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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S NEW DRUG APPLICATION (NDA) SAFETY REVIEW

NDA:	21-107, 90-day safety update
APPLICANT:	GlaxoWellcome, Five Moore Drive, P.O. Box 13398 Research Triangle Park, North Carolina 27709
DATE OF SUBMISSION:	24 September 1999
DRUG:	Alosetron hydrochloride (LOTRONEX™, GR68755) tablets 1 mg
ADMINISTRATION:	The applicant proposes to administer oral tablets, 1 mg twice daily for up to 12 weeks, with or without food, for treating women over 17 years of age with irritable bowel syndrome (IBS) who are non-constipated
INDICATIONS:	Treatment of irritable bowel syndrome (IBS) in female patients with diarrhea predominance.
MATERIAL REVIEWED:	Seven volumes, including revised labeling and 90-day safety update of the Integrated Summary of Safety (2 volumes), and the second interim report to 23 July 1999 of the year-long study S3BA3003 (5 volumes); pertinent other information and literature references.
REVIEWER:	John R. Senior, M.D./ 30 November 1999

Brief Summary of Key Safety Issues Identified in this Review

This clinical safety update is based primarily on data gathered from two dose ranging studies in 238 men and 593 women with the irritable bowel syndrome (IBS) and two principal clinical efficacy trials in 1273 women with non-constipated forms of IBS comparing alosetron 1 mg b.i.d. with placebo for 12 weeks. The dose ranging studies S3BP12 and S3BA2001 explored the range of b.i.d. dosing for 12 weeks from 0.1, 0.5, 1.0, 2.0, and 4 to 8 mg, and concluded that the dose of 1 mg b.i.d for women only was significantly effective. These finding led to the design of two identical clinical efficacy and safety studies of 626 and 647 women with IBS and average stool consistency that was not hard in studies S3BA3001 and S3BA3002, randomizing them to alosetron 1 mg b.i.d. or to placebo in each study. Significantly more patients on alosetron than on placebo in each study reported adequate relief of IBS-related abdominal discomfort or pain, and additional benefits included reduction of urgency to defecate and frequency of stooling.

The major adverse effect was constipation, seen in both genders quite commonly (about 27% of 702 patients) at the dose of 1 mg b.i.d., very significantly greater than the 5% of 834 on placebo. Further the constipation was dose-related, and was the most frequent cause for patients to withdraw from the study.

An uncommon but serious adverse event was occurrence of ischemic colitis in three Caucasian women 33, 41, and 48 years of age, manifested by crampy abdominal pain and rectal bleeding, with patchy sloughing of colonic mucosa at colonoscopy, no other lesion, and absence of inflammation by mucosal biopsy. None of them had any underlying blood clotting abnormalities, vascular disease, or circulatory events preceding the onset of the syndrome at 2 days, 8 weeks, and 3 weeks after starting alosetron in the dose-ranging S3BA2001 study and the clinical studies S3BA3001 and S3BA3002. In these three studies, 91 men and 199 women were exposed to alosetron in S3BP12, 309 and 322 women in studies S3BA3001 and S3BA3002. This represented a total incidence of 3/921 or 0.33%, for which the upper bound of the 95% confidence interval was close to 1 %. In the first interim report on a year-long study of alosetron at the same daily dose of 1 mg b.i.d. (S3BA3003), seven addition adverse event reports of rectal bleeding unexplained by hemorrhoids or menses or other cause were seen among the 542 patients in the alosetron group but none in the 175 placebo-treated patients; none of these cases was diagnosed as having ischemic colitis, but they were not further investigated. None of the three cases of ischemic colitis was life-threatening, none involved bowel infarction, and all resolved after discontinuation of alosetron. None were rechallenged.

One case of apparent alosetron-induced hepatotoxicity, with serum transaminase and total bilirubin elevations, was seen in a 33-year-old Caucasian woman after 22 days on alosetron in Study S3BA3001. The abnormalities disappeared after alosetron was stopped; no rechallenge was done. This event was considered rare, and no other cases were seen in the other three main clinical studies involving a total of 1266 patients on alosetron. No information was reported on this adverse event in the year-long study's first interim report.

Alosetron did not appear to cause prolongation of the electrocardiographic QT interval, nor was it associated with an increase in cardiac arrhythmias beyond the rare events seen in the placebo-treated patients.

Safety issues raised by these studies of the new chemical entity alosetron, a serotonin receptor type 3 antagonist, include the following:

1. How the frequent adverse effect of constipation should be interpreted, studied further, and labeled for instructions to physicians as to a regimen of administration to obtain benefits of abdominal pain reduction in IBS without causing excessive or symptomatic constipation.

2. Whether alosetron truly does cause ischemic colitis in some patients with IBS, and if so at what incidence rate, in patients with what predisposing factors and whether ischemic colitis can be proved to have occurred, and can be predicted by surrogate markers, mechanism of effect, whether milder "formes frustres" syndromes occur that may not be diagnosed as ischemic colitis, and whether severe cases of bowel infarction/gangrene may occur in some patients and be life-threatening or require resection.

3. Whether the single case of ALT, AST and bilirubin elevation seen in S3BA3001 was truly caused by alosetron, and what should be done about it (looking for more cases), assuming that this represents 1 in about 1266 patients exposed to alosetron for up to 12 weeks..

4. Should a prospective, large (3000-5000 patient cohort, observed and reported monthly on treatment) but simple study be required post-marketing as a condition of approval, looking for ischemic colitis by symptoms of unexplained rectal bleeding with abdominal pain or constipation (and monitoring ALTs) during clinical use? Should a control group be treated with an approved anti-diarrheal agent such as loperamide (Imodium, Janssen)? This could provide a denominator and reliable numerators for better estimation of the true risks of ischemic colitis (and also of drug-induced hepatotoxicity), and perhaps better ways to predict and avoid the problems.

5. Is alosetron working mainly as an anti-diarrheal agent, since it does not produce significant increment of benefit in reducing average pain/discomfort scores, even though it provides "adequate relief" to more women, some of which may be relief of the inconveniences of the diarrheal effects, urgency, disruption of life, etc.

6. If so, is the gain in benefit (over placebo) to some patients worth the risk of ischemic colitis to a few patients? How can this adverse event be recognized, how prevented, how explained?

7. There is probably no clinically significant incremental risk of cardiac arrhythmias/QT prolongation or deafness, as shown by the special studies done.

8. Much has been learned, but new questions now arise. The use of the telephone data entry system for daily capture of information about pain severity, stool frequency and description, other symptoms is innovative. The data bases thus generated need to be integrated with more conventional case reports for individual patients.

Table of Contents

I. Introduction

A. Approach to the review and conventions used

The reviewer has approached this submission by focusing first upon what the sponsor has requested in the proposed labeling, and listing what evidence has been submitted in support of that request. The title page shows the sponsor, the drug product, dates of submission and review, and materials reviewed. Immediately following is a boxed, concise, half-page summary of the key issues identified in the review, to provide the reader with a concise preliminary picture of the study purposes, context, emerging issues identified, major findings and conclusions, evaluation and regulatory recommendations developed in the text . The organization of the review and a road map to its sections in a Table of Contents follows, and that is immediately followed by this explanation of the process used to approach the information submitted in the clinical sections of the 336 volumes (and electronic submissions).

The convention used in the review, to distinguish between the applicant's **submitted** data or interpretations from the reviewer's **abstracting, paraphrasing, or summarization** of the submitted material, and from **reviewer-generated opinions** and discussion, and from pertinent literature beyond the content of the submission, was to use typeface variants:

– Text taken directly from that submitted by the applicant is shown in quotes, and tables or figures copied from the submitted material were noted "As submitted in Volume ___, page ___."
– Material summarized by the reviewer from that submitted by the sponsor is shown in plain 12-point Times New Roman font, with references to Volume and page numbers in the submitted material.
– *Commentary, opinion, discussion by the reviewer about the submitted material or about the literature or other sources (cited, wherever possible) was shown in 12-point italic Times New Roman font.*
– Material provided by the reviewer in explanation of the approach taken to review, or taken from other sources, whether pertinent literature or other regulatory material, shown in 11-point font;
– **Words, phrases, or sentences believed to be of particular importance, as identified by the reviewer, are bolded.**

Sections of the review are numbered and paginated as shown in the Table of Contents. These correspond in general with the "Guideline for the Format and Content of the Clinical and Statistical Sections of an Application," published in July 1988 by the Center for Drug Evaluation and Research of the Food and Drug Administration.

In this particular clinical safety review, the principal data submitted were from two identical major clinical trials, comprising 1273 randomized participants, according to the applicant's cover letter (Volume 1 of 336). Supporting material included data from preliminary clinical trials, clinical pharmacology studies and animal toxicology studies. The principal focus of this medical review is on the safety of the drug in its intended dose and regimen; efficacy review is being carried out by Dr. Robert Prizont (in a separate clinical efficacy review).

B. Labeling requested

The applicant has provided a statement of proposed labeling, based upon their conclusions about the studies done, as follows (Vol. 1. Pages 26-46):

LOTRONEX® (alosetron hydrochloride) Tablets, 1 mg, for oral administration are indicated for **"the treatment of irritable bowel syndrome (IBS) in female patients with diarrhea predominance."** The recommended dose for adult women at least 18 years of age is **"1 mg taken orally twice daily with or without food."** Based on the partial study report for ongoing Study S3BA3003 (Vol. 205, pages 1-60, and Vol. 209, page 143), the applicant claims that **"Safety of continuous treatment has been established in females and males for period up to 6 months."**

Comment: The

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III. Clinical Study Safety Results

A. Primary Safety Database

The proposed dose of alosetron is 1 mg b.i.d. for 12 weeks in adult women with non-constipated IBS. The studies that provide the most pertinent safety data on this regimen comprise the three U.S. studies S3BA2001, a dose-ranging study involving both men and women, and two identical phase III studies, S3BA3001 AND S3BA3002 that involved only women. In addition, the U.K. study S3B-P12 of men and women on 2 mg alosetron b.i.d. for 12 weeks is of interest for comparison of the effects of the higher dose. Partial results are also available for the U.S. study S3BA3003 of men and women on 1 mg b.i.d. for a year.

