	0	Alos 1 mg BID	37 yo WM	
31	08193	S3BA3003	Rectal bleeding	1	1	118	5	1	0	0	Alos 1 mg BID	59 yo WF	
32	12166	S3BA3003	Rectal bleeding	1	1	55	77	1	0	0	Alos 1 mg BID	38 yo WF	
33	11974 *	S3BA3003	Rectal bleeding	1	1	22	2	1	1	0	Alos 1 mg BID	47 yo BF	F/u info: 1 day of rectal bleeding reported in conjunction with severe constipation
34	11951 *	S3BA3003	Blood in stool	3	1	7	5	1	1	0	Alos 1 mg BID	56 yo WF	Meds: estrogen F/u info: Preceding the rectal bleed, subject had a h/o 4 day w/ no stools, followed by a 2 day report of small loose stool with intermittent blood and mucus; PE revealed protruding hemorrhoids; subject withdrew from study secondary to AE of Constipation and did not present for Further f/u

*Additional info. obtained from principal investigator

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Report: Effects of Alosetron on the Rat Colonic Mucosal Microcirculation

Introduction: A few incidences of ischemic colitis have been reported in patients taking Alosetron. As a result, the effects of Alosetron on the colonic mucosal microcirculation were examined to determine if there was any evidence of this drug producing ischemic colitis in rats.

Materials and Methods: The effects of Alosetron on the colonic mucosal microcirculation of male Sprague Dawley rats under pentibarbital anesthesia (0.6 mg/gm bw, i.p.) were examined using established high resolution *in vivo* microscopic methods. Briefly, a compound binocular microscope (Leitz) adapted for *in vivo* microscopy was equipped to provide either transillumination or epiillumination as well as video microscopy using a cooled CCD camera (Optronics). The large intestine was exteriorized through a mid-line abdominal incision and incised along its anti-mesenteric border. Once the colonic contents were flushed from the lumen, the exposed mucosal surface was positioned face-up over a window of optical grade mica in a specially designed tray mounted on microscope stage. The tray had provision for the drainage of irrigating fluids, and the window overlaid a long working distance condenser. Homeostasis was insured by constant suffusion of the organ with Ringer's solution maintained at body temperature. The mucosal surface was imaged using 20X water immersion objective (Olympus) which allowed observation of the mucosal microcirculation surrounding the intestinal crypts. No attempt was made to limit intestinal peristaltic movements pharmacologically since this might affect the microvascular response to Alosetron. Microvascular events were observed and recorded at least 30 seconds/microscopic field using a Sony Betacam video tape recorder.

The initial intent was to examine the effects of Alosetron at three different concentrations (0.1, 0.5, and 1.0 mg/kg bw dissolved in saline). However, after observing that the highest dosage (1 mg/kg bw) produced no significant effects on the mucosal microcirculation over a two-hour period, we decided that there was no point in evaluating the lower doses. The following groups of rats were examined: (a) rats injected i.v. with Alosetron (1 mg/kg bw) and then examined 2 hrs later (n=3); (b) animals injected i.v. with equivalent volume of saline and then examined 2 hrs later served as controls (n=3); and (c) rats examined before, during, and up to one hour after the injection of Alosetron (1 mg/kg bw) (n=4) or equivalent volumes of saline (n=2).

Results: In none of the animals were significant changes in the microcirculation noted. Blood flow was maintained in all capillaries. There was no microscopic or gross evidence of hemorrhaging during the 2-2.5 hr period of observation. Intestinal peristalsis was maintained, and, at times, made observation difficult. An unedited copy of the video tape of the *in vivo* microscopic observations from animals studied at two hours is enclosed.

Conclusions: No evidence was found in rats that a single, high dose of Alosetron interferes with intestinal blood flow in rats within the 2-2.5 hr period of observation.

Robert S. McCuskey
Professor and Head of Cell Biology & Anatomy
Professor of Pediatrics
Professor of Physiology

6 June 2000

HEPATIC (SERIOUS CASES)
A0119607A
A0120634A

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Glaxo Wellcome

Approved by the FDA (MM-2) on 31Nov99

Mfr report # A0119607A

User/Dist report #

FDA Use Only

A. Patient information

1. Patient identifier	2. Age at time of event: 75Y or Date of birth 02Apr1924	3. Sex	4. Weight (lb)
In confidence		☒ female ☐ male ☐ unknown	100.1

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)

☐ death ☐ disability
☐ life-threatening ☐ congenital anomaly
☐ hospitalization - initial or prolonged ☐ required intervention to prevent permanent impairment/damage
☐ other

3. Date of event: 31Mar2000

4. Date of this report: 09Jun2000

5. Describe event or problem

DESK COPY

A physician reported that a 75 year old female with a history of three small bowel obstructions and intractable nausea, vomiting, and abdominal pain for several years received two doses of alosetron (Lotronex) tablets to treat abdominal pain and presumed irritable bowel disease. The patient had a three to four week history of fluid retention edema felt to be due to mirtazapine which was stopped the day alosetron was started. She had also started ciprofloxacin two days earlier for exacerbation of COPD. The patient presented to the physician's office with bloody stools, systolic blood pressure between 70 and 80, and pitting edema up to her waist and pre-sacral region. Her toes were cool and blue. She was alert, afebrile, and complained of some shortness of breath. She was hospitalized with dehydration, hypotension, anasarca with third spacing, and evidence of GI bleed, possibly due to a drug

continued on next page

6. Relevant tests/laboratory data, including dates

Tests/Labs: 15Mar00: creatinine 0.7, potassium 4.8, glucose 82, BUN 21, sodium 146, chloride 93, CO2= 37; AST or GOT 42, Total protein 6.8, hemoglobin 12.8, white count 4800. Upper endoscopy, colonoscopy, and abdominal CT scan with anorectal anometry Nov98 all negative. Biopsies of colon negative Nov98; upper endocospy Aug99 was unremarkable; CT of chest Aug99 revealed

continued on next page

7. Other relevant history, including preexisting medical conditions (eg, allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

History: Multiple drug allergies or drug intolerances including alendronate, cisapride, benzylsufamide, steroids, aspirin, amitriptyline, antihistamines, omeprazole, sertraline, citalopram, sulfa; hospitalized 04Jul99 and Aug99 for intractable nausea, vomiting, and abdominal pain with a negative workup; history of chronic bronchiectasis with chronic

continued on next page

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

#1 Lotronex Tablet (Alosetron hydrochloride)

#2

2. Dose / frequency / route used

#1 1 mg / See text / Oral

#2

3. Therapy dates

#1 30Mar00 - 31Mar00

#2

4. Diagnosis for use (indication)

#1 Irritable bowel syndrome

#2

5. Event abated after use stopped or dose reduced

#1 ☒ yes ☐ no ☐ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)

#1 None

#2

7. Exp date (if known)

#1

#2

8. Event reappeared after reintroduction

#1 ☐ yes ☐ no ☒ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)

Mirtazapine	Nov99 - 30Mar00
Torasemide	UNK - Mar00
Ciprofloxacin HCl	28Mar00 - UNK
Guaiphenesin	28Mar00 - UNK

continued on next page

G. All manufacturers

1. Contact office - name/address

Glaxo Wellcome
North American Product Surveillance
PO Box 13398
Research Triangle Park
NC 27709

2. Phone number 1-888-825-5249 ext. 37070

3. Report source

☐ foreign
☐ study
☐ literature
☐ consumer
☒ health professional
☐ user facility
☒ company representative
☐ distributor
☐ other:

4. Date received by manufacturer 10Apr2000

5. (A)NDA # 21-107
IND #
PLA #
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #

7. Type of report

☐ 5-day ☒ 15-day
☐ 10-day ☐ periodic
☒ initial ☐ follow-up #

8. Adverse event term(s)

Hepatotoxicity
Acute hepatitis
Acute renal failure
Blood in stool(s)
Hypotension

continued on next page

9. Mfr. report number A0119607A

E. Initial Reporter

1. Name, address & phone #

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA?
☒ yes ☐ no	Internal Med.	☐ yes ☐ no ☒ unk

FDA Form 3500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

B5. Describe event or problem (cont'd)
interaction or secondary to mirtazapine or other medications. Hyperkalemia and thrombocytopenia were also noted. She improved after treatment with intravenous fluids, dopamine, and kayexalate enema. While hospitalized, she developed acute renal failure with oliguria, but improved after medications were stopped and she was rehydrated. Chest x-ray showed questionable congestive heart failure with small dependent effusion, superimposed upon a long standing pleural thickening at both bases. The reporter commented that although the chest x-ray showed CHF, there was no evidence of this upon discharge. Ultrasound of the liver showed a hyperechoic liver and some ascites. This was felt to be either fatty changes or cirrhosis. She was discharged after seven days. Discharge diagnosis was acute hepatitis with severe hepatotoxic reaction, possibly medication effect.

B6. Relevant tests/laboratory data (cont'd)
bronchiectasis and scarring.Last echocardiogram Oct1999 showed mild aortic insufficiency, mild mitral regurgitation and left ventricular hypertrophy. On admission 31Mar00: systolic blood pressure was 70-80, white count 11,300, hemoglobin 13.4, MCV 100.6, platelets 104, alkaline phosphatase 183, CPK troponins mildly positive; CPK/MB was 8, troponin 3.3; hepatitis profile negative; TSH 2.0, IGA 33.2, IGG and IGM normal; rheumatoid factor negative at 28; serum ammonia increased to 47 from 32; serum protein electrophoresis unremarkable; urine initially positive but showed protein nonselect proteinuria; potassium 7.0; initial prothrombin time was 19.6, d-dimer was elevated; FST also elevated; sedimentation rate was 2; amylase and lipase normal; toxicology screen negative; acetophenide level was 10.9; alcohol level not detectable; urine sodium 13; Discharge labs: sodium 145, potassium 4.7, chloride 108, CO2= 37, glucose 93; BUN 15, creatinine 0.7, calcium 8.3, bilirubin normal; alkaline phosphatase 59, AST 260, ALT 891, albumin 2.4, total protein 5.4, hemoglobin 11.8, pH 7.45, pCO2=49, pO2=67, bicarbonate 33, oxygen saturation 92%, prothrombin time 13.19 (down from 16-17), INR 1.2; blood cultures revealed no growth; platelets 124,000. Chest x-ray on admission showed questionable congestive heart failure with small dependent effusion, superimposed upon a long standing pleural thickening at both bases. The reporter commented that although the chest x-ray showed CHF, there was no evidence of this upon discharge. Ultrasound of the liver showed a hyperechoic liver and some ascites. This was felt to be either fatty changes or cirrhosis.

B6. Relevant tests/laboratory data (cont'd)

Test Date	Name	Result	Low	High
15Mar2000	Creatinine, Serum	0.7		
15Mar2000	Potassium	4,8		
15Mar2000	Glucose, Blood (random)	82		
15Mar2000	Urea Nitrogen, Blood	21		
15Mar2000	Sodium, Serum	146		
15Mar2000	Chloride, serum	93		
15Mar2000	Blood arterial carbon dioxide	37		
15Mar2000	Aspartate Transaminase, Serum	42		
15Mar2000	Protein, Serum, Total	6.8		
15Mar2000	Haemoglobin	12.8		
15Mar2000	White Blood Cell Count	4800		
31Mar2000	WhiteBloodCellCount	11,300		
31Mar2000	Haemoglobin	13.4		
31Mar2000	Mean Corpuscular Volume	100.6		
31Mar2000	Platelet Count, Blood	104		
31Mar2000	Alkaline Phosphatase, Serum	183		
31Mar2000	Creatine Phosphokinase, Serum	8		
31Mar2000	Troponin	3.3		
31Mar2000	Thyroid stimulating hormone	2.0		
31Mar2000	Immunoglobulin A, Serum	33.2		
31Mar2000	Rheumatoid factor	28		
31Mar2000	Ammonia, serum	47		
31Mar2000	Potassium	7.0		
31Mar2000	Partial Prothrombin Time	19.6		
06Apr2000	Sodium, Serum	145		

continued on next page

B6. Relevant tests/laboratory data (cont'd)

06Apr2000	Potassium	4.7
06Apr2000	Chloride, serum	108
06Apr2000	Blood arterial carbon dioxide	37
06Apr2000	Glucose, Blood (random)	93
06Apr2000	Urea Nitrogen, Blood	15
06Apr2000	Creatinine, Serum	0.7
06Apr2000	Calcium, Serum	8.3
06Apr2000	Alkaline Phosphatase, Serum	59
06Apr2000	Aspartate Transaminase, Serum	260
06Apr2000	Alanine Transaminase, Serum	891
06Apr2000	Albumin, Serum	2.4
06Apr2000	Protein, Serum, Total	5.4
06Apr2000	Haemoglobin	11.8
06Apr2000	pH, Serum	7.45
06Apr2000	Partial pressure of carbon dio	49
06Apr2000	Partial Pressure of Oxygen	67
06Apr2000	Bicarbonate	33
06Apr2000	Oxygen Saturation	92
06Apr2000	International normalised ratio	1.2
06Apr2000	Platelet Count, Blood	124,000

B7. Other relevant history (cont'd)

antibiotic use, COPD, chronic weight loss, anorexia, malnutrition; GERD, transient hyperglycemia, right partial lobectomy 1975 for benign disease secondary to bronchiectasis; fibrocystic breasts, negative biopsy left breast in the past; herpes zoster right breast 1992; ovarian cyst, history of appendectomy; small bowel obstruction with incarcerated hernia and strangulated bowel in 1970, hospitalized Oct1996 for small bowel obstruction which resolved spontaneously; hospitalized March 1997 for small bowel obstruction with lysis of adhesions surgically required; significant degree of depression; mirtazapine caused lower extremity edema; history of atypical chest pain with multiple evaluations and hospitalization in Sep1997 with a negative thallium stress test; recurrent hemoptysis with negative bronchoscopy in 1991 and negative CT of chest in Aug1999; chronic palpitations with PVC's; melanoma of right cheek resected Sep1995; total abdominal hysterectomy and salpingo-oophorectomy for benign disease Feb1996; osteroarthritis of the cervical and lumbar spine; smoked for 26 years prior to admission; occasional alcohol use; denied recent alcohol use; mother died at age 47 with cancer of the abdomen (unknown type); father died at age 69 of diabetes, hypertension, stroke. The patient had never had previous episodes of acute hepatotoxicity, renal failure, or GI bleeding.

B7. Other relevant history (cont'd)

Condition	Started	Ended	Continuing
Small bowel obstruction	1970	Unknown	No
Incarcerated hernia	1970	Unknown	No
Smoker	1974	Unknown	Unknown
Partial pulmonary lobectomy	1975	Unknown	No
Recurrent hemoptysis	1991	Unknown	Unknown
Herpes zoster	1992	Unknown	Unknown
Malignant melanoma of face	Sep1995	Unknown	No
Abdominal hysterectomy	Feb1996	Unknown	No
Salpingo-oophorectomy	Feb1996	Unknown	No
Small bowel obstruction	Oct1996	Unknown	No
Small bowel obstruction	Mar1997	Unknown	No
Lysis of adhesions	Mar1997	Unknown	No
Atypical chest pain	Sep1997	Unknown	Yes
Bronchiectasis	Unknown	Unknown	Yes
Chronic nausea	Unknown	Unknown	Yes
Chronic abdominal pain	Unknown	Unknown	Yes
Chronic weight loss	Unknown	Unknown	Yes
Vomiting	Unknown	Unknown	Unknown

continued on next page

B7. Other relevant history (cont'd)

Decreased low serum albumin	Unknown	Unknown	Unknown
Depression	Unknown	Unknown	Yes
Lower extremity edema	Unknown	Unknown	Yes
COPD	Unknown	Unknown	Yes
Malnutrition	Unknown	Unknown	Unknown
GERD	Unknown	Unknown	Unknown
Fibrocystic breast	Unknown	Unknown	Unknown
Appendectomy	Unknown	Unknown	Unknown
Ovarian cyst	Unknown	Unknown	Unknown
Palpitations	Unknown	Unknown	Unknown
Premature ventricular contractions	Unknown	Unknown	Unknown
Osteoarthritis of spine	Unknown	Unknown	Yes
Multiple drug allergies	Unknown	Unknown	Unknown

C10. Concomitant medical products (cont'd)

Clarithromycin	23Feb00	- Feb00
Paracetamol	UNK	
Guaiphenesin	UNK	
Famotidine	UNK	
Potassium salt	UNK	- Mar00
Salcatonin	UNK	

G8. Adverse event term(s) (cont'd)

Possible GI hemorrhage
Dehydration
Pitting edema
Generalized edema
Hypokalemia
Thrombocytopenia
Oliguria
Shortness of breath
Congestive heart failure
Ascites
Possible drug interaction

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Glaxo Wellcome

Approved by the FDA (11-2) on 3 NOV 93

Mfr report # A0120634A

UF/Ds: report #

FDA Use Only

A. Patient information

1. Patient identifier	2. Age at time of event: / or Date of birth	3. Sex	4. Weight (lb)
In confidence	80Y / UNK	☒ female ☐ male ☐ unknown	139.9

B. Adverse event or product problem

1 ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)

☐ death ☐ disability
☐ life-threatening ☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☒ hospitalization - initial or prolonged ☐ other

3. Date of event: 02May2000

4. Date of this report: 09Jun2000

5. Describe event or problem

DESK COPY

A physician reported that an 80 year old female received alosetron (Lotronex) tablets and after five weeks of therapy was discovered to have elevated SGOT, SGPT, and alkaline phosphatase levels. She was hospitalized with a diagnosis of hepatitis. Alosetron was discontinued and her liver enzymes normalized within three days. The reporting physician considered the events to be related to the use of alosetron.

