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 pancreatocholangiography (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."

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.

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
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

CC/CIR. January 24, 2000

/S/ 1-27-00

/S/

Hugo E. Gallo-Torres, M.D., Ph.D.

/S/ 1/27/00 (See signature comments w/ DFS)

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