Long-Term, Placebo-Controlled Alosetron Studies

Study started-ended	Sites	P M/F	A 0.1 M/F	A 0.5 M/F	A 1.0 M/F	A 2.0 M/F	A 4.0 M/F	A 8.0 M/F	*Total M/F*	Duration
S3B-P12 Jul'93-Sep'94	43 Eur	33/84	38/77	31/85		25/89			127/ 335	12 weeks
S3BA2001 Oct'95-Dec'96	71 U.S.	21/59			18/54	23/51	21/54	28/40	111/ 258	12 weeks
S3BA3001 Sep'97-Dec'98	112 U.S.	0/317			0/309				0/626	12 weeks
S3BA3002. Sep'97-Oct'98	120 U.S.	0/323			0/324				0/647	12 weeks
Subtotal, 12-week studies		54/ 783	38/ 77	31/ 85	18/ 687	48/ 140	21/ 54	28/ 40	238/ 1866	
S3BA3003* Nov'97-Feb'99	131 U.S.	46/ 129			175/ 378				221/ 507	12 months

*Note: Doses b.i.d.: P, placebo; A 0.1 to 8.0, alosetron 0.1 to 8.0 mg. M/F, males, females; *, partial report as of 26 Feb'99 on 728 of 859 patients entered by 25 Sep'98.*

The "primary safety database" identified by the applicant comprised 1263 patients (184 men, 1079 women) who received alosetron, and 834 (54 men, 780 women) who received placebo for up to 12 weeks in the four clinical studies listed above. Studies S3BP12 and S3BA2001, were dose-ranging studies (from 0.1 to 8.0 mg b.i.d.) that included some men; studies (S3BA3001 and S3BA3002) were done in women only, comparing alosetron 1 mg to placebo b.i.d.

Table 8.10: Demographic Characteristics of Patients in the Primary Safety Database (Studies S3BP12, S3BA2001, S3BA3001 and S3BA3002) ***[Vol. 1, page 402]***

	Placebo n = 834	A 0.1 n = 115	A 0.5 n = 116	A 1.0 n = 702	A 2.0 n = 187	A 4.0 n = 75	A 8.0 n = 68	Total A n= 1263
Gender: M/F % M/F	54/780 6/94%	38/77 3/67%	31/85 27/73%	18/684 3/97%	48/139 26/74%	21/54 28/72%	28/40 41/59%	184/1079 15/85%
Age: m ± sd (range)	45 ± 0.5 (18-63)	42 ± 1.2 (18-70)	45 ± 1.3 (18-74)	46 ± 0.5 (18-82)	44 ± 1.0 (18-77)	44 ± 1.4 (20-71)	45 ± 1.4 (20-93)	45 ± 1.1 (18-93)
Race: w/b/o % w/b/o	763/51/20 91/6/2%	112/2/1 97/2/1%	113/2/1 97/2/1%	635/28/39 90/28/39%	177/6/4 95/3/2%	72/2/1 97/2/1%	63/0/5 99/0/7%	1172/40/51 93/3/4%

Note: Note: Doses b.i.d.: Placebo; A 0.1 to 8.0, alosetron 0.1 to 8.0 mg; M/F, numbers of males, females; m ± sd, mean ± standard deviation; w/b/o, white/black/other.

1. On-going Domestic studies: placebo-controlled, 1-year duration

Two additional long term studies have been started in the United States, one of which has completed enrollment of 637 women and 222 men in September 1998 and an interim report is provided (S3BA3003). The other study (S3B30006) has only been underway for 9 months and enrollment is not completed.

Study S3B30006 was started at 93 centers in the United States and Canada in December 1998, where it is planned to enroll 600 women with non-constipation-prone IBS for 48 weeks for treatment on either alosetron 1 mg b.i.d. or placebo; it is scheduled to be completed in December 2000. A report is scheduled for April 2001.

Study S3BA3003 was initiated in November 1997 at 130 sites where 859 adults (637 women and 222 men) were randomized as of 25 September 1998, when enrollment was closed. A partial report is provided, dated 30 April 1999 for partial data up to end-February, for 728 patients (507 women, 221 men). Of these, 411/728 (56%) had been treated for at least 6 months, and 19 (3%) for a year. The interim report addresses only safety issues, and is focussed on long-term alosetron effects of electrocardiograms (ECGs) and audiograms. Data for 131 patients (130 women and 1 man) have not yet been reported at all, and the last patient entered will complete treatment in September 1999. A second interim report was received 27 September, and will be reviewed with the four-month safety update submitted at the same time.

Study S3BA3003 (Volume 206, pages 2-122) was begun on 30 September 1997, and is designed to extend the period of treatment and observation of alosetron 1 mg b.i.d. and placebo from 12 weeks to an additional 12 months, in approximately 600 women and 160 men with non-constipation-predominant IBS at 250 centers, mainly derived from patients who had completed studies S3BA3001 and S3BA3002. The protocol called for gender-stratified re-randomization in 3:1 ratio to alosetron:placebo. Thus, 450 women and 120 men would be studied on a dose of

alosetron 1 mg b.i.d. for up to about 15 months, compared to 150 women and 40 men on placebo, depending on randomization. The principal safety concerns were reflected in the special measurements to be made of electrocardiograms (ECGs), pure tone audiograms (PTAs), and certain laboratory tests (blood cell counts; serum electrolytes, liver enzymes [alanine and aspartate aminotransferase, alkaline phosphatase], total bilirubin, protein, albumin, calcium, phosphorus, creatinine, urea nitrogen), in addition to adverse events in general. Also planned were evaluations of changes in quality-of-life (by questionnaires) and secondarily for resource utilization (questionnaire). The reasons cited (Volume 206, page 12) for special concerns about ECGs and PTAs were the history of ECG QT prolongation by certain agents affecting serotonin receptors (especially cisapride, a 5-HT_4 agonist) and the findings in rats of decreased ear twitch reflex response to noise (Preyer test) and in dogs (BAER test).

The study size was based on assuming a 25% improvement in proportion of female patients reporting differences in quality-of-life parameters (unspecified) in the alosetron-treated compared to the placebo-treated women, at α=0.05 two-sided and power of 80%, allowing for 40% dropouts. This study size was also believed to fulfill requirements for number of patients exposed long-term to a new chemical entity, and estimated to be able to detect with 86% power a 10% increase in any AEs occurring in men and women completing study on alosetron, compared to a base rate of 10% in those completing study on placebo. An interim safety analysis of ECGs, PTAs, laboratory data, and AEs was planned when 400 patients had been treated for 6 months, with no provisions to discontinue study, partition interim α to 0.0001, 0.0499 final analysis.

Male or female patients completing either of the 12-week studies S3BA3001 or –3002 and still meeting criteria for entry, or other female patients qualified by the same criteria were to be eligible to be re-randomized into the year-long study S3BA3003. Following the initial entry visit into the extension study, follow-up was planned at 2, 4, 6, 8, 10, and 12 months, with collection of data on AEs, concurrent medications, blood for laboratory tests, dispensing of medication and accountability for study drug used. The ECGs were to be repeated at 2 months, and the PTAs at 6 and 12 months (flow chart, Volume 206, page 10).

Amendments to the protocol were made as follows (Volume 202, pages 52-122):

1. 28 October 1997 — more pregnancy tests, liberalize contraceptive use, clarify exclusions;
2. 27 January 1998 — clarify test procedures for men, clarify ECG procedure, update primary contact for SAEs, revise prohibited medications list;
3. 4 March 1998 — revise inclusion criterion for women and prohibited drug list.
4. 11 March 1998 — re-order secondary objectives, refine statistical methods for the determination of multiple endpoints, add question;
5. 20 March 1998 — collect samples for genotyping;
6. 14 May 1998 — identify and organize QoL scales for statistical analysis;
7. 25 October 1998 — modify statistical methods for QoL endpoints.

As carried out, enrollment of patients into the study began in November 1997 and was completed 25 September 1998, comprising 637 women and 22 men, 859 persons in all. A somewhat different list of protocol amendments was provided in the interim report dated 30 April 1999, on data accumulated up to 26 February 1999. At that cut-off time, data for the interim analysis were

available for 728 of the randomized patients (507 women, 221 men) but not for 130 women and 1 man. The now-reported version of protocol amendments and changes indicated:

Amendments to Protocol S3BA3003 of 30 September 1997

number	date	
1	29Oct97	add pregnancy test at each visit; allow abstinence or male sterilization; modify exclusion criteria to exclude IBD, symptomatic gallstones, GI surgery/diseases, and symptomatic uncontrolled GERD, but allow history of laxative abuse
2	29Jan98	do medical histories and physical exam only on men; central interpretation of ECGs; modify SAE contact information; allow macrolide antibiotics
3	05Mar98	lower exclusionary stool consistency score to 2.0 from <2.5; exclude generic rifampins and all anticonvulsants, redefine anticholinergics and cholinomimetics
4	02Jun98	revise roll-over procedures for patients from S3BA3001 and –3002; do histories and physical exams on women; exclude ondansetron, granisetron; identify and re-organize QoL scales for statistical analysis
5	06Nov98	modify statistical methods for QoL endpoints
6	26Jan99	further refine multiple QoL endpoint analyses; add second interim safety analysis

Comment: The amendments to the protocol were not always explained clearly, as to why the changes were being made. Some of them seem quite reasonable, others not. It is disturbing that the serious consideration of how to analyze quality-of-life data was not undertaken until the study was well along and even after enrollment was completed, when it was the primary endpoint on which study size was estimated in the original protocol.

The interim report of 30 April 1999 on partial results of S3BA3003 (Volume 205, pages 41-60) is focussed on safety issues, and does not address long-term efficacy or analysis of satisfaction with treatment or other QoL issues. It is stated that 76%, 553 of the 728 reported, were randomized to alosetron, 24% (175/728) to placebo. With respect to duration of exposure to study drug, 56%, 411 of the 728 reported upon, were treated for at least 6 months and were still on study (110/175 on placebo, 301/553 on alosetron); an additional 19 of the 728 had completed a year on drug, 4 on placebo and 15 on alosetron. Adding the 411 in their second half year of treatment and the 131 not yet reported, 542 patients were continuing on the study as of the interim analysis.