6. Relevant tests/laboratory data, including dates

Diagnostic tests/Labs: Baseline liver enzyme levels were as follows: Jun95: SGOT 35 U/L; SGPT 18 U/L; 22Apr96: SGOT 31 U/L; SGPT 10 U/L; 12Jul99: SGOT 31 U/L. Liver enzymes on 05May00: SGOT 299 U/L; SGPT 210 U/L; alkaline phosphatase 155 U/L. CT scan on 04May00 normal with exception of possible mild dilation of intrahepatic ducts. No liver biopsy was performed. Serologies

continued on next page

7. Other relevant history, including preexisting medical conditions (eg, allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Race: White

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

#1 Lotronex Tablet (Alosetron hydrochloride)

#2

2. Dose / frequency / route used	3. Therapy dates
#1 1 mg / Twice per day / Oral	#1 28Mar00 - 02May00
#2	#2

4. Diagnosis for use (indication)

#1 Irritable bowel syndrome

#2

5. Event abated after use stopped or dose reduced

#1 ☒ yes ☐ no ☐ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)	7. Exp. date (if known)
#1 None	#1
#2	#2

8. Event reappeared after reintroduction

#1 ☐ yes ☐ no ☒ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)

Lansoprazole	UNK
Spironolactone	UNK
Nadolol	UNK
Frusemide	UNK

continued on next page

G. All manufacturers

1. Contact office - name/address

Glaxo Wellcome
North American Product Surveillance
PO Box 13398
Research Triangle Park
NC 27709

2. Phone number 1-888-825-5249 ext. 37070

3. Report source

☐ foreign ☐ study ☐ literature ☐ consumer ☒ health professional ☐ user facility ☒ company representative ☐ distributor ☐ other:

4. Date received by manufacturer: 01Jun2000

5. (A)NDA # 21-107 IND # PLA # pre-1938 ☐ yes OTC product ☐ yes

6. If IND, protocol #

7. Type of report

☐ 5-day ☒ 15-day ☐ 10-day ☐ periodic ☐ initial ☒ follow-up # 1

8. Adverse event term(s)

Hepatitis
Incr.aspart.aminotransf.
Incr.alanine aminotransf.
Elevated alk.phosphatase

9. Mfr. report number: A0120634A

E. Initial Reporter

1. Name, address & phone #

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA?
☒ yes ☐ no	Physician	☐ yes ☐ no ☒ unk

FDA Form 3500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

B6. Relevant tests/laboratory data (cont'd)
negative for hepatitis B and C.

B7. Other relevant history (cont'd)

Condition	Started	Ended	Continuing
Irritable bowel syndrome	Unknown	Unknown	Yes
Hypertension	Unknown	Unknown	Yes

C10. Concomitant medical products (cont'd)

Amlodipine	UNK	
Hyoscyamine sulphate	UNK	
Rofecoxib	UNK	- 11Apr00

REPORTS WITH DESCRIPTION OF ISCHEMIC COLITIS (SERIOUS AND NON-SERIOUS)

A0119468A

A0117893A

A0120828A

A0120834A

A0121411A

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Glaxo Wellcome

Mfr report # A0119468A

Un/Dist report #

FDA Use Only

A. Patient information

1. Patient identifier	2. Age at time of event: 50Y or Date of birth 02Jul1949	3. Sex: ☒ female ☐ male ☐ unknown	4. Weight (lb): UNK
In confidence			

B. Adverse event or product problem

1 ☒ Adverse event and/or ☐ Product problem

2. Outcome(s) attributed to adverse event (check all that apply)

☐ death ☐ disability
☐ life threatening ☐ congenital anomaly
☐ hospitalization - initial or prolonged ☐ required intervention to prevent permanent impairment/damage
☒ other: See text

3. Date of event: UNK

4. Date of this report: 09Jun2000

5. Describe event or problem

DESK COPY

A gastroenterologist reported that a 50 year old female with pre-existing constipation was prescribed alosetron (Lotronex) tablets by her primary care physician. After two to three weeks of therapy, she developed increased constipation, abdominal pain, and rectal bleeding. The patient discontinued the medication on her own. When she was seen by the reporting physician, she was afebrile. Colonoscopy was performed and biopsy confirmed ischemic colitis. The patient was not hospitalized.

6. Relevant tests/laboratory data, including dates

Tests: Colonoscopy 06Apr00 showed normal mucosa to left colon, extensive ulceration with induration suggestive of ischemic change; microscopic exam of biopsy tissue showed acute inflammatory exudate. There are two small fragments of mucosa; in one there is glandular hyperplastic change and the other is focally ulcerated with some homogenization of the lamina propria and a

continued on next page

7. Other relevant history, including preexisting medical conditions (eg, allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

History of progressive constipation over several months; experienced a dramatic increase in difficulty having a bowel movement in spite of taking laxatives, enemas, etc.; experienced some nausea, but no vomiting, no fever or chills; recurrent left lower quadrant abdominal pain which is at times intense and incapacitating; some episodes of abdominal distention; weight

continued on next page

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

#1 Lotronex Tablet (Alosetron hydrochloride)

#2

2. Dose / frequency / route used

#1 UNK / UNK / Oral

#2

3. Therapy dates

#1 UNK

#2

4. Diagnosis for use (indication)

#1 Irritable bowel syndrome

#2

5. Event abated after use stopped or dose reduced

#1 ☐ yes ☐ no ☐ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)

#1 None

#2

7. Exp date (if known)

#1

#2

8. Event reappeared after reintroduction

#1 ☐ yes ☐ no ☒ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)

Lotrel	UNK
Verapamil hydrochloride	UNK
Omeprazole	UNK
Pravastatin sodium	UNK

G. All manufacturers

1. Contact office - name/address

Glaxo Wellcome
North American Product Surveillance
PO Box 13398
Research Triangle Park
NC 27709

2. Phone number: 1-888-825-5249 ext. 37070

3. Report source

☐ foreign
☐ study
☐ literature
☐ consumer
☒ health professional
☐ user facility
☒ company representative
☐ distributor
☐ other: _____

4. Date received by manufacturer: 28Apr2000

5. (A)NDA # 21-107

IND # _____

PLA # _____

pre-1938 ☐ yes

OTC product ☐ yes

6. If IND, protocol #

7. Type of report

☐ 5-day ☒ 15-day
☐ 10-day ☐ periodic
☒ Initial ☐ follow-up # ____

8. Adverse event term(s)

Ischemic colitis
Exacerb.abdominal pain
Rectal hemorrhage
Exacerb:constipation

9. Mfr. report number: A0119468A

E. Initial Reporter

1. Name, address & phone #

2. Health professional? ☒ yes ☐ no

3. Occupation: Gastroenterol.

4. Initial reporter also sent report to FDA? ☐ yes ☐ no ☒ unk

FDA Form 3500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event

B6. Relevant tests/laboratory data (cont'd)
very few small capillary thrombi; pathologist interpreted changes as consistent with ischemic colitis. (Colonoscopy and biopsy reports attached.)

B7. Other relevant history (cont'd)
loss of ten pounds (food intake agravates symptoms); hospitalized two years earlier with abdominal pain and rectal bleeding and diagnosed with small bowel obstruction; heart problems (unspecified); numerous surgeries. (GI consultation note attached.)

B7. Other relevant history (cont'd)

Condition	Started	Ended	Continuing
Irritable bowel syndrome	Unknown	Unknown	Yes
Constipation	Unknown	Unknown	Yes
Abdominal pain	Unknown	Unknown	Yes
Small bowel obstruction	Unknown	Unknown	No
Llq pain	Unknown	Unknown	Yes
Rectal bleeding	Unknown	Unknown	Unknown
Abdominal distention	Unknown	Unknown	Unknown
Weight loss	Unknown	Unknown	Unknown
Heart problems	Unknown	Unknown	Unknown
Nausea	Unknown	Unknown	Unknown
Surgeries	Unknown	Unknown	No

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Glaxo Wellcome

Mfr report # A0117893A

UF/Dist report #

FDA Use Only

A. Patient information

1. Patient identifier	2. Age at time of event / Date of birth	3. Sex	4. Weight (lb)
In confidence	55Y / or — / Date of birth 30Jun1944	☐ female ☒ male ☐ unknown	176

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death
- ☐ life-threatening
- ☐ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☒ other See text

3. Date of event: 01Apr2000

4. Date of this report: 09Jun2000

5. Describe event or problem

DESK COPY

A gastroenterologist reported that a 55 year-old male (also a physician) received alosetron (Lotronex) tablets for approximately five days to treat diarrhea-predominant irritable bowel disease. The patient's irritable bowel symptoms were much improved during his first few days of treatment. On his fifth day of therapy, he felt constipated, so he omitted his evening dose. During that night, he developed severe cramping abdominal pain (much worse that any pain he had previously experienced) and bloody diarrhea. He did not have fever, nausea, vomiting, myalgias, or rebound tenderness. Symptoms improved without treatment, but he did not restart alosetron. The next day he took a Fleet's phosphosoda prep in preparation for a previously scheduled routine colonoscopy to be performed the following day. He first reported his symptoms to his physician at this time. The colonoscopy showed an area of

continued on next page

6. Relevant tests/laboratory data, including dates

Tests: All colonoscopies in previous years had been negative; last colonoscopy prior to these events was 17Oct94 and results were negative-the colon was normal throughout as was the distal 30-40 cm of the ileum; small bowel x-ray in 1994 also negative; computerized axial tomography of abdomen and right upper quadrant ultrasound in 1999 both negative; colonoscopy 03Apr00 showed the

continued on next page

7. Other relevant history, including preexisting medical conditions (eg. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

History: Irritable bowel disease since 1969 characterized by diarrhea, urgency, tenesmus, and nocturnal cramping, occasional hematochezia; postprandial bloating, nausea when abdominal cramping is severe; has severe flatulance which is often disabling; has been diagnosed with anal fissures; recent rectal bleeding which he attributed to his hemorrhoids; also has

continued on next page

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
- #1 Lotronex Tablet (Alosetron hydrochloride)
- #2

2. Dose / frequency / route used
- #1 1 mg / Twice per day / Oral
- #2

3. Therapy dates
- #1 28Mar00 - 01Apr00
- #2

4. Diagnosis for use (indication)
- #1 Irritable bowel syndrome
- #2

5. Event abated after use stopped or dose reduced
- #1 ☒ yes ☐ no ☐ doesn't apply
- #2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
- #1 None
- #2

7. Exp. date (if known)
- #1
- #2

8. Event reappeared after reintroduction
- #1 ☐ yes ☐ no ☒ doesn't apply
- #2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)

Simvastatin	UNK
Aspirin	UNK
Phospho-Soda Fleet	02Apr00 - 02Apr00

G. All manufacturers

1. Contact office - name/address

Glaxo Wellcome
North American Product Surveillance
PO Box 13398
Research Triangle Park
NC 27709

2. Phone number: 1-888-825-5249 ext. 37070

3. Report source
- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other.

4. Date received by manufacturer: 03May2000

5. (A)NDA # 21-107
- IND #
- PLA #
- pre-1938 ☐ yes
- OTC product ☐ yes

6. If IND, protocol #

7. Type of report
- ☐ 5-day ☒ 15-day
- ☐ 10-day ☐ periodic
- ☐ initial ☒ follow-up # 2

8. Adverse event term(s)

Ischemic colitis
Pseudomembranous colitis
Bloody diarrhea
Abdominal pain
Constipation

9. Mfr. report number: A0117893A

E. Initial Reporter

1. Name, address & phone #

2. Health professional? ☒ yes ☐ no

3. Occupation: Gastroentero.

4. Initial reporter also sent report to FDA? ☐ yes ☐ no ☒ unk

FDA Form 3500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event

B5. Describe event or problem (cont'd)
circumferential colitis in the proximal descending colon which looked like Crohn's disease or cancer. He was started on oral prednisone and mesalamine. By this time, symptoms had resolved and he was not hospitalized. Biopsy of the colon showed "changes in the left colon of a pseudomembranous colitis; the etiology of which may be ischemic or infectious". The reporting physician felt that "based on the location of the lesion and the differential diagnosis provided by the pathologist that ischemic colitis is a likely scenario." Treatment medications were discontinued when biopsy results were received. At the time of this report, the patient was doing well and had experienced no further episodes of severe abdominal pain or bloody diarrhea, but his normal irritable bowel symptoms were beginning to return. Repeat colonoscopy was planned. The gastroenterologist felt that the events were probably related to alosetron due to the temporal relationship.

B6. Relevant tests/laboratory data (cont'd)
colon and terminal ileum normal except a 10cm-wide area in the proximal descending colon where circumferential colitis was noted. This area was edematous, exophytic, friable and looked like active inflammatory bowel disease or cancer; stool testing 03Apr00 for ova and parasites, C. difficile toxin, culture and sensitivity, and white blood cells all were negative; duplex doppler ultrasonography of celiac artery and superior mesenteric artery to rule out thrombosis was negative; inflammatory disease serologic profile was negative. Biopsy results 03Apr00 are as follows: Cecum: mild chronic inflammation with one poorly formed fibrotic granuloma-like focus; Terminal ileum: no significant pathological change; Colon, hepatic flexure: mild chronic inflammation; Transverse colon: focal lymphoid aggregates and patchy glandular dropout; Descending colon: extensive mucoinflammatory debris with surface erosion consistent with pseudomembrane formation; Sigmoid colon: patchy fibrosis in the lamina propria; Rectum: edema, chronic inflammation, and macrophages in the lumina propria. Note from biopsy report: "These changes are not diagnostic for inflammatory bowel disease. The changes in the left colon are of a pseudomembranous colitis, the etiology of which may be ischemic or infectious." Stain for E. coli was not performed. (Lab reports attached.)

B7. Other relevant history (cont'd)
hypertriglyceridemia, hay fever and many other allergies, tuberculosis 20 years ago, and family history of colon cancer; both mother and maternal grandmother had colon cancer in their 80's. No previous episodes of bloody diarrhea, no other bowel problems, no surgical history, no cardiac history; no history of deep vein thrombosis; patient is not a diabetic; he does not have lupus or sickle cell; he is not a smoker, rarely drinks alcohol as this aggravates his IBS, no recent antibiotic use; no use of cocaine or amphetamines, no use of coumadin, heparin, or medication for migraines. History of recent travel to a developing country was unknown. "No risk factors for ischemic colitis" according to the reporter.

B7. Other relevant history (cont'd)

Condition	Started	Ended	Continuing
Irritable bowel disease	1969	Unknown	Yes
Diarrhea	1969	Unknown	Yes
Bowel urgency	1969	Unknown	Yes
Abdominal pain	1969	Unknown	Yes
Tuberculosis	1980	Unknown	No
Hypertriglyceridemia	Unknown	Unknown	Yes
Family history of cancer	Unknown	Unknown	Unknown
Nausea	Unknown	Unknown	Unknown
Hematochezia	Unknown	Unknown	Unknown
Postprandial bloating	Unknown	Unknown	Unknown
Fissure of anus	Unknown	Unknown	Unknown
Tenesmus	Unknown	Unknown	Unknown
Bleeding hemorrhoids	Unknown	Unknown	Unknown
Flatulence	Unknown	Unknown	Unknown
Hay fever	Unknown	Unknown	Unknown
Allergies	Unknown	Unknown	Unknown

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Glaxo Wellcome

(Page 1 of 2)

Mfr report # A0120828A

FDA Use Only

A. Patient information

1. Patient identifier	2. Age at time of event / or Date of birth	3. Sex	4. Weight (lb)
In confidence	53Y / 14Mar1947	☒ female ☐ male ☐ unknown	UNK

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)

☐ death ☐ disability ☐ congenital anomaly ☐ life threatening ☐ required intervention to prevent permanent impairment/damage ☒ hospitalization - initial or prolonged ☐ other

3. Date of event	4. Date of this report
11May2000	09Jun2000

5. Describe event or problem

DESK COPY

A physician reported that a 53 year-old female with a history of diverticular disease and diarrhea predominant irritable bowel syndrome was seen in the office and given a prescription for alosetron (Lotronex) and ciprofloxacin. Two days later, she was hospitalized with rectal bleeding. She did not have fever, nausea, vomiting, abdominal pain or pre-existing constipation at the time. CT scan upon admission showed thickening of the splenic flexure suggestive of colitis or ischemic colitis. Colonoscopy and biopsy the next day confirmed ischemic colitis. Alosetron was discontinued. She remained hospitalized for 2-3 days. The patient was doing well at home at the time of this report. The reporter felt the relationship of the events to alosetron was possible.