Premature withdrawals from the study were observed in 298/728 (41%), most within the first 6 months (225/728, 31%), and more in the alosetron-treated patients (237/553, 43%) than in the placebo-treated patients (61/175, 35%). Of those leaving the study in the first 6 months, again there were relatively more in the alosetron (179/553, 32%) than placebo (46/175, 26%) group. Fewer patients in both treatment groups left the study in the second half-year of study, <3% in each group (alosetron 14/553, 2.5%; placebo 5/175, 2.9%). However, the time of withdrawal was not known for 54/728 (7%), 44/553 (8.0%) on alosetron and 10/175 (5.7%) on placebo. Again, the principal difference in withdrawals was adverse effects, especially constipation, in alosetron-treated patients. The safety subset of the 728 patients in the interim analyses excludes 11 patients randomized to alosetron who did not take any study drug, reducing the number to 717.

Comment: The dropout rate of 41% is close to the predicted 40% projected in the protocol, and the interim subset ratio of 76% on alosetron to 24% on placebo fits well with the 3:1 ratio of the re-randomization. The 728 patients in the interim analysis constitute a rather large subsample of

the 859 randomized into the study (85%), and the data may be reasonably predictive of the final analyses of results to come in the conclusive report prepared after the last patient completes a year of study in late September 1999 and the data are re-analyzed and report written.

Disposition of Patients in S3BA3003 (Interim Analysis)

	placebo	alosetron	p value	total
Randomized women/men				859 637/222
No data yet women/men				131 (↑15%) 130/001
Interim Analysis women/men	**175 (→24%)** **129/46**	**553 (→76%)** **378/175**		**728 (↑85%)** **507/221**
Completed 6 mos	110 (↑63%)	301 (↑54%)	N.S.	411 (↑56%)
Completed 1 year	4 (↑2%)	15 (↑3%)	N.S.	19 (↑3%)
Withdrawn	61 (↑35%)	237 (↑43%)	N.S.	298 (↑41%)
adverse event	**18 (↑10.3%)**	**129 (↑23.3%)**	**p <0.0002**	**147 (↑20.2%)**
death	0	2		2
pregnancy	0	2		2
consent withdrawn	13 (↑7.4%)	43 (↑7.8%)	N.S.	56 (↑7.7%)
lost to follow-up	8 (↑4.6%)	22 (↑4.0%)	N.S.	30 (↑4.1%)
lack of efficacy	**18 (↑10.3%)**	**20 (↑3.6%)**	**p <0.001**	**38 (↑5.2%)**
other reasons	4 (↑2.3%)	23 (↑4.2%)	N.S.	27 (↑3.7%)
moved away	1	2		3
medically unstable	0	1		1
protocol violation	2	5		7
sponsor action‡	1	5		6
non-compliance	0	5		5
abnormal lab test	0	2		2
ova/parasites	0	2		2
unknown	0	1		1
Took no study drug	0	-11		-11
Safety subset	**175**	**542**		**717**

Comment: In this interim analysis, the proportions randomized to the two treatments and the rate of dropout were close to estimated rates in the protocol. The significant differences between treatment groups were in greater proportion withdrawn for adverse events in the alosetron-treated patients and in greater proportion of placebo-treated patients withdrawing for lack of efficacy. In this partial analysis, the significant disparity observed in S3BA3001 for higher proportions of alosetron-treated patients withdrawn for the vague reasons of "consent withdrawn" and "lost to follow-up" was not seen. Included in adverse events were the two deaths (#10209 and 11950) and two pregnancies (#10256 and 10324) in the alosetron-treated group, for all of whom study blind was broken; these cases are described in more detail below.

Five of the 6 study participants (all on alosetron) withdrawn by sponsor action were at the site of investigator #49840, at which problems with study documentation and site management were discovered by monitoring staff (Volume 205, page 42). The investigator did not comply with attempts to correct these deviations, and the site was closed. The patients (#11968, 11971, 11972, 11973, 11974) completed final visit procedures; study drugs were returned. The sixth participant

(#8347) withdrawn by sponsor action was actually for a serious adverse event, diverticulitis, that the investigator (#3508) believed was reasonably possible to have been caused by study drug, and the drug blind was broken (alosetron).

Deaths: Two patients of the 542 who had taken alosetron in this study up to February 1999 died of sudden cardiac events; none of the 175 on placebo died. Both deaths were attributed to heart and vascular disease that long preceded the entry of the two patients into the study.

Study participant #11950, a patient of investigator #4814, was a 50-year-old Caucasian woman with a history of hypertension, carotid stenosis, hyperthyroidism, light cigarette smoking (105 per day for 35 years), and overweight (body mass index: 28.6 kg/m^2). She had previously participated in Study S3BA3001 as subject #4579, then started alosetron 16 July 1998 in S3BA3003. She developed sudden and fatal cardiac arrhythmia on 11 January 1999, on the 180^{th} day of treatment. Autopsy showed severe atherosclerotic cardiovascular disease and biventricular dilation. Her death was attributed to her vascular disease and was considered unrelated to study drug.

Study participant #10209, a patient of investigator #49963, was a 54-year-old Caucasian man with a history of hypertension and anginal chest pain, body mass index: 27.3 kg/m^2. He started alosetron on 5 June 1998, then presented at an emergency room on 10 February with nausea, shortness of breath, indigestion, and dull mid-clavicular pain. An ECG showed no abnormality, and he was referred to his physician for evaluation, but was brought back to the emergency room the next day in a state of cardiac arrest from which he could not be resuscitated. The investigator attributed his death to underlying cardiovascular disease, and considered it unrelated to his 252 days of alosetron treatment.

Pregnancies: Two women of the 378 who were randomized to alosetron became pregnant while on study; none did so in the smaller placebo group of 129 women.

Subject #10256, a 21-year-old woman, became pregnant despite taking Ortho-Novum, and was withdrawn from study. Her pregnancy was continuing at the time of reporting.

Subject #10324, a 35-year-old woman, discovered she was pregnant after 28 weeks on alosetron, stopped the drug, and had an uncomplicated elective termination of her pregnancy.

Serious Adverse Events:

There were 28 serious adverse events (SAEs) reported up to time of the cutoff date of 29 January 1999 (Volume 205, pages 50-3), 11/175 (6.3%) in placebo-treated patients and 17/542 (3.1%) in alosetron-treated patients. Some patients had more than one serious event (19 in the 11 patients on placebo, and 25 in the 17 patients on alosetron). The nature of these serious events (*indicates patient was withdrawn from study) were:

Serious Adverse Events, Study S3BA3003 Interim Report *(Vol. 205, pp 50-3, 240-376)*

Dose, mg b.i.d.	*Inv.:Patient no. & age/sex/race*	*Clinical Problem After __ days on study drug*	*Investigator's Opinion*
Placebo	05129:08342 M72c	Worsened angina pectoris after 51 days	unrelated
	50017:08487 F37c	Uterine prolapse after 53 days	unrelated
	01178:08528 F51b	Non-cardiac chest wall pain after 141 days	unrelated
	05241:08663 F55c	Chest pain syndrome after	unrelated
	04960:10049 F33h	Kidney stones after 96 days	unrelated
	02798:10099 M74c	Gallbladder stones after 61 days*	unrelated
	04989:10151 F75c	Worsened lumbar root pain after 87 days	unrelated
	00397:10225 F42c	Deep abscess left forearm after 90 days	unrelated
	50252:10416 M24c	Pancreatitis after 13 days*	caused by drug
Alosetron	06481:08165 M67c	Moderate dizziness and nausea after 142 days*	caused by drug
	50118:08331 M48c	Coronary artery disease symptoms 41 days	unrelated
	05129:08346 M52c	Torn left rotator cuff after 36 days	unrelated
	03508:08347 F68c	Diverticulitis after 73 days	caused by drug
	50017:08488 M61c	Severe vertigo and nausea after 11 days*	caused by drug
	04704:08503 F43c	Hepatic nodular hyperplasia after 43 days*	unrelated
	05734:08660 M68c	Prostate cancer after 56 days	unrelated
	03466:10017 F51c	Uterine fibroids after 41 days	unrelated
	49963:10209 M54c	Fatal cardiac arrhythmia, death after 252 days*	unrelated
	03726:10295 F59c	Open fracture left ankle after 44 days	unrelated
	05129:10594 F71c	Severe chest pain, edema after 78 days	unrelated
	04814:11950 F49c	Cardiac dysrhythmia after 180 days*	unrelated
	49826:11955 F33c	Post ERCP pain, vomiting after 15 days	unrelated
	42634:12138 F47c	Asthma, bronchitis after 154 days	unrelated
	42634:12149 M52c	Severe, worsened depression after 44 days*	unrelated

Note: Inv., Investigator; b.i.d., twice daily; M, male; F, female; c, Caucasian; b, Black; h, Hispanic.

Comment: The text on page 50 of Volume 205 states that there were four additional patients who had SAEs, two in each of the treatment groups. They were:

More Serious Adverse Events, Study S3BA3003 , Table 7.7 *(Vol. 205, pp 126-31)*

Dose, mg b.i.d.	*Inv.:Patient no. & age/sex/race*	*Clinical Problem After __ days on study drug*	*Investigator's Opinion (page)*
Placebo	03651:08397 F46c	Bronchitis, hypoxia after 197 days	Unrelated (128)
	03726:12134 F33c	Viral gastroenteritis after 9 days	Unrelated (127)
Alosetron	42816:08674 F38c	Epigastric pain, nausea after 155 days*	Unrelated (127)
	05129:08343 F58c	Cerebrovascular accident after 250 days	Unrelated (126)

Comment: There was no statistically significant difference in the proportions of patients with SAEs between the two treatment groups, with or without the 4 extra patients, although the percentages were actually numerically higher in those on placebo (9/175, 5.1%; or 11/175, 6.3%) than in those on alosetron (15/542, 2.8%; or 17/542, 3.1%). This cannot be taken to conclude that alosetron prevents SAEs.

The investigator's opinions about whether the SAEs were caused by or related to study drug in many cases were made before they broke the blind. In retrospect, it does not seem that placebo should "cause" pancreatitis (#50252:10416). On the other hand, the vertigo/dizziness and nausea that occurred in the two patients on alosetron was considered drug-induced (#06481:08165 and #50017:08488), as was the diverticulitis seen after 73 days in #03508:08347. The two patients who had the arrhythmias had prior histories of cardiac disease and had been on alosetron a long time (6 and 8 months) before the problems occurred, and their physicians did not attribute the arrhythmias to it. The woman with the hepatic mass (#04704:08503) had been on alosetron 43 days (unless she had previously been treated in either S3BA3001 or –3002), and it would seem unlikely that such a tissue reaction would develop that quickly if drug-induced. In the full report, it will be important to identify which of the patients in S3BA3003 had been on alosetron or placebo previously for 12 weeks in the earlier studies.

Listed as withdrawn for a non-serious AE in Table 7.5 (Volume 205, page 111) was patient #11951 (investigator #04814), a 56-year-old Caucasian woman who developed abdominal pain on the day after she started alosetron, then constipation two days later, severe abdominal pain and rectal bleeding on the sixth day of study treatment, and was withdrawn from the study without breaking the treatment blind. Her constipation and abdominal pain were attributed to study drug, but the bleeding was not, according to the copy of the case report provided on August 27th on electronic tape as a .pdf file. She was not studied further. It may be questioned whether the syndrome of abdominal pain, constipation, and rectal bleeding may have been manifestations of undiagnosed ischemic colitis, in view of the cases previously recognized in the controlled studies.

Adverse events for which patients were withdrawn are listed in Volume 205, pages 47-9, grouped in Table 7.4 (Volume 205, pages 95-7, and individual patients withdrawn because of adverse events are listed in Table 7.5, Volume 205, pages 98-123.

Adverse Events Causing Premature Withdrawal, S3BA3003

patients	Placebo BID n = 175	A 1 mg BID n = 542	Difference p-value
Withdrawn prematurely	61 (35%)	237 (43%)	N.S.
Any adverse event	**18 (10.3%)**	**129 (23.8%)**	**0.0001**
Gastrointestinal event	**13 (7.4%)**	**110 (20.3%)**	**< 0.0001**
constipation	**1 (0.6%)**	**88 (16.2%)**	**<< 0.0001**
all other gi events*	19 (10.9%)	59 (10.7%0	N.S.
Neurological event	5 (2.9%)	13 (2.4%)	N.S.
headache	2 (1.1%)	8 (1.5%)	N.S.
Cardiovascular event	0	3 (0.6%)	N.S.
arrhythmias	0	2 (0.4%)	N.S.
Malaise or fatigue	1 (0.6%)	2 (0.4 %)	N.S.
All other system AEs*	4 (2.3%)	26 (4.5%)	N.S.

*Note: BID, twice daily; A, alosetron; *, some patients had more than one AE.*

Comment: Again, very significant differences were found between treatment groups in the relative numbers of patients withdrawn from study because of adverse events, due almost entirely to gastrointestinal events and particularly if not entirely to constipation. These findings reconfirmed the findings made repeatedly before in the previous studies.

It is recognized that it is very difficult to be completely consistent in assessing whether or not an adverse event is serious enough to hospitalize a patient, investigate further, make reliable attributions of the causes of AEs, decide whether or not to withdraw patients from study, and other classifications of adverse events, with so many investigators and individual differences in attitudes among patients and study participants.

Adverse Events, General

Considering all AEs, regardless of whether they were serious or caused withdrawal (Table 7.2, Volume 205, pages 85-91):

Patients Showing Adverse Events, Study S3BA3002

Patients Showing	Placebo BID n = 175	A 1 mg BID N = 542	Difference p-value
Any adverse event	**121 (69.1%)**	**394 (72.7%)**	N.S.
Gastrointestinal event	**51 (29.1%)**	**262 (48.3%)**	**<< 0.0001**
Constipation	**7 (4.0%)**	**168 (31.0%)**	**<< 0.0001**
GI or Abdominal pain	13 (7.4%)	71 (13.1%)	< 0.05
Nausea or vomiting	12 (6.9%)	50 (9.2%)	N.S.
Neurological event	22 (12.6%)	77 (14.2%)	N.S.
Headaches	12 (6.9%)	44 (8.1%)	N.S.
Cardiovascular event	6 (3.4%)	22 (4.1%)	N.S.
Arrhythmias	0	5 (0.9%)	N.S.
Malaise or fatigue	9 (5.1%)	14 (2.6%)	N.S.
Psychiatric event	6 (3.4%)	17 (3.1%)	N.S.
Musculoskeletal event	17 (9.7%)	57 (10.5%)	N.S.
Pain or discomfort	8 (4.6%)	34 (6.3%)	N.S.
Lower respiratory	21 (12.0%)	38 (7.0%)	*< 0.04*
Endocrine/Metabolic	4	15	N.S.
Hepatobiliary/pancreatic	5 (2.9%)	3 (0.6%)	*< 0.02*
Blood & Lymphatic	1	8	N.S.
Urologic	9	24	N.S.
Reproductive	6	16	N.S.
Pregnancy	0	1 (0.2%)	N.S.
Skin	14	30	N.S.
Eye	4	5	N.S.
Ear, Nose & Throat	49	131	N.S.
Non-Site Specific	22	49	N.S.
Trauma/Overdose	10	28	N.S.

Note: BID, twice daily; A, alosetron

Comment: The significant increase in adverse events in patients taking alosetron again was due almost entirely to more constipation; the combined abdominal and gastrointestinal pain or discomfort showed a marginally significant increase in alosetron-associated events.

Adverse Events Considered Drug-Related, Study S3BA3003

Patients Showing	Placebo BID n = 175	A 1 mg BID N = 542	Difference p-value
Any adverse event	**32 (18.3%)**	**222 (41.0%)**	**<< 0.0001**
Gastrointestinal event	**13 (7.4%)**	**192 (35.4%)**	**<< 0.0001**
Constipation	**4 (2.3%)**	**160 (29.5%)**	**<< 0.0001**
GI or Abdominal pain	4 (2.3%)	38 (7.0%)	< 0.025
Nausea or vomiting	3 (1.7%)	16 (3.0%)	N.S.
Neurological event	2 (1.1%)	30 (5.5%)	< 0.02
Headaches	1 (0.6%)	19 (3.5%)	< 0.05
Cardiovascular event	0	4 (0.7%)	N.S.
Arrhythmias	0	1 (0.2%)	N.S.
Malaise or fatigue	4	7	N.S.
Psychiatric event	0	2	N.S.
Musculoskeletal event	2	2	N.S.
Endocrine/Metabolic	1	2	N.S.
Hepatobiliary/pancreatic	2	0	N.S.
Blood & Lymphatic	0	5	N.S.
Urologic	1	2	N.S.
Reproductive	0	1	N.S.
Skin	1	6	N.S.
Eye	1	0	N.S.
Ear, Nose & Throat	13	33	N.S.
Non-Site Specific	4	12	N.S.

Note: BID, twice daily; A, alosetron

When attribution of causality was considered, as provided by the investigators taking care of the patients, statistically significant increases, in proportions of patients on alosetron compared to those on placebo, were seen for gastrointestinal events in general, particularly for constipation, but also for pain or discomfort in the abdomen or gastrointestinal tract. *(Comment: It is unclear why a distinction was made between these in the Applicant's analyses; therefore I combined them.)* Also notable was a significant increase in headaches thought to be study drug-related (Table 7. 3, Volume 205, pages 92-4):

Analyses by subgroups revealed that alosetron-related constipation was relatively more frequent in women (129/375, 34.4%) than in men (39/167, 23.4%), and the difference was statistically significant ($p = 0.01$). Alosetron-treated women who took estrogenic hormones (84/216, 39%) showed significantly ($p < 0.04$) more constipation than those who did not (45/159, 28%). White women taking alosetron showed more constipation (160.497, 32%) than did Black women (8/45, 18%), also significant ($p < 0.05$). Elderly women 65 years of age or older showed more alosetron-related constipation (21/49, 43%) and did younger women (147/493, 30%), but the difference was borderline ($p > 0.06$). There was no report of how many participants in S3BA3003 had study drug interruption because of constipation (no stools for 4 days).

Because of the case of apparent alosetron-induced hepatotoxicity in which both serum aminotransferases and total bilirubin were elevated in patient #4595 in Study S3BA3001, search was made for any other cases in this study in which the combination occurred. The submitted Table 7.8 (Volume 205, pages 132-3) provides tabulation of the mean and median values for the

serum enzyme activity for alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (AP), and for serum total bilirubin (Bt), which show no significant changes in the groups of 167 patients of those on placebo or 530 of those on alosetron, over the course of the study (not all patients had baseline tests, and diminishing numbers had data over the study period). Although individual patient data were provided in Listing 4 (Volume 205, pages 397-431) for laboratory values outside the predefined "threshold" range for blood counts, electrolytes, and serum albumin and total protein, no data were provided for the liver-related serum enzyme activities or Bt ((Volume 205, page 33; threshold range: more 2x ULN for enzymes, more than 1.5x ULN for Bt).

Comment: The S3BA3001 study concluded in September 1999, and it is important that the applicant provide as quickly as possible a listing of individuals who have ALT elevations that increase while on study drug, especially if accompanied by Bt elevations.