6. Relevant tests/laboratory data, including dates

Tests: Flexible sigmoidoscopy one and one half weeks prior to starting alosetron showed diverticular disease; CT scan upon admission to hospital showed thickening of the splenic flexure suggestive of colitis or ischemic colitis; colonoscopy one day later confirmed ischemic colitis.

7. Other relevant history, including preexisting medical conditions (eg allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

History of diverticular disease and diarrhea predominant irritable bowel syndrome with abdominal cramping; hypothyroidism; otherwise healthy; no history of hemorrhoids, no other bowel problems, no diabetes, heart disease, or vascular disease. Had not used Coumadin, heparin, NSAIDs, or hormone replacement therapy. Hycosamine was not effective for IBS

continued on next page

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

#1 Lotronex Tablet (Alosetron hydrochloride)

#2

2. Dose / frequency / route used	3. Therapy dates
#1 1 mg / Twice per day / Unknown	#1 09May00 - 11May00
#2	#2

4. Diagnosis for use (indication)	5. Event abated after use stopped or dose reduced
#1 Irritable bowel syndrome	#1 ☒ yes ☐ no ☐ doesn't apply
#2	#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)	7. Exp date (if known)	8. Event reappeared after reintroduction
#1 None	#1	#1 ☐ yes ☐ no ☒ doesn't apply
#2	#2	#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)

Ciprofloxacin HCl 09May00 - UNK

G. All manufacturers

1. Contact office - name/address

Glaxo Wellcome
North American Product Surveillance
PO Box 13398
Research Triangle Park
NC 27709

2. Phone number 1-888-825-5249 ext. 37070

3. Report source
☐ foreign ☐ study ☐ literature ☐ consumer ☒ health professional ☐ user facility ☒ company representative ☐ distributor ☐ other:

4. Date received by manufacturer 02Jun2000

5. (A)NDA # 21-107 IND # PLA # pre-1938 ☐ yes OTC product ☐ yes

6. If IND, protocol #

7. Type of report
☐ 5-day ☒ 15-day ☐ 10-day ☐ periodic ☐ initial ☒ follow-up # 1

8. Adverse event term(s)
Ischemic colitis
Rectal hemorrhage

9. Mfr. report number
A0120828A

E. Initial Reporter

1. Name, address & phone #

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA?
☒ yes ☐ no	Physician	☐ yes ☐ no ☒ unk

FDA Form 3500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

B7. Other relevant history (cont'd)
symptoms and was discontinued prior to starting alosetron.

B7. Other relevant history (cont'd)

Condition	Started	Ended	Continuing
Irritable bowel disease	Unknown	Unknown	Yes
Diverticular disease	Unknown	Unknown	Yes
Hypothyroidism	Unknown	Unknown	Yes
Abdominal cramping	Unknown	Unknown	Yes

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Glaxo Wellcome

(Page 1 of 2)

Mfr report # A0120834A

FDA Use Only

A. Patient information

1 Patient identifier	2. Age at time of event: 46Y or Date of birth 21Jan1954	3. Sex ☒ female ☐ male ☐ unknown	4. Weight (lb) UNK
In confidence			

B. Adverse event or product problem

1 ☒ Adverse event and/or ☐ Product problem

2 Outcomes attributed to adverse event (check all that apply)

☐ death ☐ disability
☐ life-threatening ☐ congenital anomaly
☒ hospitalization - initial or prolonged ☐ required intervention to prevent permanent impairment/damage
☐ other

3 Date of event: 12May2000

4. Date of this report: 09Jun2000

5 Describe event or problem

DESK COPY

A physician reported that a 46 year-old female received alosetron (Lotronex) tablets to treat diarrhea predominant irritable bowel syndrome. After a few weeks, she developed constipation and was started on psyllium and casanthranol plus docusate. She was doing well and had significant improvement in her irritable bowel symptoms, but after approximately six and one half weeks of therapy, she developed severe crampy lower abdominal pain and rectal bleeding. She did not have fever, chills, nausea, vomiting, or lightheadedness. She was seen in the office and complained of severe constipation and mucous and blood in her stools. Hypertension was also noted. She was hospitalized and colonoscopy and biopsy confirmed ischemic colitis. Alosetron was discontinued. She was discharged home the next day and the events resolved without sequelae. The physician attributed the events to alosetron.

6 Relevant tests/laboratory data, including dates

Tests: Upper endoscopy 1999 showed gastritis, gastric erosion, hiatal hernia, esophageal reflux with globus sensation; abdominal ultrasound 29Mar00 was unremarkable; CBC 12May00 normal; hematocrit 39%; normal MCV, PT, and INR. Colonoscopy 13May00 showed a 10cm segment of the descending colon with significant mucosal erythema, ulcerations, and submucosal edema.

continued on next page

7 Other relevant history, including preexisting medical conditions (eg. allergies, race, pregnancy smoking and alcohol use, hepatic/renal dysfunction, etc.)

History of irritable bowel syndrome with intermittent diarrhea, abdominal cramping and pain for one year; significant GERD with gastritis, gastric erosion, hiatal hernia; no family history of colon cancer, polyps, and no inflammatory bowel disease; hysterectomy 1981; no use of alcohol or tobacco.

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 Lotronex Tablet (Alosetron hydrochloride)
#2

2. Dose / frequency / route used	3. Therapy dates
#1 1 mg / Twice per day / Oral	#1 27Mar00 - 12May00
#2	#2

4. Diagnosis for use (indication)
#1 Irritable bowel syndrome
#2

5 Event abated after use stopped or dose reduced
#1 ☒ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)	7. Exp date (if known)
#1 None	#1
#2	#2

8 Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)

Conjugated estrogens	UNK
Centrum	UNK
Calcium carbonate	UNK
Psyllium husk	UNK

continued on next page

G. All manufacturers

1. Contact office - name/address

Glaxo Wellcome
North American Product Surveillance
PO Box 13398
Research Triangle Park
NC 27709

2. Phone number: 1-888-825-5249 ext. 37070

3 Report source
☐ foreign ☐ study ☐ literature ☐ consumer ☒ health professional ☐ user facility ☐ company representative ☐ distributor ☐ other:

4. Date received by manufacturer: 22May2000

5. (A)NDA # 21-107
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #

7. Type of report
☐ 5-day ☒ 15-day ☐ 10-day ☐ period c ☒ initial ☐ follow-up # ____

8. Adverse event term(s)
Ischemic colitis
Rectal hemorrhage
Abdominal pain
Constipation
Mucus in stool
Hypertension

9 Mfr. report number: A0120834A

E. Initial Reporter

1 Name, address & phone #

2 Health professional?	3. Occupation	4 Initial reporter also sent report to FDA?
☒ yes ☐ no	Gastroenterolo	☐ yes ☐ no ☒ unk

FDA Form 3500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event

B6. Relevant tests/laboratory data (cont'd)

The remaining colon mucosa remained normal with no evidence of polyps, diverticular obstructing lesions. On retroflex views in the rectum, there was no evidence of internal hemorrhoids. Biopsy 13May00 showed colonic mucosa with acute inflammation, superficial degeneration and laminar hemorrhage consistent with ischemic colitis; a fibrin vascular thrombus also seen, felt to be consistent with ischemic colitis. Comment from the biopsy: "Also in the differential, though less likely, would be a very early pseudomembraneous colitis, so clinical correlation is suggested." Colonoscopy and biopsy reports attached.

B7. Other relevant history (cont'd)

Condition	Started	Ended	Continuing
Hysterectomy	1981	Unknown	No
IBS	Unknown	Unknown	Yes
Abdominal cramping	Unknown	Unknown	Yes
Intermittent diarrhea	Unknown	Unknown	Yes
GERD	Unknown	Unknown	Yes
Gastritis	Unknown	Unknown	Yes
Gastric erosion	Unknown	Unknown	Yes
Hiatal hernia	Unknown	Unknown	Yes

C10. Concomitant medical products (cont'd)

Omeprazole	UNK
Peri-colace	UNK

MEDWATCH

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Glaxo Wellcome

(Page 1 of 2)

Mfr report # A0121411A

Uf/Dist report #

FDA Use Only

A. Patient information

1 Patient identifier	2. Age at time of event: 51Y or Date of birth UNK	3. Sex ☒ female ☐ male ☐ unknown	4 Weight (lb) UNK
In confidence			

B. Adverse event or product problem

1 ☒ Adverse event and/or ☐ Product problem

2 Outcomes attributed to adverse event (check all that apply)

☐ death ☐ disability
☐ life-threatening ☐ congenital anomaly
☒ hospitalization - initial or prolonged ☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event: 09Apr2000

4. Date of this report: 09Jun2000

5. Describe event or problem

DESK COPY

A physician reported that a 51 year old female with a history of depression, diverticulosis, and migraine headaches received alosetron (Lotronex) tablets for treatment of recently diagnosed irritable bowel syndrome. After two weeks of therapy, she presented with bloody diarrhea and abdominal pain. She was hospitalized. Her maximum temperature reached 100.8 degrees F. Alosetron was discontinued at time of admission. Two days after admission, colonoscopy was performed which revealed segmental colitis that was circumferential in areas from 50 cm to the splenic flexure. Photographs of affected area were taken. Stool microbiology and Clostridium difficile studies were not done. Biopsy of three areas of colon showed fibrin with enmeshed neutrophils. Diagnosis was "Descending colon: features consistent with ischemic colitis". On the day following her colonoscopy, the patient was discharged in

continued on next page

6 Relevant tests/laboratory data, including dates

Tests/Labs: 11Apr00: Colonoscopy revealed segmental colitis that was circumferential in areas from 50 cm to the splenic flexure. Photographs of affected areas were taken. Biopsy of colon revealed the following: Gross: Received in Hollandes labeled "Descending colon" are three irregular mucosal segments measuring 0.3 -0.4 cm. in greatest dimension. All in/1. Microscopic:

continued on next page

7. Other relevant history, including preexisting medical conditions (eg allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

History of probable bulimia with intermittent weight loss; ruptured ovarian cyst; depression; migraine headaches (not currently on treatment); total hysterectomy for contol of uterine cancer several years prior to reporting. No current evidence of cancer. Physician did not know whether the cancer was treated with radiation or chemotherapy. Patient described by

continued on next page

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 Lotronex Tablet (Alosetron hydrochloride)
#2

2. Dose / frequency / route used	3. Therapy dates
#1 1 mg / Twice per day / Oral	#1 27Mar00 - 09Apr00
#2	#2

4. Diagnosis for use (indication)	5 Event abated after use stopped or dose reduced
#1 Irritable bowel syndrome	#1 ☒ yes ☐ no ☐ doesn't apply
#2	#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)	7 Exp. date (if known)	8 Event reappeared after reintroduction
#1 None	#1	#1 ☐ yes ☐ no ☒ doesn't apply
#2	#2	#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)

Venlafaxine hydrochloride UNK
Conjugated estrogens UNK

G. All manufacturers

1. Contact office - name/address

Glaxo Wellcome
North American Product Surveillance
PO Box 13398
Research Triangle Park
NC 27709

2. Phone number 1-888-825-5249 ext. 37070

3 Report source
☐ foreign ☐ study ☐ literature ☐ consumer ☒ health professional ☐ user facility ☐ company representative ☐ distributor ☐ other:

4. Date received by manufacturer 31May2000

5. (A)NDA # 21-107
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #

7. Type of report
☐ 5-day ☒ 15-day ☐ 10-day ☐ periodic ☒ initial ☐ follow-up # ____

8. Adverse event term(s)
Ischemic colitis
Bloody diarrhea
Abdominal pain
Fever

9 Mfr. report number A0121411A

E. Initial Reporter

1. Name, address & phone #

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA?
☒ yes ☐ no	Physician	☐ yes ☐ no ☒ unk

FDA Form 3500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

B5. Describe event or problem (cont'd)
good condition. The reporting physician considered the events to be related to the use of alosetron.

B6. Relevant tests/laboratory data (cont'd)
Sections are of fragments of colonic mucosa containing straight glands which reach down to the level of muscularis mucosae. In several tiny areas, the surface epithelium is absent. Fibrin with a few enmeshed neutrophils is present on the luminal surface. Lamina propria exhibits focal superficial interstitial red blood cells and focal minimal superficial infiltration by segmented neutrophils and is otherwise normocellular. No atypia or tumor cells are seen. Diagnosis: Descending colon, biopsies: Features consistent with ischemic colitis. See attached.

B7. Other relevant history (cont'd)
physician as having a histrionic-type personality. Patient returned from a trip to Mexico in Feb2000 with a diarrheal like illness manifested by intermittent diarrhea and significan left-sided abdominal pain. She was treated emprically with ciprofloxacin with some response; however, the diarrhea and pain persisted. On 22Mar00, she presented to a walk-in clinic with severe pain. She was thought to have diverticulitis. Her exam was described as unreliable as she was experiencing significant psychosocial stressors. She was hospitalized on that same day for further evaluation. Diagnostic testing including CT scan was unremarkable. Colonoscopy (25Mar00) was normal. She continued to experience diarrhea and was dischared on 27Mar00 with a diagnosis of irritable bowel syndrome. Therapy with alosetron was commenced. At time of commencement of treatment with alosetron, the patient was not constipated.

B7. Other relevant history (cont'd)

Condition	Started	Ended	Continuing
Irritable bowel syndrome	Unknown	Unknown	Yes
Depression	Unknown	Unknown	Yes
Ruptured ovarian cyst	Unknown	Unknown	No
Migraine	Unknown	Unknown	Unknown
Total hysterectomy	Unknown	Unknown	Unknown
Uterine cancer	Unknown	Unknown	Unknown
Diverticulosis	Unknown	Unknown	Unknown
Alcohol abuse	Unknown	Unknown	No
Abdominal pain	Unknown	Unknown	Unknown

CONSTIPATION (SERIOUS)
A0117392A
A0120067A
A0118883A
A0117431A

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Glaxo Wellcome

Approved by the FDA (HF-2) on 3 Nov 93

Mfr report # A0117392A

UF/Dist report #

FDA Use Only

A. Patient information

1. Patient identifier	2. Age at time of event: / or Date of birth	3. Sex	4. Weight (lb)
– In confidence	51Y / 02Feb1949	☒ female ☐ male ☐ unknown	144.1

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)

☐ death _____ ☐ disability

☐ life-threatening ☐ congenital anomaly

☐ hospitalization - initial or prolonged ☐ required intervention to prevent permanent impairment/damage

☐ other: _____

3. Date of event	4. Date of this report:
02Apr2000	09Jun2000

5. Describe event or problem

DESK COPY

A physician reported that a 51 year old female received alosetron (Lotronex) tablets to treat irritable bowel syndrome and experienced no bowel movements for four days. She presented to the emergency room with abdominal pain. Alosetron was discontinued. She was admitted to the hospital and an evaluation indicated a small bowel obstruction with fecal impaction. She received supportive care including enemas and the obstruction resolved. She was discharged home after a 23 hour hospital stay. Causality was not reported.

6 Relevant tests/laboratory data, including dates

UNK

7 Other relevant history, including preexisting medical conditions (eg. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

History of irritable bowel syndrome since 1997; abdominal pains, gastritis, GERD, and dyspepsia.