Adverse Events, General

Considering all AEs, (Volume 205: pp 45-6; Table 7.2, pp 85-91; Listing 1, pp 202-376):

Patients Showing Adverse Events, Study S3BA3003

Patients Showing, During partial study	Placebo BID n = 175	A 1 mg BID N = 542	Difference p-value
Any adverse event	**121 (69.1%)**	**394 (72.7%)**	N.S.
Gastrointestinal event	**51 (29.1%)**	**262 (48.3%)**	**<< 0.0001**
Constipation	**7 (4.0%)**	**168 (31.0%)**	**<< 0.0001**
GI or Abdominal pain	13 (7.4%)	71 (13.1%)	< 0.05
Nausea or vomiting	11 (6.3%)	46 (8.5%)	N.S.
Colitis	***0***	***1 (0.2%)***	N.S.
Neurological event	22 (12.6%)	77 (14.2%)	N.S.
Headaches	12 (6.9%)	44 (8.1%)	N.S.
Cardiovascular event	6 (3.4%)	22 (4.1%)	N.S.
Arrhythmias	0	5 (0.9%)	N.S.
Malaise or fatigue	9 (5.1%)	14 (2.6%)	N.S.
Psychiatric event	6 (3.4%)	17 (3.1%)	N.S.
Musculoskeletal event	17 (9.7%)	57 (10.5%)	N.S.
Pain or discomfort	9 (5.1%)	35 (6.5%)	N.S.
Lower respiratory	21 (12.0%)	38 (7.0%)	*< 0.04*
Endocrine/Metabolic	4	15	N.S.
Hepatobiliary/pancreatic	5 (2.9%)	3 (0.6%)	*< 0.04*
Blood & Lymphatic	1	8	N.S.
Urologic	9	24	N.S.
Reproductive	6	16	N.S.
Skin	14	30	N.S.
Eye	4	5	N.S.
Ear, Nose & Throat	58 (33.1%)	66 (12.2%)	*< 0.001*
Non-Site Specific	45 (25.7%)	20 (3.7%)	*< 0.001*
Trauma/Overdose	10	28	N.S.

Note: BID, twice daily; A, alosetron

Comment: The significant increase in adverse events in patients taking alosetron was due almost entirely to constipation. The placebo-treated group showed statistically significantly more hepatobiliary/pancreatic, ear-nose-throat problems and lower respiratory tract problems, as well as unspecific events. Decreases on hepatobiliary events in patients on alosetron were noted also in S3BA3002 but not in other studies, and they are not likely to be of any clinical consequence. If enough comparisons are made, the probability of chance differences of significance rises; it is not claimed by the applicant that alosetron prevents colds or coughs.

Listings of individual patients who had adverse events, regardless of whether they were serious, considered drug-related, or caused withdrawal from study were provided as Listing 1 (Volume 205, pages 202-376).

Comment: A syndrome of constipation, abdominal pain, and rectal bleeding not accounted for by hemorrhoids or menstrual bleeding or other known cause may be an indicator of* ***ischemic colitis****, which was diagnosed by colonoscopy in three patients, one in each of three controlled studies. These included in Study S3BA2001: Patient #2829, a 33-year-old White woman, 1 of 290 patients (91 men, 199 women) given alosetron; in Study S3BA3001: Patient #15687, a 41-year-old White woman, 1 of 309 women given alosetron; and in Study S3BA3002: Patient #7195, a 48-year-old White woman, 1 of 322 given alosetron. In the absence of known cardiovascular disease, shock or hypotension, drugs known to cause ischemic colitis, this disorder would be considered unlikely or at most a remote possibility of occurring; there were no cases among the 720 patients on placebo in these three studies. All three of these patients were withdrawn from study, but attribution of the adverse event to alosetron was made by the investigator in only one case (#15687 in S3BA3001). Therefore, it seemed appropriate to peruse the listing of individual patients who may have had this syndrome but clinical recognition of it was not made.*

Patients Reporting "Ischemic Colitis" Syndrome* in S3BA3003

Inv.:Pt No,, sex-age-race	*Symptoms (__days on drug)*	*Vol.205, p:*
Placebo (of 121)		
(None)		
Alosetron (of 394)		
04814: 11951 F56c	*Abdominal pain (2 d), constipation (4d), blood in stools (7d); not considered serious or drug-related, withdrawn[x]*	*296*
49157: 08419 F40c	*Constipation (14d), bloody stool (16d), colitis (51d), not considered serious but bloody stool related*	*307*
49840: 11970 F56c	*Gastrointestinal gaseous symptoms (14d), rectal bleeding (55d), not considered serious or related, withdrawn[x]*	*323*
49840: 11974 F47b	*Abdominal cramps (18d), rectal bleeding (22d), constipation (100d), considered not serious but related*	*324*
50273: 10206 F49c	*Constipation (28, 42d), low abdominal pain and rectal bleeding (142d), not considered serious or related*	*344*
05241: 08664 M59c	*Constipation and headache (4d), abdominal cramps (10d), rectal bleeding (15d), not serious but related, withdrawn[x]*	*354*
06481: 08160 M44c	*Rectal bleeding (4d), lower abdominal cramps (169d), not considered serious or related, but withdrawn[x]*	*377*

*Note: *constipation, abdominal pain, unexplained rectal bleeding; Inv., investigator; Pt., patient; No., number; p, page; c, Caucasian; b, Black; [x], withdrawn.*

Comment: It cannot be stated with any confidence that these seven patients represented cases of ischemic colitis, since it does not appear that they were investigated further to establish diagnosis by colonoscopy, biopsy, or barium enema. However, in view of the cases that were more fully studied, they must be considered highly suspicious. Further attention to this will need to be paid in the analyses of the completed study, and in future observations of patients on alosetron. Case reports for four (#8160, 8664, 11951, 11970) but not all of the seven patients in the table above were provided with the partial, interim report of study S3BA3003; the others were requested.

Because of the apparent alosetron-induced hepatotoxicity in which both serum aminotransferases and total bilirubin were elevated in patient #4595 in Study S3BA3001, special interest is appropriate in abnormalities of serum activities of liver-associated enzymes (ALT, AST, AP) and total bilirubin. However, no listing of abnormalities of these variables for individual patients was provided in the interim report of S3BA3003, although abnormal values beyond the "threshold" limits (Volume 205, page 33) were listed for blood counts, serum electrolytes, calcium, phosphorus, protein, and albumin in Listing 4 (Volume 205, pages 397-431).

Comment: It is unfortunate that the applicant did not list the measures of liver dysfunction (serum enzyme elevations) and function (total bilirubin) in the interim report. The provision of group mean value changes in Table 7.8 (Volume 205, pages 132-3) is useless for detecting an individual with abnormalities. There were no significant differences in proportions of patients with baseline elevations of serum enzymes or bilirubin between treatment groups (Table 7.10: Volume 205, page 136), nor in shifts to elevated level on treatment (Table 7.12: Volume 205, page 140). This does not, however, rule the uncommon cases of an uncommon individual reaction.

Electrocardiographic Changes

Expert commentary on the ECG results (Volume 205, pages 433-4) by Dr. Julie Fetters, dated 10 April 1999, reached the conclusion that alosetron treatment does not cause significant abnormalities, based on review of 723 patients in S3BA3003, randomized 3:1 to alosetron or placebo. Of these 723 patients, 232 had pre-study abnormalities that persisted, but were not worsened by alosetron , 83 had pre-study abnormalities that disappeared after two months on study, another 362 showed no abnormalities before or after study drug, and 46 patients developed new abnormalities. Focus of attention on the last group showed that 33 alosetron-treated patients most often showed bradycardia in 14, non-specific ST/T wave changes in 4, sinus tachycardia in 3, rare premature atrial or ventricular beats in 3, left ventricular hypertrophy in 2, left axis deviation in 2, increased QTc interval in 2, probable myocardial infarction in 1, right axis deviation in 1, incomplete right bundle branch block in 1. Among 13 placebo-treated patients, 6 showed bradycardia, incomplete right bundle branch block in 3, and one each showed increased QTc interval, sinus tachycardia, myocardial infarction, and rare premature beats. Among the 232 patients with pre-study abnormalities, sinus bradycardia was the most prevalent abnormality in both the alosetron-treated and placebo-treated patients, and the only clinically significant change was atrial flutter in 1 patient on placebo. There were no cases of serious ventricular arrhythmias in either treatment group. There was no significant difference in the incidence of any of these abnormalities between the treatment groups.

Comment: Dr. Fetter did not indicate how many of each subset of patients showing changes or no changes were treated with alosetron or with placebo, except for the 46 (33 alosetron, 13 placebo) who were normal pre-study and developed abnormalities. Somewhat different numbers were provided by the applicant in Table 7.15 (Volume 205, page 144), but these were not segregated by change from baseline to on-treatment, as done by Dr. Fetter.

Summary of ECG Results, S3BA3003

	Placebo n = 175	Alosetron n = 542	p-value (Fisher exact)	Total n = 717
Baseline	170	515	N.S. (0.274)	685
normal	95	275		370
abnormal	75	240		315
median rate	68	70		
After 2 months	166	502	N.S. (0.156)	668
normal	96	291		387
abnormal	70	211		281
median rate	70	72		

Audiometry Testing

The other special study done in S3BA3003 was of hearing acuity and tinnitus. Results displayed in Tables 7.16 and 7.17 (Volume 205, pages 145-6) showed no significant differences in either pure tone audiometry results or development of tinnitus between treatment groups. No expert assessment of the audiometry results was provided in this interim report, but it was promised for the second interim report due end-September 1999.

IV. Integrated Summary of Efficacy

Note: The clinical efficacy review of this submission was done by Dr. Robert Prizont (q.v.), of the Division of Gastrointestinal and Coagulation Drug Products, Center for Drug Evaluation and Research, Food and Drug Administration HFD-180. The document should be consulted for details and critical interpretive commentary. This brief summary is taken from the applicant's submitted comments, and is not critically reviewed here.

The applicant has summarized the clinical effectiveness of alosetron tablets 1 mg twice daily in Volume 208. Following two 12-week, dose-ranging studies (S3BP12 and S3BA2001) in 238 men and 593 women (about 71%), done in Europe and North America, it was observed that the women but not the men showed a greater proportion of patients with decreased abdominal pain or discomfort, reduced urgency of stooling, increased percentage of pain-free days, and patients' impression of adequate relief. The range of doses explored in S3BP12 was 0.1, 0.5, and 2.0 mg of alosetron b.i.d., compared to placebo; in S3BA2001 the range of doses was 1, 2, 4, and 8 mg of alosetron b.i.d., compared to placebo. The best dose appeared to be 1 mg of alosetron taken twice daily. The drug was significantly more constipating than placebo, and led to significantly more voluntary discontinuation of treatment in both men and women taking alosetron than taking placebo.