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

#1 Lotronex Tablet (Alosetron hydrochloride)

#2

2. Dose / frequency / route used	3. Therapy dates
#1 1 mg / Twice per day / Oral	#1 Mar00 - 02Apr00
#2	#2

4. Diagnosis for use (indication)

#1 Irritable bowel syndrome

#2

5. Event abated after use stopped or dose reduced

#1 ☒ yes ☐ no ☐ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)	7. Exp. date (if known)
#1 None	#1
#2	#2

8 Event reappeared after reintroduction

#1 ☐ yes ☐ no ☒ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)

Conjugated estrogens 98 - UNK

G. All manufacturers

1 Contact office - name/address

Glaxo Wellcome
North American Product Surveillance
PO Box 13398
Research Triangle Park
NC 27709

2. Phone number 1-888-825-5249 ext. 37070

3. Report source

☐ foreign ☐ study ☐ literature ☐ consumer ☒ health professional ☐ user facility ☒ company representative ☐ distributor ☐ other: _____

4. Date received by manufacturer	5.
05May2000	(A)NDA # 21-107
6. If IND, protocol #	IND # _____
	PLA # _____
7 Type of report	pre-1938 ☐ yes
☐ 5-day ☒ 15-day	OTC product ☐ yes
☐ 10-day ☐ periodic	
☐ Initial ☒ follow-up # 1	

8. Adverse event term(s)

Obstruction:small bowel
Fecal impaction
Abdominal pain
Inability to defecate

9. Mfr. report number A0117392A

E. Initial Reporter

1. Name, address & phone #

2 Health professional?	3. Occupation	4. Initial reporter also sent report to FDA?
☒ yes ☐ no	Physician	☐ yes ☐ no ☒ unk

FDA Form 3500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

B7. Other relevant history (cont'd)

Condition	Started	Ended	Continuing
Irritable bowel syndrome	1997	Unknown	Yes
Abdominal pain	Unknown	Unknown	Unknown
Gastritis	Unknown	Unknown	Unknown
GERD	Unknown	Unknown	Unknown
Dyspepsia	Unknown	Unknown	Unknown

MEDWATCH
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Glaxo Wellcome

Approved by the FDA (HF-2) on 3 Nov 93

Mfr report # A0120067A

User/Dist report #

FDA Use Only

A. Patient information

1. Patient identifier	2. Age at time of event: / or Date of birth	3. Sex	4. Weight (lb)
– In confidence	72Y / 06Jul1927	☒ female ☐ male ☐ unknown	133.1

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death
- ☒ life-threatening
- ☒ hospitalization - initial or prolonged
- ☒ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other

3. Date of event: 06Apr2000

4. Date of this report: 09Jun2000

5. Describe event or problem

DESK COPY

A physician reported that a 72 year-old female received alosetron (Lotronex) tablets to treat irritable bowel syndrome. After approximately two and one half weeks, she experienced sudden severe abdominal pain and was seen in the emergency room. CT scan showed air fluid levels and a mass outside the bowel. She was taken to surgery for repair of a ruptured sigmoid colon with abscess. She was treated with antibiotics and remained hospitalized for approximately two weeks. At the time of this report, she had been discharged home, but continued on antibiotics. She was still in pain and had a low grade fever, leukocytosis, and increased sedimentation rate. A follow-up CT scan showed improvement. The reporter was unsure of the relationship of the events to alosetron, but felt the events were life-threatening and disabling.

6. Relevant tests/laboratory data, including dates

Tests: CT scan in the emergency room showed air fluid levels and a mass outside the bowel; surgical findings were perforated sigmoid colon and fecal material in the peritoneum; white blood cell count on admission was greater than 20,000, decreased to 13,000 at the time of this report.

7. Other relevant history, including preexisting medical conditions (eg, allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

History of irritable bowel disease; alternating constipation and diarrhea; pain predominant; used narcotics approximately three times per week; depression; no history of heart disease, diabetes, or other bowel problems.

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
- #1 Lotronex Tablet (Alosetron hydrochloride)
- #2

2. Dose / frequency / route used
- #1 1 mg / Twice per day / Oral
- #2

3. Therapy dates
- #1 17Mar00 - 06Apr00
- #2

4. Diagnosis for use (indication)
- #1 Irritable bowel syndrome
- #2

5. Event abated after use stopped or dose reduced
- #1 ☒ yes ☐ no ☐ doesn't apply
- #2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
- #1 None
- #2

7. Exp. date (if known)
- #1
- #2

8. Event reappeared after reintroduction
- #1 ☐ yes ☐ no ☒ doesn't apply
- #2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)

Citalopram hydrobromide	UNK
Hydrocodone	UNK

G. All manufacturers

1. Contact office - name/address

Glaxo Wellcome
North American Product Surveillance
PO Box 13398
Research Triangle Park
NC 27709

2. Phone number: 1-888-825-5249 ext. 37070

3. Report source
- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☒ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer: 08May2000

5. (A)NDA # 21-107
- IND #
- PLA #
- pre-1938 ☐ yes
- OTC product ☐ yes

6. If IND, protocol #

7. Type of report
- ☐ 5-day ☒ 15-day
- ☐ 10-day ☐ periodic
- ☒ Initial ☐ follow-up #

8. Adverse event term(s)

Perforation of colon
Abdominal pain
Colonic abscess
Fever
Leukocytosis
Increased ESR

9. Mfr. report number: A0120067A

E. Initial Reporter

1. Name, address & phone #

2. Health professional? ☒ yes ☐ no

3. Occupation: Int.Medicine

4. Initial reporter also sent report to FDA? ☐ yes ☐ no ☒ unk

FDA Form 3500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event

B7. Other relevant history (cont'd)

Condition	Started	Ended	Continuing
IBS	Unknown	Unknown	Yes
Constipation	Unknown	Unknown	Unknown
Diarrhea	Unknown	Unknown	Unknown
Abdominal pain	Unknown	Unknown	Unknown

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Glaxo Wellcome

Approved by the FDA (HF-2) on 3 Nov 93

Mfr report # A0118883A

User/Dist report #

FDA Use Only

A. Patient information

1. Patient identifier	2. Age at time of event	3. Sex	4. Weight (lb)
--	68Y	☒ female ☐ male ☐ unknown	UNK
In confidence	or Date of birth 24Jul1931		

B. Adverse event or product problem

1 ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)

- ☐ death
- ☐ life-threatening
- ☒ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☒ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event	4. Date of this report
18Mar2000	09Jun2000

5. Describe event or problem

DESK COPY

A physician reported that a 68 year old female received alosetron (Lotronex) tablets and after approximately two days of therapy (five tablets total) developed constipation. Alosetron was discontinued. She presented to her physician (20Mar00) with her complaint of constipation of several days duration. Physical examination revealed abdominal tenderness and abdominal distention. Acute abdominal series was performed and showed nonspecific findings. Air was seen in the right colon. No air was present in the small intestine. CT scan was suggestive of diverticulitis as no abscess or obstruction was noted. The patient was admitted for management and treatment with antibiotics and clear liquid diet. She was discharged on 24Mar00 doing well but she remained on clear liquids. No bowel movements were noted but patient was comfortable. Two weeks later, she returned to her physician on a scheduled follow-up

continued on next page

6. Relevant tests/laboratory data, including dates

Tests/Labs: 17May00: 'A': Biopsy of right colon polyp revealed tubulovillous adenoma. 'B': Biopsy of right colon revealed colonic mucosa with no significant pathologic abnormalities. 'C': Biopsy of 25 cm distal loop of double barrel colostomy revealed benign colonic mucosa with mild chronic inflammation of lamina propria and focal superficial erosion with associated acute

continued on next page

7. Other relevant history, including preexisting medical conditions (eg allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

History of irritable bowel syndrome (IBS) since the 1960's. Patient had IBS which manifest itself as intractable diarrhea resulting in numerous accidents in public places. As a result of this, patient had chronic depression. Recent sinus infection requiring treatment with antibiotics. Patient subsequently had worsening diarrhea which resulted in two to three accidents.

continued on next page

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

#1 Lotronex Tablet (Alosetron hydrochloride)

#2

2. Dose / frequency / route used	3. Therapy dates
#1 1 mg / Twice per day / Oral	#1 16Mar00 - 18Mar00
#2	#2

4. Diagnosis for use (indication)

#1 Irritable bowel syndrome

#2

5. Event abated after use stopped or dose reduced

#1 ☐ yes ☒ no ☐ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)	7. Exp. date (if known)
#1 None	#1
#2	#2

8. Event reappeared after reintroduction

#1 ☐ yes ☐ no ☒ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)

Darvocet-N	Mar00 - UNK
Doxazosin mesylate	UNK
Semisodium valproate	UNK
Cetirizine hydrochloride	UNK

continued on next page

G. All manufacturers

1. Contact office - name/address

Glaxo Wellcome
North American Product Surveillance
PO Box 13398
Research Triangle Park
NC 27709

2. Phone number 1-888-825-5249 ext. 37070

3. Report source

- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☒ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer: 01Jun2000

5. (A)NDA # 21-107

IND #

PLA #

pre-1938 ☐ yes

OTC product ☐ yes

6. If IND, protocol #

7. Type of report

☐ 5-day ☒ 15-day

☐ 10-day ☐ periodic

☐ initial ☒ follow-up # 1

8. Adverse event term(s)

Chronic constipation
Constipation
Colitis
Colostomy
Abdominal tenderness

continued on next page

9. Mfr. report number: A0118883A

E. Initial Reporter

1. Name, address & phone #

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA?
☒ yes ☐ no	Physician	☐ yes ☐ no ☒ unk

FDA Form 3500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event

B5. Describe event or problem (cont'd)
visit._ She complained of abdominal discomfort, abdominal distention and lack of bowel movements. She had only been passing mucous. Physical examination revealed abdominal tenderness. She was readmitted with suspected sigmoid diverticulitis. X-ray revealed residual contrast dye in her colon from her prior CT scan. Colon was noted to be full of stool. No obstruction was seen. She was given mineral oil enemas. The next day she had additional enemas and a gastrograph was performed. The following day the patient felt sick. The surgeon on the case felt that she might have an ischemic bowel so a laparoscopy was performed. No ischemia was found. No abscess, phlegmon, or diverticulitis was noted. A temporary transverse loop colostomy was performed. Over the ensuing four days, the patient passed stool, decompressed, and was discharged.
Subsequent information revealed that the patient had polyps in her right colon and splenic flexure. Biopsy of those polyps diagnosed tubulovillous adenoma and tubular adenoma, respectively. Biopsy of right colon revealed colonic mucosa with no significant pathologic abnormalities. Biopsy of 25 cm distal loop of double barrel colostomy revealed benign colonic mucosa with mild chronic inflammation of lamina propria and focal superficial erosion with associated acute inflammation. The splenic flexure was biopsied and revealed active colitis characterized by mild to moderate acute and chronic inflammation of the lamina propria, focal cryptitis, crypt abscesses, and crypt architectural distortion. No dysplastic changes identified. Rectal mucosa showed minimal chronic inflammation of the lamina propria and increased superficial muciphages. Biopsy of 25 cm from rectum showed mucosa with mild chronic inflammation of the lamina propria, focal mild superficial acute inflammation within the lamina propria, and a single associated crypt abscess. The inflammatory changes seen in the biopsy were not specific as to etiology. The reporting physician stated "Patient developed obstipation requiring surgery with diverting colostomy. Subsequent colonoscopy through double barreled colostomy revealed sigmoid stricture - less than 8 mm with left side colitis. Biopsy: Nonspecific for etiology."

B6. Relevant tests/laboratory data (cont'd)
inflammation. 'D': Biopsy of splenic flexure polyp revealed tubular adenoma. 'E': Biopsy of splenic flexure revealed active colitis characterized by mild to moderate acute and chronic inflammation of the lamina propria, focal cryptitis, crypt abscesses, and crypt architectural distortion. No dysplastic changes identified, see comment. 'F': Biopsy of rectum revealed rectal mucosa with minimal chronic inflammation of the lamina propria and increased superficial muciphages, see comment. 'G': Biopsy of 25 cm section from rectum revealed rectal mucosa with mild chronic inflammation of the lamina propria, focal mild superficial acute inflammation within the lamina propria, and a single associated crypt abscess, see comment.
"Comment: The inflammatory changes identifed in specimen 'E' through 'G' are not specific as to etiology. Clinically and endoscopic correlation is suggested." See attached.

B7. Other relevant history (cont'd)
At this point, the patient was placed on therapy with alosetron.

B7. Other relevant history (cont'd)

Condition	Started	Ended	Continuing
Diverticulosis	Unknown	Unknown	Yes
Irritable bowel syndrome	Unknown	Unknown	Yes
Sinus infection	Unknown	Unknown	No

C10. Concomitant medical products (cont'd)

Frusemide	UNK
Temazepam	UNK

G8. Adverse event term(s) (cont'd)
Abdominal pain
Abdominal distention
Abdominal discomfort
Sickness
Adenoma

continued on next page

Approved by the FDA on 3Nov93

Mfr report # A0118883A

UF/Dist report #

FDA Use Only

G8. Adverse event term(s) (cont'd)

Proctitis
Polyp(s) of colon
Fecal impaction

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Glaxo Wellcome

(Page 1 of 2)

Approved by the FDA (HF-2) on 3 Nov 93

Mfr report # A0117431A

UF/Dist report #

FDA Use Only

A. Patient information

1. Patient identifier	2. Age at time of event	3. Sex	4. Weight (lb)
--	48Y	☒ female ☐ male ☐ unknown	192.9
In confidence	or Date of birth 31Aug1951		

B. Adverse event or product problem

1 ☒ Adverse event and/or ☐ Product problem

2 Outcomes attributed to adverse event (check all that apply)

☐ death ☐ disability
☐ life-threatening ☐ congenital anomaly
☐ hospitalization - initial or prolonged ☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event: 31Mar2000

4. Date of this report: 09Jun2000

5. Describe event or problem

DESK COPY

A physician reported that a 48 year-old female with a history of idiopathic constipation received alosetron (Lotronex) tablets and after seven to ten days of use developed constipation of five days duration. The constipation was unresponsive to outpatient treatment. The patient was hospitalized with impaction and obstipation resulting in bowel obstruction. Alosetron was discontinued. Colonoscopy revealed a 1 to 1.5 cm area of ulceration in her distal transverse colon, consistent in appearance with constipation induced ulcer, i.e. stercoral ulcer. No other abnormalities were noted. Biopsy of the lesion revealed focal ischemic ulceration. The reporting gastroenterologist stated that the lesion was not colitis but was ulceration related to pressure from the patient's constipation. He stated that the patient did not have a fever, leucocytosis or rectal bleeding. The patient was discharged from the hospital and

continued on next page

6. Relevant tests/laboratory data, including dates

Labs/Tests: Colonoscopy 31Mar00 showed normal ascending and proximal transverse colon; in the distal transverse colon, 1 to 1.5 cm ischemic ulceration was noted, consistent in appearance with constipation induced ulcer, i.e. stercoral ulcer. No other abnormalities were noted in the descending or rectosigmoid area. Retroflexed views of the rectum were

continued on next page

7 Other relevant history, including preexisting medical conditions (eg, allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

History of irritable bowel syndrome since 05Oct99; idiopathic constipation. Patient's treatment regimen consisted of antispasmodics which were discontinued upon initiation of therapy with alosetron.

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

#1 Lotronex Tablet (Alosetron hydrochloride)

#2

2. Dose / frequency / route used	3. Therapy dates
#1 1 mg / Twice per day / Oral	#1 14Mar00 - 31Mar00
#2	#2

4. Diagnosis for use (indication)

#1 Irritable bowel syndrome

#2

5. Event abated after use stopped or dose reduced

#1 ☒ yes ☐ no ☐ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

6 Lot # (if known)	7. Exp. date (if known)
#1 None	#1
#2	#2

8 Event reappeared after reintroduction

#1 ☐ yes ☐ no ☒ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)

Hyoscyamine sulphate 02Nov99 - UNK

G. All manufacturers

1. Contact office - name/address

Glaxo Wellcome
North American Product Surveillance
PO Box 13398
Research Triangle Park
NC 27709

2. Phone number 1-888-825-5249 ext. 37070

3. Report source

☐ foreign ☐ study ☐ literature ☐ consumer ☒ health professional ☐ user facility ☒ company representative ☐ distributor ☐ other:

4. Date received by manufacturer: 10May2000

5. (A)NDA # 21-107 IND # PLA #

pre-1938 ☐ yes

OTC product ☐ yes

6. If IND, protocol #

7. Type of report

☐ 5-day ☒ 15-day ☐ 10-day ☐ periodic ☐ initial ☒ follow-up # 2

8 Adverse event term(s)

Ischemic colonic ulcer
Intestinal obstruction
Constipation
Fecal impaction
Chronic constipation

9. Mfr. report number: A0117431A

E. Initial Reporter

1. Name, address & phone #

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA?
☒ yes ☐ no	Gastroenterol.	☐ yes ☐ no ☒ unk

FDA Form 3500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

B5. Describe event or problem (cont'd)
placed on bulking agents.

B6. Relevant tests/laboratory data (cont'd)
unremarkable. Biopsy of the transverse colon ulcer showed focal ischemic ulceration. Routine urinalysis negative upon admission 29Mar00, except pH of greater than 9.0; WBC 12.1; potassium 5.8; AST 74; total billirubin 1.8; direct billirubin 1.4. (Lab reports and test results attached.)