Therefore, Phase III clinical trials (S3BA3001 and S3BA3002) were designed to be carried out in women only, seeking to avoid any who had the constipation-predominant form of IBS, using the patients' weekly retrospective assessment of the "adequate relief" of IBS pain/discomfort as the primary outcome measure. Results of surveys (Volume 208, pages 16-17) of women with non-constipation-predominant IBS from 678 patients from those trials revealed that the symptom that bothered them most were abdominal pain or discomfort (35-36%), urgency of bowel movements (26-28%), excessive numbers of bowel movements (22-23%), and bloating (12-14%). Relatively few were most-bothered by mucus in stools (1-2%). The survey results were interpreted to indicate that patients most desired a therapeutic agent that would reduce or relieve abdominal pain or discomfort associated with stool frequency and urgency.

Data on daily pain and stool scores were collected each day by telephone calls from participating patients, according to a standardized question-and-scoring system, using a special software program developed and implemented by a consulting contract research organization for Glaxo Wellcome. Patients were asked to report each day by touch-tone telephone entry system whether they had pain that day, and if so, how severe was the maximally severe pain on a scale of 0 to 4 (0, none; 1, mild; 2, moderate; 3, intense; 4, severe). They also were asked how many stools they had that day, and the consistency of the stool(s) on a scale of 0 to 5 (0, no stool; 1, very hard; 2, hard; 3, formed; 4, loose; 5, watery). Finally, they were asked whether or not they had a sense of urgency with the stooling, whether or not they felt a sense of incomplete evacuation, and whether or not they had a feeling of bloating that day. The date and time of the call were recorded by the telephone data entry system. In addition, once each week they were asked "In the past seven days, have you had had adequate relief of your irritable bowel syndrome-pain or discomfort?" Results of the daily reports averaged over the 12-14 days of the screening period were used to establish eligibility for entry into the study, which for the principal clinical trials S3BA3001 and S3BA3002 required average maximum daily pain score of 1.0 to 3.3 and

average daily stool consistency score of at least 2.5 (Volume 158, pages 20, 27-8 for S3BA3001; the same criteria were used for S3BA3002). The primary outcome measure was weekly adequate relief, and "responders" were defined as patients who reported adequate monthly response rates. An adjustment was made to compensate for the statistical significance of analytical multiplicity of three monthly response rates (See statistical review by Dr. D. Hoberman, FDA statistician).

Comment: The entry criterion of average stool consistency of 2.5 or more would hardly justify the characterization of patients at the lower bound of the range from 2.5 to 5.0 as having "diarrhea," since a score of 2.5 would describe stools a semi-hard-formed, and not until scores between 4 and 5 were reached would they be diarrheal in consistency. Actually the characterization of the patients into diarrhea-predominant, alternating, or constipation-predominant IBS was done by the investigators independently of the scoring system and was based on the medical history rather than by collected and analyzed data. This led, as might be expected, to inconsistencies between the averaged scores from daily telephone reports and categorization based on recollections. With respect to the range of average daily pain scores to establish eligibility, the very mild or minimal and very severely afflicted patients were excluded for the study, which will need to be reflected as appropriate in the labeling. It is unclear how patients could distinguish between "intense" and "severe" pain to choose whether to enter a 4 or a 5 into the telephone data collection system.

The critical data, on daily pain/discomfort-urgency/bloating/straining-number and consistency of stools, were captured by an innovative touch-tone telephone diary system (Harding, et al., 1997) developed by Glaxo Welcome and their consultants. The system was introduced for S3BA2001, and participants were asked both daily and weekly questions. The responses were made by number entries on touch-tone telephones, in response to recorded questions, and were captured in a computerized central database, including date and time of responses and subject identification. The system was available to participants for 8040 of 8135 hours (99%), and a subsequent survey revealed that patients found the system satisfactory or very satisfactory to use. Compliance for data entry was about 82%, and there was assurance that the data were entered at the prescribed times, as well as assuring the reliability and security of the data. Because of the success in using this innovative method, it was used again during principal efficacy trials S3BA3001 and –3002.

Comment: This novel method of data collection overcame some major objections to diary data. In use of paper diaries, collected at visit intervals, there has not been any reliable assurance that the patients wrote in their symptom scores on the day associated, for there was no way to prevent or detect entry of data just prior to the visit and reliance on recollections of data. Another problem that the system overcame was transcription error, from diaries to case report forms to electronic databases for analysis. On the other hand, in these studies there were some drawbacks that were not addressed or solved: 1) the data for the screening periods were not made available either to the investigator or study site, so that average pain and stool consistency scores could not be correlated with patient histories categorizing their IBS subtype as diarrhea-predominant, alternating, or constipation-predominant, leading to some question as to the validity of the categorization; and 2) the data for individual patients were not linked to the case report forms (CRFs), so that evaluation of any adverse events or problems from CRFs provided for review lacked any of the critical data on daily IBS pain scores and stool characteristics. This should be remedied in future studies. Also, data summaries should be printed from the databases for inclusion with each CRF.

The principal support for the claim of alosetron efficacy rests on the analyses of results from the two large clinical trial S3BA3001 and S3BA3002 in 1273 women with IBS of mild-to-moderate average severity and not showing stools that were hard or very hard during the two-week screening period. The two studies used identical protocols, and were conducted at about the same time, although S3BA3002 was completed two months earlier (14 October 1998) than S3BA3001 (18 December 1998) despite both being started at about mid-September 1997.

Comment: The difference in completion time was not entirely inconsequential, since some findings and analyses from –3002 were used to influence interpretations of data from –3001, as is discussed in much more detail in the clinical efficacy review by Dr. Robert Prizont (q.v.).

In these two 12-week studies, the eligible women were randomized to receive either placebo or alosetron 1 mg twice daily:

Treatment Randomization of Women Participating in Pivotal Clinical Trials

	placebo	alosetron	total
Study S3BA3001	317	309	626
Study S3BA3002	323	324	647
both	640	633	1273

The results summarized from these two trials (Volume 208, page 25) were as follows:

Monthly Responders for Adequate Relief of IBS Discomfort in Women with Diarrhea-Predominant IBS Patterns in Pivotal Clinical Trials

Study S3BA3001	MONTH 1	MONTH 2	MONTH 3
alosetron	112/224 (50%)	129/224 (58%)	135/224 (60%)
placebo	87/222 (39%)	96/222 (43%)	92/222 (41%)
p-value	0.022	0.003	<0.001
Study S3BA3002	MONTH 1	MONTH 2	MONTH 3
alosetron	139/237 (59%)	140/237 (59%)	145/237 (61%)
placebo	89/221 (40%)	104/221 (47%)	100/221 (45%)
p-value	<0.001	0.013	<0.001

Also highly significant ($p < 0.001$) were reductions in the number of days on which stool urgency was reported, number of stools per day, and firmer stools in those months among study participants taking alosetron, compared to those on placebo. These results were seen at all three months in both studies.

Comment: The results tabulated above, as taken from the applicant's table (Volume 208, page 25) in the submitted integrated summary of efficacy, must be interpreted as a subset of all patients treated, which in turn is a subset of women with IBS, and of all persons with IBS symptoms. Only 998 of the 1273 patients randomized completed the study, and only 904 were included in the data tabulated above, not all of whom completed the study. There were 169 women with self-classified "alternating" and 11 with constipation-predominant IBS in S3BA3001, and 180 alternating and 9 constipation-predominant IBS in S3BA3002, who are not considered in the above results. More detailed review and commentary are in Dr. Prizont's clinical efficacy review (q.v.).

V. Integrated Summary of Safety

The integrated safety summary, provided in the applicant's submission Volume 209 and supplemented by listings in Volumes 210-215, and briefly summarized in Volume 1, mainly repeats and recapitulates results from the individual studies. The major studies for safety data are the two 12-week dose-ranging studies in 228 men and 593 women, and the two principal efficacy studies done in 1273 women only. This group is referred to as the "primary safety database" that is analyzed to support the claim for a dose of 1 mg of alosetron twice daily for treatment of women with a subset of IBS symptoms. Most of the data are for the 1 mg b.i.d. dose, and for women with self-characterized diarrhea-predominant forms of IBS, but there are some data for a total of 184 men on alosetron (and 54 on placebo) at doses from 0.1 to 16 mg alosetron b.i.d. and for 395 women at alosetron doses other than 1 mg b.i.d.

12-Week, Placebo-Controlled Alosetron Studies (Primary Safety Database)

Study started-ended	Sites	P M/F	A 0.1 M/F	A 0.5 M/F	A 1.0 M/F	A 2.0 M/F	A 4.0 M/F	A 8.0 M/F	*Total M/F*	Duration
S3B-P12 Jul'93-Sep'94	43 Eur	33/84	38/77	31/85		25/89			127/ 335	12 weeks
S3BA2001 Oct'95-Dec'96	71 U.S.	21/59			18/54	23/51	21/54	28/40	111/ 258	12 weeks
S3BA3001 Sep'97-Dec'98	112 U.S.	0/317			0/309				0/626	12 weeks
S3BA3002 Sep'97-Oct'98	120 U.S.	0/323			0/324				0/647	12 weeks

Note: Doses b.i.d.: P, placebo; A 0.1 to 8.0, alosetron 0.1 to 8.0 mg. M/F, males, females.
S3BA3003, partial report as of 26 Feb'99 on 728 of 859 patients entered by 225 Sep'98.*

The "primary safety database" identified by the applicant comprised 1263 patients (184 men, 1079 women) who received alosetron, and 834 (54 men, 780 women) who received placebo for up to 12 weeks in the four clinical studies listed above. Studies S3BP12 and S3BA2001, were dose-ranging studies (from 0.1 to 8.0 mg b.i.d.) that included some men; studies (S3BA3001 and S3BA3002) were done in women only, comparing alosetron 1 mg to placebo b.i.d.