B6. Relevant tests/laboratory data (cont'd)

Test Date	Name	Result	Low	High
29Mar2000	pH, Urine	>9.0	5.0	8.0
29Mar2000	Neutrophils,Blood1:32pm	7.56th/cmm	2.5	7.0
29Mar2000	WhiteBloodCellCount, 08:26	10.8th/cmm	3.5	11.0
29Mar2000	WhiteBloodCellCount, 1:32pm	12.1th/cmm	3.5	11.0
29Mar2000	Neutrophils,Blood 08:26am	8.05th/cmm	2.5	7.0
29Mar2000	Lymphocytes, Blood08:26am	1.89th/cmm	1.0	4.0
29Mar2000	Lymphocytes,Blood 1:32pm	3.05th/cmm	1.0	4.0
29Mar2000	Monocytes,Blood 08:26	.710th/cmm	0.1	0.8
29Mar2000	Monocytes,Blood 1:32pm	1.08th/cmm	0.1	0.8
29Mar2000	Eosinophils,Blood 08:26	.106th/cmm	0	0.3
29Mar2000	Eosinophils,Blood 1:32pm	.318th/cmm	0	0.3
29Mar2000	Basophil 08:26	.048th/cmm	0	0.1
29Mar2000	Basophil 1:32pm	0.90th/cmm	0	0.1
29Mar2000	Sodium,Serum 08:26am	136mEq/L	135	153
29Mar2000	Sodium,Serum 1:32pm	135mEq/L	135	153
29Mar2000	Potassium 08:26am	4.8mEq/L	3.5	5.3
29Mar2000	Potassium 1:32pm	5.8mEq/L	3.5	5.3
29Mar2000	Bicarbonate 08:26	23mEq/L	24	32
29Mar2000	Bicarbonate 1:32pm	21mEq/L	24	32
29Mar2000	Glucose,Blood(random) 08:26	112mg/dl	70	100
29Mar2000	Glucose,Blood(random) 1:32pm	110mg/dl	70	110
29Mar2000	UreaNitrogen,Blood 08:26	8mg/dl	5	25
29Mar2000	UreaNitrogen,Blood 1:32pm	9mg/dl	5	25
29Mar2000	Bilirubin,total 08:26	1.0U/L	0.3	1.2
29Mar2000	AspartateTransaminase, 1:32pm	74U/L	14	36
29Mar2000	Bilirubin,total 1:32pm	1.8U/L	0.3	1.2
29Mar2000	Bilirubin,direct 08:26	0.7U/L	0.3	1.0
29Mar2000	Bilirubin,direct 1:32pm	1.4U/L	0.3	1.0

B7. Other relevant history (cont'd)

Condition	Started	Ended	Continuing
Irritable bowel syndrome	05Oct1999	Unknown	Yes
Constipation	Unknown	Unknown	Yes

OTHER SERIOUS CASES

A0116622A
A0116681A
A0116681A
A0117081A
A0117657A
A0118362A
A0118368A
A0118717A
A0119716A
A0120076A
A0120697A

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Glaxo Wellcome

Mfr report # A0116622A

UF/Ds report #

FDA Use Only

A. Patient information

1. Patient identifier	2. Age at time of event: 40-49Y or Date of birth 1956	3. Sex	4. Weight (lb)
In confidence		☒ female ☐ male ☐ unknown	UNK

B. Adverse event or product problem

1 ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)

☐ death ☒ disability
☐ life-threatening ☐ congenital anomaly
☐ hospitalization - initial or prolonged ☐ required intervention to prevent permanent impairment/damage
☐ other

3. Date of event: 08Mar2000

4. Date of this report: 09Jun2000

5. Describe event or problem

DESK COPY

A physician reported that a female patient in her 40's received alosetron (Lotronex) tablets and experienced "severe abdominal pain for a couple of days". The physician thought that the patient possibly had colitis. Subsequent information from the physician revealed that the patient experienced severe cramping and diarrhea for several hours after her dose of alosetron. He spoke with the patient via telephone. Alosetron was discontinued and the symptoms resolved the following day. No diagnostic tests, including biopsy were performed. No definitive diagnosis was made. The patient did not experience fever, rectal bleeding, nausea or vomiting. The physician considered the event to be disabling. Causality was not provided.

6. Relevant tests/laboratory data, including dates

UNK

7. Other relevant history, including preexisting medical conditions (eg allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

See attachment

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

#1 Lotronex Tablet (Alosetron hydrochloride)

#2

2. Dose / frequency / route used	3. Therapy dates
#1 1 mg / Unknown / Oral	#1 08Mar00 - 08Mar00
#2	#2

4. Diagnosis for use (indication)	5. Event abated after use stopped or dose reduced
#1 Irritable bowel syndrome	#1 ☒ yes ☐ no ☐ doesn't apply
#2	#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)	7. Exp. date (if known)	8. Event reappeared after reintroduction
#1 None	#1	#1 ☐ yes ☐ no ☒ doesn't apply
#2	#2	#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)

Loperamide hydrochloride UNK
Dicyclomine UNK

G. All manufacturers

1. Contact office - name/address

Glaxo Wellcome
North American Product Surveillance
PO Box 13398
Research Triangle Park
NC 27709

2. Phone number 1-888-825-5249 ext. 37070

3. Report source
☐ foreign ☐ study ☐ literature ☐ consumer ☒ health professional ☐ user facility ☒ company representative ☐ distributor ☐ other

4. Date received by manufacturer: 11Apr2000

5. (A)NDA # 21-107
IND #
PLA #
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #

7. Type of report
☐ 5-day ☒ 15-day ☐ 10-day ☐ periodic ☒ initial ☐ follow-up #

8. Adverse event term(s)
Abdominal pain
Possible colitis
Diarrhea
Colic

9. Mfr. report number: A0116622A

E. Initial Reporter

1. Name, address & phone #

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA?
☒ yes ☐ no	Physician	☐ yes ☐ no ☒ unk

FDA Form 3500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

B7. Other relevant history (cont'd)

Condition	Started	Ended	Continuing
Irritable bowel syndrome	1982	Unknown	Yes

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Glaxo Wellcome

Mfr report # A0116681A

UF/Dist report #

FDA Use Only

A. Patient information

1. Patient identifier	2. Age at time of event: 44Y or Date of birth: 06Jul1955	3. Sex	4. Weight (lb)
In confidence		☒ female ☐ male ☐ unknown	118.8

B. Adverse event or product problem

1 ☒ Adverse event and/or ☐ Product problem

2 Outcomes attributed to adverse event (check all that apply):

☐ death
☒ life-threatening
☒ hospitalization - initial or prolonged
☒ disability
☐ congenital anomaly
☒ required intervention to prevent permanent impairment/damage
☐ other

3. Date of event: 27Mar2000

4. Date of this report: 09Jun2000

5. Describe event or problem

DESK COPY

A pharmacist reportec that a 44 year old female received an overdose of multiple medications and was found comatose after "being down" for 36 hours. The pharmacist reported that the patient had a 24 hour history of drowsiness manifested by the patient falling asleep on the phone during a conversation with her brother. The patient was taking alosetron (Lotronex) tablets. zolpidem (Ambien) tablets, sertraline (Zoloft) tablets, generic butalbital/caffeine/aspirinl capsules and generic orphenadrine/aspirin/caffeine capsules. She was transported to the hospital and was admitted. She was diagnosed as having rhabdomyolysis as a result of not moving for an extended period of time. Urine screen was positive for myoglobin. Her CPK levels were elevated. (Maximum level was 5487). She also had increased AST and ALT levels, tachycardia, prolonged prothrombin time, hypokalemia,

continued on next page

6. Relevant tests/laboratory data, including dates

Tests/Labs: Upon initial examination, patient's heart rate was 127, blood pressure was 110/47 mm Hg. Urine drug screen was positive for barbiturates and benzodiazepines which was felt by the Poison Control Center pharmacist to be due to zolpidem. Blood toxicology screen: Acetaminophen less than 10 mcg/ml; blood alcohol level 0.04; salicylate 3.8 mg/dL;

continued on next page

7 Other relevant history, including preexisting medical conditions (eg. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

History of "stability problems" and staying in bed and sleeping for long periods of time.

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known) cont'd next page

#1 Lotronex Tablet (Alosetron hydrochloride)

#2 Zolpidem tartrate Tablet (Zolpidem tartrate)

2. Dose / frequency / route used	3 Therapy dates
#1 UNK / UNK / Oral	#1 UNK
#2 UNK / UNK / Oral	#2 UNK

4. Diagnosis for use (indication)	5. Event abated after use stopped or dose reduced
#1 Non-specific condition	#1 ☐ yes ☐ no ☒ doesn't apply
#2 Non-specific condition	#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)	7. Exp. date (if known)	8. Event reappeared after reintroduction
#1 None	#1	#1 ☐ yes ☐ no ☐ doesn't apply
#2 None	#2	#2 ☐ yes ☐ no ☐ doesn't apply

9 NDC # - for product prob'ems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)

UNK

G. All manufacturers

1. Contact office - name/address

Glaxo Wellcome
North American Product Surveillance
PO Box 13398
Research Triangle Park
NC 27709

2. Phone number: 1-888-825-5249 ext. 37070

3 Report source: ☐ foreign ☐ study ☐ literature ☐ consumer ☒ health professional ☐ user facility ☐ company representative ☐ distributor ☐ other:

4 Date received by manufacturer: 24May2000

5. (A)NDA # 21-107 IND # PLA # pre-1938 ☐ yes OTC product ☐ yes

6. If IND, protocol #

7. Type of report: ☐ 5-day ☒ 15-day ☐ 10-day ☐ periodic ☐ Initial ☒ follow-up # 2

8. Adverse event term(s)

Cerebral hypoxia
Myolysis
Coma
Renal failure
Incr.aspart.aminotransf.

continued on next page

9. Mfr. report number: A0116681A

E. Initial Reporter

1. Name, address & phone #

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA?
☒ yes ☐ no	Pharmacist	☐ yes ☐ no ☒ unk

FDA Form 3500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Glaxo Wellcome

Mfr report # A0116681A

UF/Dist report #

FDA Use Only

A. Patient information

1 Patient identifier	2 Age at time of event: or Date of birth	3. Sex	4. Weight (lb)
In confidence		☐ female ☐ male ☐ unknown	

B. Adverse event or product problem

1 ☐ Adverse event and/or ☐ Product problem

2 Outcomes attributed to adverse event (check all that apply)

☐ death ☐ disability
☐ life-threatening ☐ congenital anomaly
☐ hospitalization - initial or prolonged ☐ required intervention to prevent permanent impairment/damage
☐ other

3 Date of event	4. Date of this report

5 Describe event or problem

pressure sores, and respiratory depression. She experienced kidney failure manifested by anuria, followed by oliguria, elevated BUN and creatinine levels. She was also suspected of having hypoxic brain injury. She was treated with bicarbonate, bumetanide, furosemide, and chlorothiazide. She was placed on a ventilator. CT scan showed right frontal petechial hemorrhage. Neurology evaluation was planned. Tube feeding was attempted but was discontinued due to intolerance ("increased residuals"). Urine drug screen was positive for benzodiazepines. After pill counts, the pharmacist initially determined that the patient had ingested large amounts of zolpidem and sertraline and "very little" alosetron. Subsequent information from the pharmacist revealed that the physician wrote in the patient's discharge summary "It was impossible to ascertain how many pills [the patient] had taken, but ...did not appear to take many of the Ambien or Zoloft because of the amount left after [the] last

continued on next page

6. Relevant tests/laboratory data, including dates

phenobarbital less than 5.0. Elevated AST, ALT, BUN, creatinine, and CPK levels. 28Mar00: urine output 14 cc per hour. Oxygen saturation 98% on 50% Fi02. 29Mar00: INR 1.6 CT scan showed right petechial hemorrhage. Neurology evaluation planned. 03Apr00: Oxygen saturation 98% on Fi02 30%. 09Apr00: urine output 600 cc/24 hour. 13Apr00: CT scan showed occipital

continued on next page

7 Other relevant history, including preexisting medical conditions (eg allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known) cont'd next page

#3 Sertraline hydrochloride Tablet (Sertraline hydrochloride)

#4 Aspirin+butalbital+caffn. Capsule (Generic) (Aspirin+butalbital+caffn.)

2. Dose / frequency / route used	3. Therapy dates
#3 UNK / UNK / Oral	#3 UNK
#4 UNK / UNK / Oral	#4 UNK

4. Diagnosis for use (indication)	5. Event abated after use stopped or dose reduced
#3 Non-specific condition	#3 ☐ yes ☐ no ☐ doesn't apply
#4 Non-specific condition	#4 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)	7. Exp. date (if known)	8. Event reappeared after reintroduction
#3 None	#3	#3 ☐ yes ☐ no ☐ doesn't apply
#4 None	#4	#4 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

10 Concomitant medical products and therapy dates (exclude treatment of event)

G. All manufacturers

1. Contact office - name/address

Glaxo Wellcome
North American Product Surveillance
PO Box 13398
Research Triangle Park
NC 27709

2. Phone number 1-888-825-5249 ext. 37070

3 Report source
☐ foreign ☐ study ☐ literature ☐ consumer ☐ health professional ☐ user facility ☐ company representative ☐ distributor ☐ other.

4. Date received by manufacturer

5 (A)NDA # IND # PLA # pre-1938 ☐ yes OTC product ☐ yes

6. If IND, protocol #

7. Type of report
☐ 5-day ☐ 15-day ☐ 10-day ☐ periodic ☐ initial ☐ follow-up # ___

8. Adverse event term(s)
Incr.alanine aminotransf.
Increased CPK levels
Drowsiness
Incr.blood urea nitrogen
Incr.creatinine levels

continued on next page

9. Mfr. report number
A0116681A

E. Initial Reporter

1. Name, address & phone #

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA?
☐ yes ☐ no		☐ yes ☐ no ☐ unk

FDA Form 3500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Glaxo Wellcome

Mfr report # A0116681A

Uf/Dist report #

FDA Use Only

A. Patient information

1 Patient identifier	2 Age at time of event: _____ or Date of birth	3 Sex	4 Weight (lb)
In confidence		☐ female ☐ male ☐ unknown	

B. Adverse event or product problem

1 ☐ Adverse event and/or ☐ Product problem

2 Outcomes attributed to adverse event (check all that apply)

☐ death _____ ☐ disability

☐ life-threatening ☐ congenital anomaly

☐ hospitalization - initial or prolonged ☐ required intervention to prevent permanent impairment/damage

☐ other: _____

3 Date of event	4. Date of this report

5 Describe event or problem

prescription refill." The patient was felt to have ingested the medications in a suicide attempt. At time of initial reporting, the patient's condition was dire. Subsequent information revealed that the patient's condition had improved. During the last two days of her hospitalization she showed increased signs of neurological activity manifested by being able to squeeze her physician's hand with each hand, could follow her physician, and could respond appropriately with facial movement. Because of her continuing kidney failure, she was transferred on 02Apr00 to a facility that provided dialysis. At that time, she was noted to still exhibit minimal neurological responses. By the following day, after two dialysis treatments, she was responsive and able to follow commands. While at the new facility, the patient was treated for aspiration pneumonia. She also spiked intermittent fevers. Eight days after admission, the patient became confused and agitated requiring use of restraints.

continued on next page

6 Relevant tests/laboratory data, including dates

infarction.

7. Other relevant history, including preexisting medical conditions (eg. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

#5 Aspirin+caffeine+orphenad Tablet (Aspirin+caffeine+orphenad)

#6

2. Dose / frequency / route used	3 Therapy dates
#5 UNK / UNK / Oral	#5 UNK
#6	#6

4 Diagnosis for use (indication)	5. Event abated after use stopped or dose reduced
#5 Non-specific condition	#5 ☐ yes ☐ no ☐ doesn't apply
#6	#6 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)	7. Exp. date (if known)	8 Event reappeared after reintroduction
#5 None	#5	#5 ☐ yes ☐ no ☐ doesn't apply
#6	#6	#6 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)

G. All manufacturers

1. Contact office - name/address

Glaxo Wellcome
North American Product Surveillance
PO Box 13398
Research Triangle Park
NC 27709

2. Phone number 1-888-825-5249 ext. 37070

3. Report source

☐ foreign ☐ study ☐ literature ☐ consumer ☐ health professional ☐ user facility ☐ company representative ☐ distributor ☐ other: _____

4 Date received by manufacturer

5. (A)NDA # _____ IND # _____ PLA # _____ pre-1938 ☐ yes OTC product ☐ yes

6 If IND, protocol #

7. Type of report: ☐ 5-day ☐ 15-day ☐ 10-day ☐ periodic ☐ initial ☐ follow-up # ____

8. Adverse event term(s)

Overdose
Attempted suicide
Decubitus ulcer
Decubitus ulcer infection
Tachycardia

continued on next page

9. Mfr. report number A0116681A

E. Initial Reporter

1. Name, address & phone #

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA?
☐ yes ☐ no		☐ yes ☐ no ☐ unk

FDA Form 3500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

B5. Describe event or problem (cont'd)
Her decubitus ulcers were found to be infected. A CT scan the following day revealed occipital infarction. Two weeks after being admitted to the dialysis facility, the patient was awake, alert and oriented. Daily dialysis treatments were discontinued. Patient was to be discharged to home. The pharmacist considered the events possibly related to the use of alosetron.