Table 8.10: Demographic Characteristics of Patients in the Primary Safety Database (Studies S3BP12, S3BA2001, S3BA3001 and S3BA3002) *[Vol. 1, page 402]*

	Placebo n = 834	A 0.1 n = 115	A 0.5 n = 116	A 1.0 n = 702	A 2.0 n = 187	A 4.0 n = 75	A 8.0 n = 68	Total A n= 1263
Gender: M/F % M/F	54/780 6/94%	38/77 3/67%	31/85 27/73%	18/684 3/97%	48/139 26/74%	21/54 28/72%	28/40 41/59%	184/1079 15/85%
Age: m ± sd (range)	45 ± 0.5 (18-63)	42 ± 1.2 (18-70)	45 ± 1.3 (18-74)	46 ± 0.5 (18-82)	44 ± 1.0 (18-77)	44 ± 1.4 (20-71)	45 ± 1.4 (20-93)	45 ± 1.1 (18-93)
Race: w/b/o % w/b/o	763/51/20 91/6/2%	112/2/1 97/2/1%	113/2/1 97/2/1%	635/28/39 90/28/39%	177/6/4 95/3/2%	72/2/1 97/2/1%	63/0/5 99/0/7%	1172/40/51 93/3/4%

Note: Note: Doses b.i.d.: Placebo; A 0.1 to 8.0, alosetron 0.1 to 8.0 mg; M/F, males, females; m ± sd, mean ± standard deviation; w/b/o, white/black/other.

In addition, Study S3BA3003 was a year-long, placebo-controlled observation of 637 women and 222 men with IBS randomized (or rerandomized) to either placebo or 1 mg alosetron b.i.d. The

study started in November 1997, enrollment was completed on 28 September 1998, and the study was finished in September 1999. A partial, interim report on 728 patients (507 women and 221 men) including data up to February 1999 was provided for review with this submission. A second interim report was just submitted on 27 September, and includes at least some data on all 859 of the patients, but the final report is not expected until the end of calendar 1999.

Additional information on alosetron safety is available from 41 completed clinical pharmacology studies in healthy volunteers and patients with IBS, including 623 men and 230 women, who received single or repeat doses of the drug, generally for shorter periods of time. However, these results are less pertinent to the intended prescription use of alosetron in women at 1 mg b.i.d. for periods of up to 12 to 48 weeks, as best revealed by the four 12-week studies of the primary safety database (S3Bp12, S3BA2001; S3BA3001 and S3BA3002) and the just completed year-long S3BA3003.

In all studies, safety was evaluated by monitoring adverse events, reasons for patient withdrawals, and by periodic clinical blood testing for cell counts and chemistries. Special study of ECG effects and pure-tone audiograms were done to exclude possible arrhythmogenic or deafness-inducing effects of alosetron.

Results of these combined analyses revealed very clearly that the incidence of alosetron-induced gastrointestinal adverse events was significantly greater than in placebo-treated patients, and that the differences between the treatments was almost entirely explained by constipation. Further, it clear from the dose-ranging studies that alosetron-induced constipation occurred in both men and women, and was definitely dose-related.

Treatment-Emergent Adverse Events in 2097 Patients, Primary Safety Database (Studies S3BP12, S3BA2001, S3BA3001, S3BA3002)

	P n = 834	A, 0.1 n = 115	A, 0.5 n = 116	A, 1.0 n = 702	A, 2 n = 187	A, 4 n = 75	A, 8 n = 68
Any event	63%	50%	54%	73%	60%	72%	74%
Constipation	5%	3%	**13%**	**27%**	**20%**	**20%**	**29%**
GI discomfort	4%	<1%	2%	5%	2%	3%	7%
Abdominal pain	3%	7%	9%	5%	6%	8%	7%
Nausea	6%	3%	7%	7%	7%	9%	3%
Vomiting	3%	<1%	2%	2%	5%	3%	3%
Diarrhea	5%	3%	0	6%	2%	5%	1%
Headaches	12%	14%	11%	9%	10%	7%	13%
Malaise/fatigue	5%	5%	4%	2%	4%	3%	9%

Note: P, placebo, b.i.d.; A, __ mg b.i.d.; n, number of patients.

Only constipation was seen as significantly more frequent in incidence on alosetron-treated patients compared to those on placebo, and the incidence appeared to be broadly dose-related. No significant differences were seen from these results when subgroups were analyzed by gender, race, age, and hormonal status. Significantly more patients on alosetron dropped out of the study because of constipation, and significantly more were judged by investigators to be study drug-related. Similar findings were made in the partial analyses of the year-long study S3BA3003. The mean time to reporting constipation was 22 days, and its duration was about 15 days; among

patients on placebo with spontaneously occurring constipation, onset was later at a mean of 37 days and duration was shorter at about 9 days. The applicant summarizes these findings as indicating that alosetron was associated with "" greater severity, as well as slightly earlier onset, of constipation," and that this "may have contributed to patients withdrawing from the studies secondary to constipation." In concluding statements (Volume 1, page 421) the applicant states that "constipation is a class effect following treatment with 5HT3 receptor antagonists . ." and also that ". . . the majority of patients who developed constipation during treatment with 1 mg b.i.d. alosetron did not withdraw from the study secondary to the AE."

The proposed labeling mentions that constipation was reported in 28% of patients treated with LOTRONEX® (compared to 5% on placebo, in the table) in the section on Adverse Reactions .It is further stated that "However, only 10% of patients treated with LOTRONEX® withdrew from studies due to constipation." And "Most occurrences of constipation were mild to moderate in intensity, transient, and resolved with continued treatment or were managed with a brief interruption of drug therapy."

Comment: There is no mention in the proposed labeling of how prescribing physicians should adjust the regimen of alosetron administration, take precautions not to give the drug to patients who are constipated, what to do if they become constipated. The conclusions of the study seriously underplay the problem of alosetron-induced constipation, and the proposed labeling does not address this important adverse effect of alosetron that commonly (more than 25% of patients) affects patients taking the drug.

The applicant mentions in the concluding part of the section on Adverse Reactions (Volume 1, page 37) that adverse events reported during treatment with LOTRONEX were not necessarily caused by it, classifies adverse events as infrequent if their incidence is 1/100 to 1/1000, and rare if the incidence is less than 1/1000 patients. For the systemic listing, they propose:

Gastrointestinal –Infrequent: Abnormal stools. ***Rare:*** Ischemic colitis and perianal abscess.

Comment: This is inappropriate. Constipation was NOT infrequent, but occurred in more than a quarter of the patients; it was COMMON, and almost to be expected. The incidence of the much more serious lesion of ischemic colitis is "buried in the fine print" and minimized by being termed rare. By their own definition it was not rare, but probably infrequent. This review disclosed one case of diagnosed ischemic colitis in each of three separate studies (S3BA2001: 1 in 290 (91 men, 199 women) exposed to alosetron, from 1 to 8 mg b.i.d.; S3BA3001, 1 in 309 women exposed to 1 mg alosetron b.i.d., and S3BA3002, 1 in 322 women exposed to 1 mg alosetron b.i.d.). This represents a combined incidence of 3/921, or 1/307, and may be considered uncommon ~~or~~ infrequent but not rare. A request has been sent to the epidemiology branch to make an estimate of the 95% confidence limits for the probable true incidence of ischemic colitis based on these findings in the controlled studies. It is suggested that this finding represents a signal of a potentially serious problem that should be anticipated, perhaps even more severely expressed, if the drug is approved for clinical use in hundreds of thousands of women with IBS. No cases of occlusive or infarcting ischemic colitis were observed as yet in the controlled trials, but it may be possible that predisposed patients with extensive mesenteric atherosclerotic disease, coagulation disorders, or circulatory disturbances may show infarction of bowel, perforation,

and life-threatening forms of ischemic colitis. This possibility is sufficiently great to justify consideration of a required prospective clinical trial after approval for prescription and marketing to establish more precisely the true incidence of the problem, and to define better which patients may be at increased risk.

Another item in the systemic listing is:

Hepatobiliary Tract and Pancreas – Infrequent: Abnormal bilirubin levels.

Comment: Again, the applicant downplays an important problem. The patient who had the serious adverse event of pulmonary edema after an endoscopic retrograde pancreato-cholangiography (ERCP) procedure under anesthesia had shown an apparently alosetron-induced hepatotoxicity that was the reason for the ERCP to be done. It has been the experience of several decades that other drugs which cause both ALT and bilirubin elevations, indicating both hepatocellular injury and loss of overall liver function, may show idiosyncratic rates of hepatic failure in 10% or more of patients treated long-term with the drug after marketing and use in large numbers of patients under less well controlled conditions. It is premature to conclude that this will be the case with this drug, but is grounds for some caution and another reason to carry out a prospective study after marketing.

VI. Summary of Benefits, Risks of the Proposed Formulation

In a very brief summation (Volume 216, pages 489-92), the applicant states that the irritable bowel syndrome (IBS) is a common problem, estimated to affect 10-15% of the population, and 70-75% of those with IBS are women. They further state that 70% of the patients enrolled in the two large Phase III studies were classified as having the diarrhea-predominant form of IBS, and that in women with non-constipated IBS no therapeutic agent has been proved effective in relieving the most bothersome IBS symptoms of IBS-related abdominal pain, urgency and increased stool frequency. Even the few agents approved for treatment of IBS symptoms are labeled as "adjunctive" treatment or as "possibly" effective, and that these agents were introduced before regulatory standards were put into place that required substantial evidence of effectiveness before approval. These points are taken to indicate an unmet need for new therapy.

Comment: Much of what is claimed above is true, which is why this application was granted accelerated review. However, it does not seem correct to say that 70% of women with IBS have the "diarrhea-predominant" form of IBS, based on recruitment into the studies S3BA3001 and S3BA3002, whose protocols required selection of IBS patients to avoid those with hard stools.