B6. Relevant tests/laboratory data (cont'd)

Test Date	Name	Result	Low	High
27Mar2000	Aspartate Transaminase, Serum	12,199		
27Mar2000	Alanine Transaminase, Serum	5845		
27Mar2000	Urea Nitrogen, Blood	56		
27Mar2000	Creatine Phosphokinase, Serum	5487		
27Mar2000	Urea Nitrogen, Blood	55		
27Mar2000	Creatinine, Serum	4.3		
27Mar2000	Creatine Phosphokinase, Serum	5345		
27Mar2000	Creatinine, Serum	4.6		
28Mar2000	Aspartate Transaminase, Serum	2780		
28Mar2000	Creatine Phosphokinase, Serum	4413		
28Mar2000	Urea Nitrogen, Blood	65		
28Mar2000	Creatinine, Serum	5.4		
28Mar2000	Potassium	3.4		
28Mar2000	Creatine Phosphokinase, Serum	4782		
28Mar2000	Creatine Phosphokinase, Serum	3892		
28Mar2000	Creatinine, Serum	5.7		
28Mar2000	Urea Nitrogen, Blood	66		
28Mar2000	Alanine Transaminase, Serum	2449		
29Mar2000	Aspartate Transaminase, Serum	1754		
29Mar2000	Alanine Transaminase, Serum	2037		
29Mar2000	Urea Nitrogen, Blood	77		
29Mar2000	Aspartate Transaminase, Serum	1733		
29Mar2000	Creatinine, Serum	6.7		
30Mar2000	Aspartate Transaminase, Serum	959		
30Mar2000	Creatinine, Serum	8.0		
30Mar2000	Urea Nitrogen, Blood	99		
30Mar2000	Alanine Transaminase, Serum	1634		
31Mar2000	Aspartate Transaminase, Serum	265		
31Mar2000	Urea Nitrogen, Blood	133		
31Mar2000	Alanine Transaminase, Serum	936		
31Mar2000	Creatinine, Serum	9.7		
01Apr2000	Aspartate Transaminase, Serum	114		
01Apr2000	Alanine Transaminase, Serum	566		
01Apr2000	Urea Nitrogen, Blood	160		
01Apr2000	Creatinine, Serum	10.9		
03Apr2000	Creatinine, Serum	5.6		
04Apr2000	Creatinine, Serum	4.5		
04Apr2000	UreaNitrogen,Blood	45		

G8. Adverse event term(s) (cont'd)
Increase:prothrombin time
Hypokalemia
Respiratory depression
Oliguria
Anuria
Myoglobinuria
Fever
Confusion
Agitation
Frontal lobe hemorrhage
Aspiration pneumonia

continued on next page

G8. Adverse event term(s) (cont'd)
Cerebral infarction

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Glaxo Wellcome

Mfr report # A0117081A

FDA Use Only

A. Patient information

1. Patient identifier	2. Age at time of event: / or Date of birth	3. Sex	4. Weight (lb)
In confidence	58Y / 01Apr1942	☒ female ☐ male ☐ unknown	UNK

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death
- ☐ life-threatening
- ☒ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other

3. Date of event: 30Mar2000

4. Date of this report: 09Jun2000

5. Describe event or problem

DESK COPY

A physician reported that an adult female received alosetron (Lotronex) tablets and after seven days of use was found comatose by her husband. She was postulated to have been in that state for two to three hours. Concurrent medications included but not limited to Darvocet-N 100, oxycodone (OxyContin), and alprazolam (Xanax). Her oxygen saturation was found to be 68 per cent on room air. She was transported to the emergency room via ambulance on supportive oxygen via face mask. In the emergency room, she was given oxygen via nasal canula. She received injectable naloxine (Narcan) and injectable flumazenil (Romazicon) and immediately awoke and remained alert for her 23 hour observation period. Upon awakening, the patient commented that the last thing she remembered was taking a couple of Darvocet N tablets for her leg pain. The patient was discharged to home. Alosetron was

continued on next page

6. Relevant tests/laboratory data, including dates

Tests/Labs: Oxygen saturation was 68 per cent on room air.

7. Other relevant history, including preexisting medical conditions (eg, allergies, race, pregnancy, smoking and alcohol use, hepatorenal dysfunction, etc.)

History of congenital Arnold-Chiari Syndrome, Type I, resulting in chronic leg pain. No history of loss of consciousness.

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
- #1 Lotronex Tablet (Alosetron hydrochloride)
- #2

2. Dose / frequency / route used	3. Therapy dates
#1 1 mg / Twice per day / Oral	#1 23Mar00 - 30Mar00
#2	#2

4. Diagnosis for use (indication)
- #1 Irritable bowel syndrome
- #2

5. Event abated after use stopped or dose reduced
- #1 ☒ yes ☐ no ☐ doesn't apply
- #2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)	7. Exp date (if known)
#1 None	#1
#2	#2

8. Event reappeared after reintroduction
- #1 ☐ yes ☐ no ☒ doesn't apply
- #2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)

Darvocet-N	UNK
Alprazolam	UNK
Oxycodone hydrochloride	UNK

G. All manufacturers

1. Contact office - name/address

Glaxo Wellcome
North American Product Surveillance
PO Box 13398
Research Triangle Park
NC 27709

2. Phone number 1-888-825-5249 ext. 37070

3. Report source
- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☒ company representative
- ☐ distributor
- ☐ other

4. Date received by manufacturer: 22May2000

5. (A)NDA # 21-107
- IND #
- PLA #
- pre-1938 ☐ yes
- OTC product ☐ yes

6. If IND, protocol #

7. Type of report
- ☐ 5-day ☒ 15-day
- ☐ 10-day ☐ periodic
- ☐ initial ☒ follow-up # 1

8. Adverse event term(s)

Coma
Weakness
Decreas.oxygen saturation

9. Mfr. report number: A0117081A

E. Initial Reporter

1. Name, address & phone #

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA?
☒ yes ☐ no	Physician	☐ yes ☐ no ☒ unk

FDA Form 3500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event

B5. Describe event or problem (cont'd)
discontinued. Three days later, she presented to the emergency room complaining of diffuse weakness and was kept under observation for six hours and sent home. Her symptoms resolved. The physician stated that the patient was compliant with regards to her medication and he considered the events to be possibly related to the use of alosetron.

B7. Other relevant history (cont'd)

Condition	Started	Ended	Continuing
Arnold-Chiari syndrome	04Apr1942	Unknown	Yes
Irritable bowel syndrome	Unknown	Unknown	Yes

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Glaxo Wellcome

Mfr report # A0117657A

Mfr/Dist report #

FDA Use Only

A. Patient information

1 Patient identifier	2 Age at time of event / or Date of birth	3. Sex	4 Weight (lb)
In confidence	50Y / UNK	☒ female ☐ male ☐ unknown	UNK

B. Adverse event or product problem

1 ☒ Adverse event and/or ☐ Product problem

2 Outcomes attributed to adverse event (check all that apply)

☐ death ☐ disability
☐ life-threatening ☐ congenital anomaly
☐ hospitalization - initial or prolonged ☐ required intervention to prevent permanent impairment/damage
☒ other See text

3. Date of event: 21Mar2000

4 Date of this report: 09Jun2000

5. Describe event or problem

DESK COPY

A 50 year old female reported that she received two doses of alosetron (Lotronex) tablets and on the following morning while driving, she experienced stomach pains and cramping which became unbearable. She felt the urge to have a bowel movement so she went to the restroom of a fast food restaurant. In the bathroom, she felt nauseated, had cold sweats, chills, felt faint, and felt sick. She called a friend on her cell phone who came to her aid. Emergency Medical Service (EMS) was called and while they were there, she began to vomit large amounts of liquid. (The patient stated that she had not had breakfast that morning). She stated that she was unable to move and felt like she was dying. The EMS technicians told her that they were having a hard time locating her" heart rate and pulse rate" and that her blood pressure was elevated. She was placed on supplemental oxygen and transported to the emergency room

continued on next page

6 Relevant tests/laboratory data, including dates

UNK

7 Other relevant history, including preexisting medical conditions (eg allergies, race, pregnancy smoking and alcohol use, hepatic/renal dysfunction, etc.)

History of high blood pressure which had been well controlled with medication for years. Patient had irritable bowel syndrome which cuased her to have associated pain and stomach problems which she treated with hydrocodone and hyoscyamine, respectively.

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

#1 Lotronex Tablet (Alosetron hydrochloride)

#2

2. Dose / frequency / route used

#1 1 mg / Twice per day / Oral

#2

3. Therapy dates

#1 20Mar00 - 20Mar00

#2

4. Diagnosis for use (indication)

#1 Irritable bowel syndrome

#2

5 Event abated after use stopped or dose reduced

#1 ☒ yes ☐ no ☐ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)

#1 None

#2

7. Exp. date (if known)

#1

#2

8. Event reappeared after reintroduction

#1 ☐ yes ☐ no ☒ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)

Atenolol	UNK
Hydrocodone	UNK
Hyoscyamine	UNK
Sodium rabeprazole	UNK

G. All manufacturers

1. Contact office - name/address

Glaxo Wellcome
North American Product Surveillance
PO Box 13398
Research Triangle Park
NC 27709

2. Phone number 1-888-825-5249 ext. 37070

3 Report source

☐ foreign
☐ study
☐ literature
☒ consumer
☐ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other

4. Date received by manufacturer: 25Apr2000

5. (A)NDA # 21-107

IND #

PLA #

pre-1938 ☐ yes

OTC product ☐ yes

6. If IND, protocol #

7. Type of report

☐ 5-day ☒ 15-day
☐ 10-day ☐ periodic
☐ initial ☒ follow-up # 1

8. Adverse event term(s)

Syncope
Increased blood pressure
Weak pulse
Vomiting
Loss of mobility

continued on next page

9. Mfr. report number: A0117657A

E. Initial Reporter

1. Name, address & phone #

2. Health professional? ☐ yes ☒ no

3. Occupation: UNK

4. Initial reporter also sent report to FDA? ☐ yes ☐ no ☒ unk

FDA Form 3500A Fax-mile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event

B5. Describe event or problem (cont'd)
via ambulance. En route to the hospital, she fainted. The emergency room medical staff thought the events were related to the use of alosetron and alosetron was discontinued. She was given an injection of an unspecified medication so that she could rest and sent home. She was not admitted. When she awoke the next morning, she felt fine, all symptoms had resolved.

B7. Other relevant history (cont'd)

Condition	Started	Ended	Continuing
Irritable bowel syndrome	Unknown	Unknown	Yes
High blood pressure	Unknown	Unknown	Yes

G8. Adverse event term(s) (cont'd)
Gastric pain
Colic
Sense of impending doom
Sickness
Cold sweat(s)
Nausea
Chills
Faintness

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Glaxo Wellcome

Mfr report # A0118362A
UF/Dist report #
FDA Use Only

A. Patient information

1. Patient identifier	2. Age at time of event / or Date of birth	3. Sex	4. Weight (lb)
In confidence	64Y / UNK	☒ female ☐ male ☐ unknown	UNK

B. Adverse event or product problem

1 ☒ Adverse event and/or ☐ Product problem

2 Outcomes attributed to adverse event (check all that apply)
- ☐ death
- ☐ life-threatening
- ☒ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☒ other: See text

3 Date of event: 04Apr2000
4 Date of this report: 09Jun2000

5. Describe event or problem

DESK COPY

A 64 year old female with a history of hypertension and seeing flashing lights of six months duration reported that she received alosetron (Lotronex) tablets and developed constipation on the second day of use. She stated that the constipation occurred every other day. Her dose of alosetron was reduced to one tablet every other day and the constipation improved. Approximately three weeks later, while on a motor home trip, she experienced right-sided weakness and right-sided numbness. She was admitted to the hospital overnight. She was diagnosed as having suffered a stroke and placed on a treatment regimen of spironolactone (Aldactone), furosemide (Lasix), clopidogrel (Plavix), and numerous anti-hypertensives. At time of reporting, her condition has improved as she is currently only experiencing tiredness and shortness of breath. She stated that her next doctor's appointment is scheduled for

continued on next page

6. Relevant tests/laboratory data, including dates
UNK

7. Other relevant history, including preexisting medical conditions (eg, allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)
History or hypertension; swelling of legs when seated for extended periods of time (as in sitting in a car); endometriosis requiring hysterectomy (ovaries were initially left but were subsequently removed due to advancing endometriosis); scarring of colon due to endometriosis; slight arthritis in legs; six month history of seeing flashing lights. On first episode, patient

continued on next page

FDA Form 3500A Fax-mile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 Lotronex Tablet (Alosetron hydrochloride)
#2

2. Dose / frequency / route used
#1 1 tablet / Per day / Oral
#2

3. Therapy dates
#1 03Apr00 - 25Apr00
#2

4. Diagnosis for use (indication)
#1 Irritable bowel syndrome
#2

5. Event abated after use stopped or dose reduced
#1 ☒ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
#1 None
#2

7. Exp. date (if known)
#1
#2

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)

Losartan potassium	UNK
Unknown	UNK
Conjugated estrogens	UNK
Hydroxyzine	UNK

G. All manufacturers

1. Contact office - name/address

Glaxo Wellcome
North American Product Surveillance
PO Box 13398
Research Triangle Park
NC 27709

2. Phone number: 1-888-825-5249 ext. 37070

3 Report source
- ☐ foreign
- ☐ study
- ☐ literature
- ☒ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4 Date received by manufacturer: 31May2000

5. (A)NDA # 21-107
IND #
PLA #
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #

7. Type of report
- ☐ 5-day ☒ 15-day
- ☐ 10-day ☐ periodic
- ☐ Initial ☒ follow-up # 0

8. Adverse event term(s)
Cerebrovascular accident
Constipation
Weakness of side(s)
Numbness
Tiredness
Shortness of breath

9. Mfr report number: A0118362A

E. Initial Reporter

1. Name, address & phone #

2. Health professional? ☐ yes ☒ no

3. Occupation: UNK

4. Initial reporter also sent report to FDA? ☐ yes ☐ no ☒ unk

B5. Describe event or problem (cont'd)
July 2000.

B7. Other relevant history (cont'd)
presented to her ophthalmologist who was unable to determine etiology. Referred her back to her general practitioner. On second episode of seeing flashing lights, she presented to the emergency department where her blood pressure was found to be 169/94 mm Hg. Numerous food allergies including corn, rice, barley, lentils, shrimp, and apples.

B7. Other relevant history (cont'd)

Condition	Started	Ended	Continuing
Irritable bowel syndrome	Unknown	Unknown	Yes
Circulatory problems	Unknown	Unknown	Yes
Blood pressure changes	Unknown	Unknown	Yes
Hypertension	Unknown	Unknown	Yes
Food allergies	Unknown	Unknown	Yes

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Glaxo Wellcome

Approved by the FDA (11-92) on 5 NOV 93

Mfr report # A0118368A

User/Dist report #

FDA Use Only

A. Patient information

1. Patient identifier	2. Age at time of event / or Date of birth	3. Sex	4. Weight (lb)
In confidence	59Y / UNK	☒ female ☐ male ☐ unknown	UNK

B. Adverse event or product problem

1 ☒ Adverse event and/or ☐ Product problem

2 Outcomes attributed to adverse event (check all that apply)

☐ death ☐ disability
☐ life-threatening ☐ congenital anomaly
☒ hospitalization - initial or prolonged ☐ required intervention to prevent permanent impairment/damage
☐ other

3. Date of event: 06Apr2000

4. Date of this report: 09Jun2000

5. Describe event or problem

DESK COPY

A gastroenterologist reported to a sales representative that a female in her mid-fifites received alosetron (Lotronex) tablets and after 48 hours of therapy developed ischemic colitis requiring hospitalization for two days. Alosetron was discontinued. The gastroenterologist felt the event was almost certainly related to the use of alosetron.
Subsequent information from a nurse in the gastroenterologist's office revealed that a 59 year old female received alosetron (Lotronex) tablets and after 48 hours of therapy developed abdominal pain, change in urgency of bowel movements, and macroscopically bloody diarrhea. She presented to the emergency room. Diagnostic tests revealed an elevated white blood cell count (22,000) and elevated erythrocyte sedimentation rate (29 mm). She was admitted and placed on metronidazole therapy. CT scan revealed slight mucosal

continued on next page

6 Relevant tests/laboratory data, including dates

Tests/Labs: Colonoscopy performed on 04Apr00, prior to the start of therapy with alosetron, was consistent with pathology/histology of irritable bowel syndrome. WBC count at time of admission was 22,000. Count had dropped to 19,000 at time of discharge. Erythrocyte sedimentation rate was elevated at 29 mm. Stool assays were negative for Clostridium

continued on next page

7 Other relevant history, including preexisting medical conditions (eg allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

No history of drug allergies.

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 Lotronex Tablet (Alosetron hydrochloride)
#2

2. Dose / frequency / route used
#1 1 mg / Twice per day / Oral
#2

3. Therapy dates
#1 04Apr00 - 06Apr00
#2

4. Diagnosis for use (indication)
#1 Irritable bowel syndrome
#2

5. Event abated after use stopped or dose reduced
#1 ☒ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
#1 None
#2

7. Exp. date (if known)
#1
#2

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

10 Concomitant medical products and therapy dates (exclude treatment of event)

Hydroxyzine hydrochloride	UNK
Lisinopril	UNK
HRT	UNK

G. All manufacturers

1 Contact office - name/address

Glaxo Wellcome
North American Product Surveillance
PO Box 13398
Research Triangle Park
NC 27709

2. Phone number: 1-888-825-5249 ext. 37070

3. Report source
☐ foreign ☐ study ☐ literature ☐ consumer ☒ health professional ☐ user facility ☒ company representative ☐ distributor ☐ other

4. Date received by manufacturer: 17Apr2000

5. (A)NDA # 21-107
IND #
PLA #
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #

7 Type of report
☐ 5-day ☒ 15-day ☐ 10-day ☐ periodic ☒ initial ☐ follow-up #

8 Adverse event term(s)
Ischemic colitis
Bloody diarrhea
Abdominal pain
Leukocytosis
Mucosal alteration

continued on next page

9. Mfr. report number: A0118368A

E. Initial Reporter

1. Name, address & phone #

2 Health professional? ☒ yes ☐ no

3. Occupation: Physician

4. Initial reporter also sent report to FDA? ☐ yes ☐ no ☒ unk

FDA Form 3500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event

B5. Describe event or problem (cont'd)
irregularities in transverse colon possibly related to ulcerative colitis. Repeat WBC count was 19,000. The nurse reported that the event was an "ischemic attack" and was not ulcerative colitis as the patient's prior colonoscopy did not reveal signs of ulcerative colitis. No repeat colonoscopy was performed during the patient's hospital stay. The patient recovered and was discharged to home. Alosetron was discontinued. The events were felt to be related to the use of alosetron.

B6. Relevant tests/laboratory data (cont'd)
difficile toxin, negative for ova and parasites. Microscopic stool exam revealed rare WBC. Stool cultures grew normal flora only (negative for bacterial pathogens). CT scan revealed slight mucosal irregularities of transverse colon possibly related to ulcerative colits. No thickening in loops of small intestine.

B7. Other relevant history (cont'd)

Condition	Started	Ended	Continuing
Irritable bowel syndrome	Unknown	Unknown	Yes
Post-menopausal	Unknown	Unknown	Yes
Hypertension	Unknown	Unknown	Yes

G8. Adverse event term(s) (cont'd)
Increased ESR
Urgency of defecation

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Glaxo Wellcome

Mfr report # A0118717A

Mfr/Dist report #

FDA Use Only

A. Patient information

1 Patient identifier	2 Age at time of event: / or Date of birth	3. Sex	4. Weight (lb)
In confidence	Adult / UNK	☒ female ☐ male ☐ unknown	UNK

B. Adverse event or product problem

1 ☒ Adverse event and/or ☐ Product problem

2 Outcome(s) attributed to adverse event (check all that apply)

☐ death ☐ disability

☐ life-threatening ☐ congenital anomaly

☒ hospitalization - initial or prolonged ☐ required intervention to prevent permanent impairment/damage

☐ other:

3. Date of event: Apr2000

4 Date of this report: 09Jun2000

5 Describe event or problem

DESK COPY

A physician reported to a sales representative that an adult female received alosetron (Lotronex) tablets and experienced chest pains 15 to 20 minutes after every dose. The patient was hospitalized. Alosetron was discontinued. Outcome not known at time of reporting.

6 Relevant tests/laboratory data, including dates

UNK

7. Other relevant history, including preexisting medical conditions (eg. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

No cardiac history.

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

#1 Lotronex Tablet (Alosetron hydrochloride)

#2

2. Dose / frequency / route used	3 Therapy dates
#1 1 mg / Twice per day / Oral	#1 Unknown - Apr00
#2	#2

4. Diagnosis for use (indication)

#1 Irritable bowel syndrome

#2

5. Event abated after use stopped or dose reduced

#1 ☐ yes ☐ no ☐ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)	7. Exp. date (if known)
#1 None	#1
#2	#2

8. Event reappeared after reintroduction

#1 ☐ yes ☐ no ☒ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)

UNK

G. All manufacturers

1. Contact office - name/address

Glaxo Wellcome
North American Product Surveillance
PO Box 13398
Research Triangle Park
NC 27709

2. Phone number 1-888-825-5249 ext. 37070

3 Report source

☐ foreign ☐ study ☐ literature ☐ consumer ☒ health professional ☐ user facility ☒ company representative ☐ distributor ☐ other:

4. Date received by manufacturer: 12Apr2000

5. (A)NDA # 21-107 IND # PLA #

pre-1938 ☐ yes

OTC product ☐ yes

6. If IND, protocol #

7. Type of report

☐ 5-day ☒ 15-day ☐ 10-day ☐ periodic ☒ initial ☐ follow-up #

8 Adverse event term(s)

Chest pain

9. Mfr. report number

A0118717A

E. Initial Reporter

1. Name, address & phone #

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA?
☒ yes ☐ no	Physician	☐ yes ☐ no ☒ unk

FDA Form 3500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

B7. Other relevant history (cont'd)

Condition	Started	Ended	Continuing
Bronchitis	Unknown	Unknown	Yes
Irritable bowel syndrome	Unknown	Unknown	Yes

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Glaxo Wellcome

Mfr report # A0119716A

Mfr/Dist report #

FDA Use Only

A. Patient information

1. Patient identifier	2. Age at time of event: or Date of birth	3. Sex	4. Weight (lb)
In confidence	61Y / 12Jul1961	☒ female ☐ male ☐ unknown	104.1

B. Adverse event or product problem

1 ☒ Adverse event and/or ☐ Product problem

2 Outcomes attributed to adverse event (check all that apply)

☐ death
☐ life-threatening
☒ hospitalization - initial or prolonged
☐ disability
☐ congenital anomaly
☒ required intervention to prevent permanent impairment/damage
☐ other

3 Date of event: 29Apr2000

4 Date of this report: 09Jun2000

5 Describe event or problem

DESK COPY

A gastroenterologist reported that a 61 year-old female with a three year history of diarrhea predominant irritable bowel disease received alosetron (Lotronex) tablets for approximately two and one half weeks without difficulty. She then developed severe lower abdominal pain (more severe than her usual abdominal cramps), diarrhea, nausea and vomiting. The patient did not have rectal bleeding or rebound tenderness. She was seen in the physician's office the following day and hospitalized. Alosetron was discontinued. Lactate level was noted to be elevated. Other labs including stool cultures were normal. Abdominal x-rays showed non-specific findings. Computerized tomography showed a fairly normal colon, but there was significant edema of the small bowel as well as thickening of the wall of the small bowel, particularly of the distal jejunum and proximal ileum. Moderate amount of abdominal ascites noted. Biopsy not

continued on next page

6 Relevant tests/laboratory data, including dates

Lab results: Stools heme negative upon admission to hospital; stool culture for bacteria, ova and parasites, and C.difficile toxin all negative; WBC normal; liver panel including amylase and lipase normal; thrombosis panel not done; lactate level in emergency room 01May00 was 2.1; lactate down to 0.9 on 04May00; abdominal x-ray was nonspecific and showed questionable ileus

continued on next page

7. Other relevant history, including preexisting medical conditions (eg, allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

History: Irritable bowel syndrome for three years, diarrhea predominant; depression; anal sphincterotomy one month earlier for anal fissure; hemorrhoids, diverticulosis; possible migraines (reporter believed patient had received sumatriptan in the past); pancreatitis three years earlier; no history of diabetes, no heart or vascular disease, no history of thrombosis; no use of

continued on next page

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

#1 Lotronex Tablet (Alosetron hydrochloride)

#2

2. Dose / frequency / route used

#1 1 mg / Twice per day / Oral

#2

3 Therapy dates

#1 13Apr00 - 29Apr00

#2

4 Diagnosis for use (indication)

#1 Irritable bowel syndrome

#2

5. Event abated after use stopped or dose reduced

#1 ☒ yes ☐ no ☐ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)

#1 None

#2

7. Exp. date (if known)

#1

#2

8. Event reappeared after reintroduction

#1 ☐ yes ☐ no ☒ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

10 Concomitant medical products and therapy dates (exclude treatment of event)

Clonazepam Years

Nefazodone hydrochloride Years

G. All manufacturers

1. Contact office - name/address

Glaxo Wellcome
North American Product Surveillance
PO Box 13398
Research Triangle Park
NC 27709

2. Phone number 1-888-825-5249 ext. 37070

3. Report source

☐ foreign
☐ study
☐ literature
☐ consumer
☒ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other

4. Date received by manufacturer: 26May2000

5. (A)NDA # 21-107

IND #

PLA #

pre-1938 ☐ yes

OTC product ☐ yes

6. If IND, protocol #

7. Type of report

☐ 5-day ☒ 15-day
☐ 10-day ☐ periodic
☐ initial ☒ follow-up # 1

8. Adverse event term(s)

Acute enteritis
Abdominal pain
Nausea
Vomiting
Bowel edema

continued on next page

9. Mfr. report number: A0119716A

E. Initial Reporter

1 Name, address & phone #

2. Health professional? ☒ yes ☐ no

3. Occupation: Gastroenterol.

4. Initial reporter also sent report to FDA? ☐ yes ☐ no ☒ unk

FDA Form 3500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event

B5. Describe event or problem (cont'd)
performed. The diagnosis, according to the gastroenterologist, was acute enteritis of possible infectious or possible ischemic origin. The patient was made NPO and treated with intravenous ciprofloxacin and metronidazole. She had improved at the time of reporting but remained hospitalized. The reporting physician considered the events to require intervention to prevent a serious outcome.

B6. Relevant tests/laboratory data (cont'd)
vs. small bowel obstruction; abdominal CT scan showed that colon was fairly normal, but small bowel was markedly abnormal with significant edema and thickening of the wall of the distal jejunum and proximal ileum. Findings may be due to infectious enteritis, inflammatory bowel disease or possibly ischemia. No intramural air was seen within the thickened and distended bowel loops. No evidence of obstruction seen. Moderate amount of ascites noted. Biopsy not performed. Endoscopy not performed.

B7. Other relevant history (cont'd)
coumadin, heparin, NSAIDs, antibiotics, amphetamine or cocaine.

B7. Other relevant history (cont'd)

Condition	Started	Ended	Continuing
IBS	1997	Unknown	Yes
Diarrhea	1997	Unknown	Yes
Pancreatitis	1997	Unknown	No
Rectal surgery	Apr2000	Unknown	No
Depression	Unknown	Unknown	Yes
Diverticulosis	Unknown	Unknown	Unknown
Hemorrhoids	Unknown	Unknown	Unknown
Anal fissure	Unknown	Apr1999	No
Possible migraine	Unknown	Unknown	Unknown
Cholecystectomy	Unknown	Unknown	Yes
Hysterectomy	Unknown	Unknown	Yes

G8. Adverse event term(s) (cont'd)
Inc.serum lactic acid
Ascites

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Glaxo Wellcome

(Page 1 of 2)

Mfr report # A0120076A

Mfr/Dist report #

FDA Use Only

A. Patient information

1. Patient identifier	2. Age at time of event: 76Y or Date of birth 28Dec1923	3. Sex	4. Weight (lb)
In confidence		☒ female ☐ male ☐ unknown	UNK

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death
- ☐ life-threatening
- ☒ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other

3. Date of event: 01May2000

4. Date of this report: 09Jun2000

5. Describe event or problem

DESK COPY

A physician reported that his 76 year-old wife received alosetron (Lotronex) tablets to treat irritable bowel syndrome with good results initially. After approximately seven weeks of therapy, she experienced increased bowel symptoms (frequency) with incontinence. The next day, she developed severe progressive abdominal pain and disorientation. She was hospitalized in intensive care; all medications were discontinued. An electrocardiogram on the morning of admission showed marked ST segment ischemic changes, but a repeat EKG that afternoon was normal. Her white blood cell count was elevated, but there was no bleeding. Red blood cell count and hematocrit were slightly decreased. All other labs and tests were normal. According to the reporter, the patient's Internist felt that in the absence of a diagnosis, a mesenteric artery thrombus or acute mesenteric ischemia was a reasonable

continued on next page

6. Relevant tests/laboratory data, including dates

Tests: White blood cell count on admission was greater than 20,000; chest x-ray and cardiac echo normal on admission; EKG showed marked ST segment elevation, but repeat EKG several hours later was normal; all labs normal except RBC and hematocrit slightly decreased; colonoscopy three days after admission showed no ischemia.

7. Other relevant history, including preexisting medical conditions (eg allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

History of both diarrhea and constipation, irritable bowel syndrome confirmed by colonoscopy one and one half years ago; during a colonoscopy as part of an investigation for iron deficiency anemia eight years ago, sigmoid colon was ruptured leading to a temporary colostomy; three months later during the colostomy take-down, the anesthesiologist punctured the

continued on next page

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
- #1 Lotronex Tablet (Alosetron hydrochloride)
- #2

2. Dose / frequency / route used
- #1 1 mg / Twice per day / Oral
- #2

3. Therapy dates
- #1 Mar00 - 01May00
- #2

4. Diagnosis for use (indication)
- #1 Irritable bowel syndrome
- #2

5. Event abated after use stopped or dose reduced
- #1 ☒ yes ☐ no ☐ doesn't apply
- #2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
- #1 None
- #2

7. Exp date (if known)
- #1
- #2

8. Event reappeared after reintroduction
- #1 ☐ yes ☐ no ☒ doesn't apply
- #2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)

Digoxin	UNK
Estrogen	35 Years
Chlorpheniramine maleate	UNK
Verapamil	UNK

continued on next page

G. All manufacturers

1. Contact office - name/address

Glaxo Wellcome
North American Product Surveillance
PO Box 13398
Research Triangle Park
NC 27709

2. Phone number: 1-888-825-5249 ext. 37070

3. Report source
- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other

4. Date received by manufacturer: 09May2000

5. (A)NDA #: 21-107
- IND #
- PLA #
- pre-1938 ☐ yes
- OTC product ☐ yes

6. If IND, protocol #

7. Type of report
- ☐ 5-day ☒ 15-day
- ☐ 10-day ☐ periodic
- ☒ initial ☐ follow-up #

8. Adverse event term(s)

Thrombus:mesentery artery
Abdominal pain
Inc.freq.bowel movements
Leukocytosis
Disorientation

continued on next page

9. Mfr. report number: A0120076A

E. Initial Reporter

1. Name, address & phone #

2. Health professional? ☒ yes ☐ no

3. Occupation: Physician

4. Initial reporter also sent report to FDA? ☒ yes ☐ no ☐ unk

FDA Form 3500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event

B5. Describe event or problem (cont'd)
possibility. She was treated with low molecular weight heparin. A colonoscopy performed three days after admission showed no signs of ischemia. Symptoms resolved and she was discharged from the hospital after five days.

B7. Other relevant history (cont'd)
innominate artery which resulted in bleeding into the right pleural space; many medication allergies; possible corproporphyria; hypertension; occasional dependent edema; endometriosis many years ago treated with radiation therapy; during workup for possible gallbladder disease nine years ago, an echo of the kidney revealed carcinoma in situ; cholecystectomy 1998; appendectomy in past; no CHF, no history of infarcts; no rectal bleeding.

B7. Other relevant history (cont'd)

Condition	Started	Ended	Continuing
Carcinoma in situ	1991	Unknown	Unknown
Perforation of sigmoid colon	1992	Unknown	No
Iron deficiency anemia	1992	Unknown	Unknown
Colostomy placement	1992	Unknown	No
Colostomy reversal	1992	Unknown	No
Intraoperative artery laceration	1992	Unknown	No
IBS	1998	Unknown	Yes
Surgical removal of gall bladder (cholec	1998	Unknown	No
Diarrhea	Unknown	Unknown	Unknown
Constipation	Unknown	Unknown	Unknown
Drug allergy	Unknown	Unknown	Unknown
Porphyria	Unknown	Unknown	Unknown
Hypertension	Unknown	Unknown	Unknown
Dependent edema	Unknown	Unknown	Yes
Endometriosis	Unknown	Unknown	No
Radiation therapy	Unknown	Unknown	No
Appendectomy	Unknown	Unknown	No

C10. Concomitant medical products (cont'd)

Amlodipine	UNK
Diuretic	UNK

G8. Adverse event term(s) (cont'd)
Incontinence of feces
Decreased hematocrit
Erythrocytopenia
Elevated ST segment

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Glaxo Wellcome

Mfr report # A0120697A

User/Dist report #

FDA Use Only

A. Patient information

1 Patient identifier	2 Age at time of event: 34Y or Date of birth UNK	3 Sex ☐ female ☒ male ☐ unknown	4. Weight (lb) UNK
In confidence			

B. Adverse event or product problem

1 ☒ Adverse event and/or ☐ Product problem

2 Outcomes attributed to adverse event (check all that apply)

☐ death ☐ disability
☐ life-threatening ☐ congenital anomaly
☐ hospitalization - initial or prolonged ☐ required intervention to prevent permanent impairment/damage
☐ other

3 Date of event: May2000

4 Date of this report: 09Jun2000

5. Describe event or problem

DESK COPY

A 34 year old male reported that he received alosetron (Lotronex) tablets for approximately two months and developed severe headache and nausea. After three days of enduring these symptoms, he presented to his physician who diagnosed him with a bacterial infection. He was prescribed antibiotics, anti-nausea medication, and painkillers. Upon taking his first dose of these medications, the patient vomited. He discontinued alosetron. The following day, when his symptoms persisted, he presented to the emergency room. He was admitted and given intravenous fluids and an empirical regimen of antibiotics. Subsequently he was diagnosed with viral spinal meningitis. He was discharged to home after three days. He stated that he feels better but has not completely recovered. The reporter did not consider that the meningitis was related to the use of alosetron.