The applicant further states that they have carried out two large, identically designed and almost simultaneous, adequate and well controlled Phase III studies of alosetron as a novel pharmacologic treatment that showed consistent benefit for the most bothersome symptoms of IBS in women with diarrhea-predominant forms of the disorder throughout the treatment period of 12 weeks, with return of symptoms when treatment was stopped. The applicant points out that 3670 patients and healthy volunteers enrolled in 52 studies worldwide have contributed to the efficacy and safety conclusions, including 1810 patients with IBS who have been treated with alosetron alone. The final summary statement (Section 8.11.6, Volume 216, page 492) states:

"In comparison to existing therapies, alosetron represents a significant improvement for the treatment of females with diarrhea-predominant IBS. Alosetron provides robust efficacy in relieving the most bothersome IBS symptoms: pain, urgency to defecate, and frequency of stooling. The compelling evidence of effectiveness combined with a very favorable safety profile provides persuasive evidence for alosetron as a therapeutic advance and a first-line monotherapy for the significant population of females with diarrhea-predominant IBS patients." [sic: did they mean patients or symptoms?]

With respect to the safety of alosetron, the applicant claims that alosetron is "well tolerated in the treatment of females with diarrhea-predominant IBS," and that the "extensive non-clinical and clinical database confirms an excellent safety profile across all populations studied." In the Phase II and III studies, constipation was the only adverse event occurring at substantially higher frequency in alosetron-treated patients, in comparison to those receiving placebo." They further state that "If constipation occurred, it tended to do so within the first month of therapy," and was transient in the majority of cases, and that a third of the patients who reported constipated withdrew from the study. Therefore the majority of subjects who reported constipation continued to derive benefit from alosetron therapy, since comparable relief was reported by constipated or non-constipated subjects. Finally, they state that "No other adverse event, serious adverse event, or laboratory values were noteworthy during the alosetron clinical development program."

Comment: It is very disturbing that the applicant has chosen to downplay so strongly the important issue of constipation induced commonly and predictably by alosetron, and has totally ignored the potentially very serious although uncommon problems of ischemic colitis and perhaps rare alosetron-induced hepatitis with both serum transaminase and bilirubin elevations.

The applicant has a duty to recognize, admit, and publicize the constipation problem, and to investigate it much more thoroughly in analysis of the excellent data gathered in the studies carried out. The daily telephone data entry system was an innovative contribution to the field of clinical investigation of this functional bowel disorder, as was the development of consensus on what patients and their physicians wanted from treatment, the "adequate relief of IBS-related pain and discomfort" and the bothersome symptoms of urgency and excessive stool frequency. In the further analysis of the constipation problem, clear distinction should be made between the physicians' classification of what type of IBS the patients had, based on histories taken at screening or entry, and the data on stool characteristics and frequency gathered during the two-week screening period that were not available to the investigators. These need to be compared and contrasted and explained. Further attention should be paid to the program of the 4-day interruption of treatment if constipation occurred. There may be an important clue in that data that could illuminate the question of how the alosetron regimen might be adjusted for each of the individual patients, perhaps not taking 1 mg. b.i.d. every day continuously, but maybe once daily, or intermittently, to avoid constipation yet obtain relief of pain/discomfort and the other symptoms. This will have to be dealt with in the labeling, in the instructions to physicians and patients as to how best to use this new agent, and in the advertising and promotion of the product if it is approved for prescribed clinical use and marketing.

The serious clinical adverse event of ischemic colitis cannot be ignored. It must be dealt with constructively and thoroughly. Although only 3 cases out of 921 patients (91 men, 830 women) exposed were diagnosed, preliminary inspection of the adverse events reported in the first interim report of the year-long study S3BA3003 indicates that there were several cases in the alosetron-treated patients of unexplained and uninvestigated rectal bleeding. This issue will be explored further in the upcoming safety review of the second interim report of that study just received on 27 September, and the review of the 4-month safety update received at the same time. It will be important to re-examine the adverse events of the 12-week studies of dose-ranging and clinical efficacy of 1 mg b.i.d. in women to see if other cases of unexplained rectal bleeding may be identified. We requested this of the sponsor at the meeting held last week on 6 October 1999.

Ischemic colitis caused by drugs may be mild and transient if no occlusion of major mesenteric vessels occurs, but can be catastrophic if it does, resulting in bowel infarction, segmental gangrene, perforation, peritonitis, and death if the dead bowel is not resected in time. Such problems might be anticipated to occur rarely, in patients predisposed by underlying vascular disease or circulatory events such as hypotension or cardiac failure. On the other hand, there may be milder cases of slight ischemic colitis that are not recognized or diagnosed, not investigated, not treated. The index of suspicion among physicians and patients needs to be raised to deal with this uncommon but potentially very serious adverse effect of alosetron. The calculated 95% confidence interval for the true incidence of ischemic colitis (Graham, 1999) has an upper bound between 1 and 2% of women with IBS taking alosetron at a dose of 1 mg b.i.d. for 12 weeks, based on the three cases discovered. It is not yet known whether the risk of ischemic colitis diminishes after the first few months on treatment, or continues at some continued hazard rate beyond the period of well studied treatment, 12 weeks. The further analyses of S3BA3003 data, and of data from other trials, may help illuminate this point.

The single case of apparent alosetron-induced hepatitis in patient #4595 in S3BA3001 may be just that—a single case, or it may be the first of more to come. No other cases of combined serum ALT and total bilirubin increase were detected in the other major trials of dose-ranging or efficacy (S3BP12, S3BA2001; S3BA3002), but the first interim report of the year-long study S3BA3003 omitted any data on serum activities of liver enzymes and concentration of bilirubin, while including results of blood counts and serum electrolytes and other chemical concentrations. We shall look again in the review of the second interim report, and request additional information from the applicant on the point.

It is this reviewer's opinion that, if alosetron is approved for marketing, a prospective study of a sufficient cohort of patients starting treatment with alosetron should be observed on treatment to detect and investigate cases of rectal bleeding, to improve our estimate of its true incidence, obtain information on risk factors, and other useful information pertinent to ischemic colitis. The study should be designed to be large enough to provide significant data and perhaps large enough to detect ALT rises (with appropriate follow-up and further study) as well. Design of the study will be very important, and commitment to initiate it promptly is another key consideration. A major question may be whether to include a control group, using an approved anti-diarrheal agent such as loperamide, and a set of rules for adjusting treatment regimens for individuals with both agents.

VII. Regulatory Recommendations

Based on review of the safety data of this submission for marketing of alosetron hydrochloride (LOTRONEX®, Glaxo Wellcome) for treatment of women with diarrhea-predominant forms of IBS, the following recommendations are made:

1. The frequent problem of alosetron-induced constipation must be recognized much more clearly by Glaxo Wellcome, and the labeling revised to recognize it. Further, precautions to be taken when prescribing alosetron should be specified, and instructions written as to how the problem of constipation should be handled by adjustment of the treatment regimen.

2. The infrequent but serious problem of alosetron-induced ischemic colitis must also be much more clearly recognized and addressed in the labeling, including a warning to physicians that it may occur with an incidence of about 1:300 patients

3. The rare but also potentially serious problem of alosetron-induced hepatitis, or idiosyncratic hepatotoxicity, must be recognized and addressed in revised labeling.

4. A post-marketing prospective study of sufficient patients on the approved regimen of alosetron 1 mg b.i.d. should be a condition for approval. The study should be powered to detect ischemic colitis and possible hepatotoxicity and provide better data to establish their true incidence, as well as to learn about predisposing factors. Ideally the study should be controlled with a reasonably safe agent such as loperamide (IMODIUM®, Janssen) 2 mg capsules as labeled for treatment of diarrhea.

5. The term "diarrhea-predominant" as a defining subtype of the IBS patients is probably not appropriate, and should be called "non-constipated" IBS to emphasize the concern that the drug should not be given to constipated patients, and may produce constipation frequently if given to patients with IBS who are not constipated previously.

It is clear that a number of other issues have been raised from this safety review of the submitted data, from which a number of suggestions have emerged. We suggest that the applicant firm:

i. Carry out selected pharmacodynamic studies of esophageal, gastric, small bowel and colonic motility using the *1 mg b.i.d. dose and regimen of alosetron in women with IBS*, basing the study sizes for significance on the previously obtained data for men, healthy subjects, and higher alosetron doses;
ii. Develop a format for displaying all of the telephone data for an individual patient on a single sheet, if possible, for inclusion with the case report forms;
iii. Specify a more consistent process for categorizing IBS into constipation-predominant, diarrhea-predominant, or alternating forms, and correlate those categories with data from the daily telephone entry system;
iv. Consider initiating additional studies of effects of alosetron, and comparable agents, on the microvasculature of and circulation to the colon, perhaps using suitable animal models;
v. Investigate further and seek to understand and explain the gender effect, its mechanisms and other characteristics;

vi. Allow use of their data on ischemic colitis for preparation of an abstract to be submitted for the upcoming Digestive Disease Week meetings in May 2000, and for writing a manuscript for publication in a leading peer-reviewed journal in the field of gastroenterology to be submitted at about that same time;

vii. Include in future clinical protocols the instruction to patients, investigators, and study coordinators at all sites that withdrawal from study is permitted but good reason should be given and follow-up will expected off study treatment until the end of the planned study period. Vague and non-specific "reasons" such a consent withdrawn, lost to follow-up, did not return, refused medication, etc. will not be considerable acceptable.

The applicant is commended for carrying out these well controlled studies and for introducing new and effective methods for gathering valid data from patients.

/S/ signed 24 Jan 2000
done 30 Nov 1999

John R. Senior, M.D., Medical Officer date
Division of Gastrointestinal & Coagulation Drug Products

cc:
NDA 21-107
HFD-180
HFD-180/LTalarico /S/ 1-27-00
HFD-180/SAurecchia
HFD-180/HGallo-Torres
HFD-180/RPrizont
HFD-180/JSenior
HFD-180/JChoudary
Hfd-180/KZhang
HFD-180/EDuffy
HFD-180/MYsern
HFD-870/DLee
HFD-870/RKavanagh
HFD-720/PFlyer
HFD-715/DHoberman
HFD-733/DGraham
HFD-181/PLevine

Cleared. January 24, 2000

/S/ M.D., Ph.D.

/S/ 1/27/00 (see signature comments in DFS)

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