6 Relevant tests/laboratory data, including dates

UNK

7. Other relevant history, including preexisting medical conditions (eg allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

See attachment

C. Suspect medication(s)

1 Name (give labeled strength & mfr/labeler, if known)

#1 Lotronex Tablet (Alosetron hydrochloride)

#2

2. Dose / frequency / route used

#1 1 mg / Twice per day / Oral

#2

3. Therapy dates

#1 Mar00 - 11May00

#2

4 Diagnosis for use (indication)

#1 Irritable bowel syndrome

#2

5. Event abated after use stopped or dose reduced

#1 ☒ yes ☐ no ☐ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

6 Lot # (if known)

#1 None

#2

7. Exp. date (if known)

#1

#2

8 Event reappeared after reintroduction

#1 ☐ yes ☐ no ☒ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

10 Concomitant medical products and therapy dates (exclude treatment of event)

No concurrent medication UNK

G. All manufacturers

1. Contact office - name/address

Glaxo Wellcome
North American Product Surveillance
PO Box 13398
Research Triangle Park
NC 27709

2. Phone number 1-888-825-5249 ext. 37070

3. Report source

☐ foreign ☐ study ☐ literature ☒ consumer ☐ health professional ☐ user facility ☐ company representative ☐ distributor ☐ other.

4. Date received by manufacturer: 18May2000

5. (A)NDA # 21-107 IND # PLA #

pre-1938 ☐ yes

OTC product ☐ yes

6. If IND, protocol #

7. Type of report

☐ 5-day ☒ 15-day ☐ 10-day ☐ periodic ☒ initial ☐ follow-up #

8 Adverse event term(s)

Viral meningitis
Headache
Nausea
Vomiting

9. Mfr. report number: A0120697A

E. Initial Reporter

1. Name, address & phone #

2 Health professional? ☐ yes ☒ no

3. Occupation: UNK

4. Initial reporter also sent report to FDA? ☐ yes ☐ no ☒ unk

FDA Form 3500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event

B7. Other relevant history (cont'd)

Condition	Started	Ended	Continuing
Irritable bowel syndrome	Unknown	Unknown	Yes

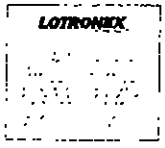
Appendix A-1

Appropriate Use Program

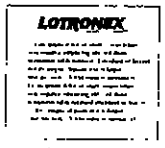
PATIENTS

Phase 1

Figure 2.



Prescribing Information



Patient Package Insert

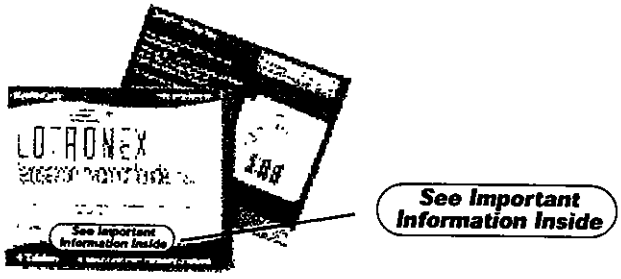


Figure 1.
Sample Pack

Figure 3.
"Important Information" Card

Appendix A-1

Appropriate Use Program

PATIENTS

Phase 2

(Precise packaging to be determined)

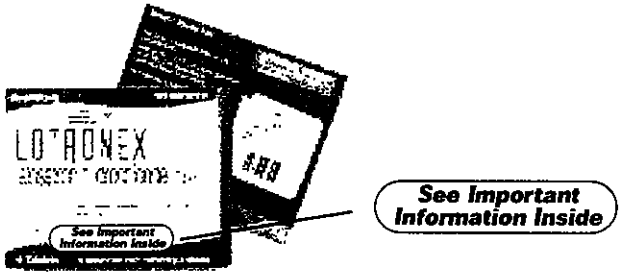


Figure 1.
Sample Pack

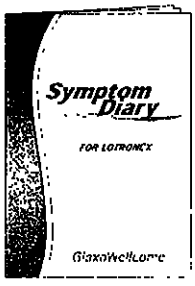


Figure 7.
Symptom Diary

Figure 6.
Magnet

Figure 5.
Patient Brochure

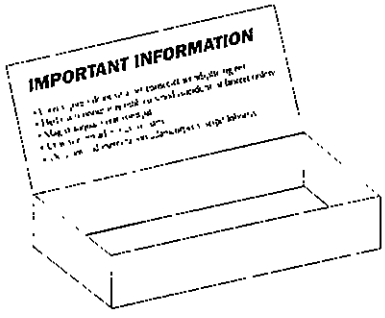
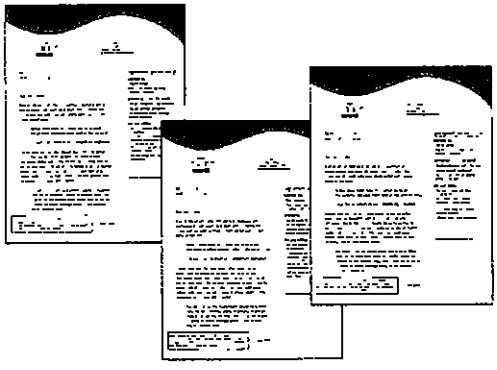


Figure 4. Patient Starter Kit

Figure 8.
Business Reply Card



Direct-to-Consumer Mailings
[See following page]

Newsletter

A-1

(Referenced in Figure 8)

LOTRONEX®
(alosetron HCl)

Joan Q. Public
1234 Main Street
Pleasant Heights IL 60301

Brevi vel toto
est iunior anno.

Dear Joan Q. Public,

Brevi vel toto est iunior anno. Utor permisso, caudaeque pilos ut equinae paulatim vello unum, demo etiam unum. Si meliora dies, ut vina poemata reddit scire velim, chartis perficit quotus pretium quotus arroget annus.

Scriptor abhinc recdit misso annos centum qui decidit
inter perfectos veteresque referri debet an inter perfectos novos?

PLAUTUS AD EXEMPLAR SICULI PROPERARE EPICHARMI

Excludat iurgia finis. "Est vetus atque probus, centum qui perficit annos." Quid, qui deperiit minis perfectos anno mense vel anno? "Iste quidem veteres inter ponetur honeste, qui vel mense brevi vel toto est iunior anno." Utor permisso, caudaeque nisi pilos ut equinae paulatim vello et virtutem, demo etiam unum, dum cadat elusus ratione ruentis acervi, qui redit in fastos et virtutem aestimat annis miraturque nihil nisi quod Libitina sacravit.

Hos ediscit et hos arto stipatus theatro spectat Roma potens,
habet hos numeratque poetas ac ambigitur tempus iam
scriptoris ab aevo. Interdum volgus rectum videt, est ubi peccat.
Si veteres ita miratur laudatque poetas ut nihil anteferat
nihil illis comparet, errat.

IMPORTANT INFORMATION

Lotronex is...

- Only for women
- Only for you if your main bowel symptom is diarrhea

Lotronex is NOT for you if:

- You are constipated most of the time
- You are currently constipated
- You have had a serious intestinal problem in the past

For your safety...

- The most common side effect is constipation. In rare cases, constipation resulted in a serious intestinal problem. Call your doctor if you become constipated.
- If you experience a new or sudden worsening of abdominal pain or if you see blood in the stool, this may be a sign of a serious intestinal problem. Stop taking Lotronex and call your doctor right away.

* More than three bowel movements per week

Pending Labeling Revision

Letter will reinforce the appropriate patient selection and side effect information via the call out box on the right hand side. Final letter to be cleared by DDMAC.

(over please)

A-1

(Referenced in Figure 8)

Ennius et sagines et fortis et alter Homerus, ut critici dicunt leviter curare vicetur, quo promissa cadant et somnia Pythagorea

Naevius in manibus non est et sanctum mentibus haeret paene recens? Adeo sanctum est vetus omne poema. Ambigitur quotiens, uter utro sit prior, aufert Pacuvius docti famam senis Accius alti, dicitur Afrani toga convenisse Menandro, Plautus ad exemplar Siculi properare Epicharmi. Si quaedam nimis antique, si peraque dure dicere credit eos ignave multa fatetur, et sapit et mecum facit et Iova iudicat aequo

BREVI VEL TOTO EST IUNIOR ANNO

Non equidem insector delendave carmina Livi esse reor, sed emendata videri pulchraque et exactis minimum distantia miror

Inter quae verbum emicuit si forte decorum, et si versus paulo concinnior unus et alter, iniuste totum ducit venditque poema indignor quicquam reprehendi, non quia crasse compositum illepedeve putetur, sed quia nuper, nec veniam antiquis sed honorem et praemia posci

Sincerely,

Eric Carter, MD
International Therapeutic Director
GI/Metabolic

PS: Our Web site – www.ibscentral.com – is also an excellent source of information on IBS and its management

Please see accompanying Important Product Information

Letter will reinforce the appropriate patient selection and side effect information via the call out box on the right hand side. Final letter to be cleared by DDMAC.

GlaxoWellcome

Appendix A-2

Appropriate Use Program

PHYSICIAN AND OFFICE STAFF

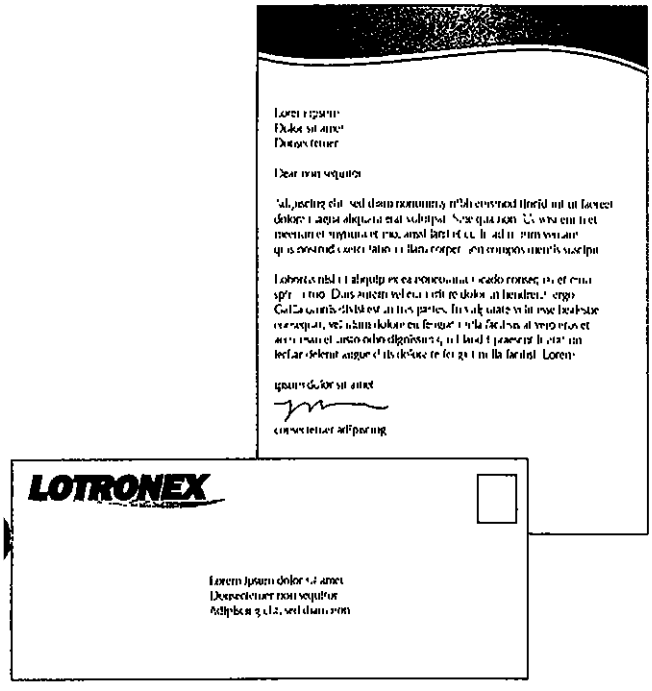


Figure 9. Health Care Practitioner Letter

Figure 10.
Patient Selection Card

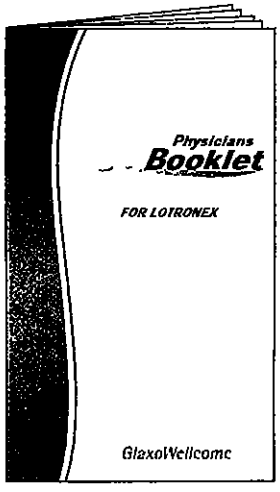


Figure 11.
Physician Booklet

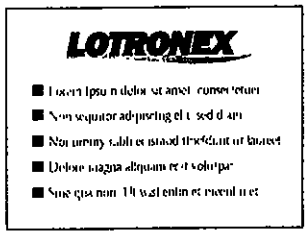


Figure 12.
Frequently Asked Questions

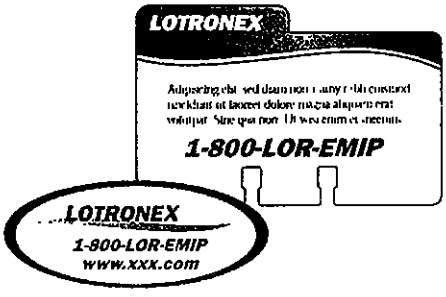


Figure 13.
Rolodex Card/Magnet

Appendix A-3

Appropriate Use Program

PHARMACISTS

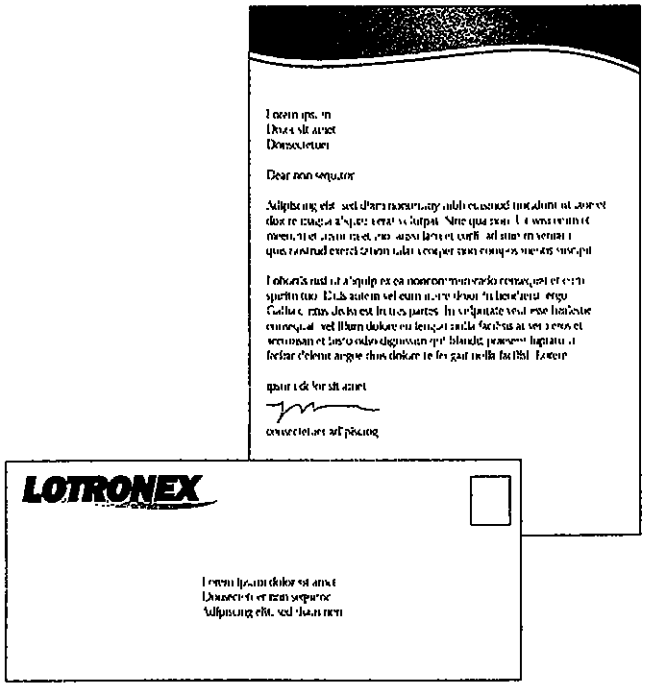
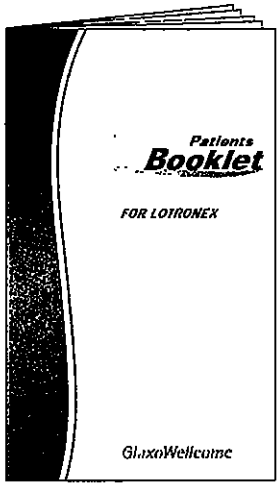


Figure 14.
Pharmacist Letter



Patient Brochure

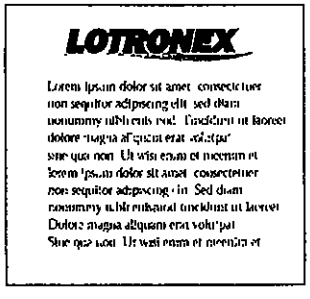


Figure 15.
Patient Package Insert

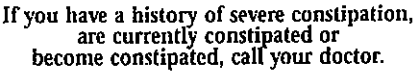
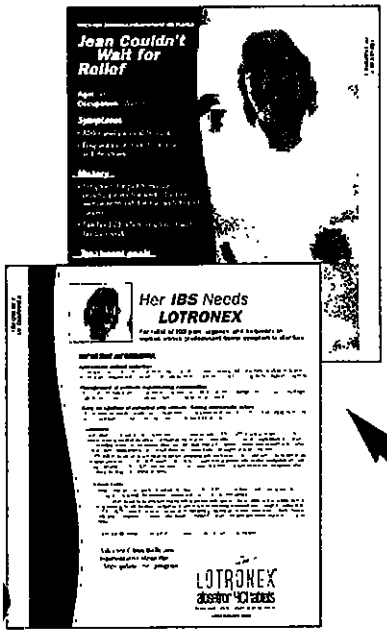


Figure 16.
Prescription Bottle Sticker

Appendix A-4

KEY MESSAGE PLACEMENT



Visual Aid

Sales Brochure

IMPORTANT INFORMATION

Appropriate patient selection

Lorem ipsum dolor sit amet, consectetuer adipiscing elit, sed diam nonummy nibh euismod tincidunt ut laoreet dolore magna aliquam erat volutpat. Ut wisi ullamcorper suscipit lobortis nisl ut aliquip ex ea commodo consequat

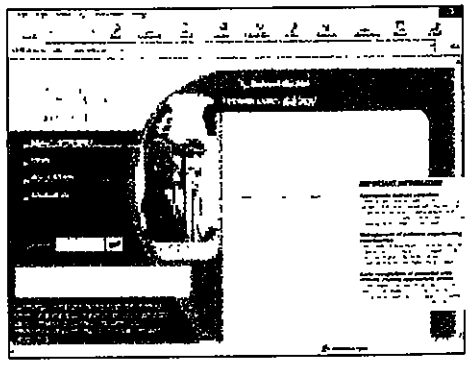
Management of patients experiencing constipation

Duis autem vel eum iriure dolor in hendrerit in vulputate velit esse molestie consequat, vel illum dolore eu feugiat nulla facilisis at vero eros et accumsan et iusto odio dignissim qui blandi.

Early recognition of potential side effects/taking appropriate action

Ut wisi enim ad minim veniam, quis nostrud exerci tation ullamcorper suscipit lobortis nisl ut aliquip ex ea commodo consequat.

Post-Launch Ad



Web Page