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."

[NOTE: The Division proposes two post-marketing approval studies: a safety study to address the issue of better characterization of rectal bleeding and an efficacy study aimed at better (individual patient) characterization of the alosetron regimen; also proposed is an *in vitro* study to evaluate effects of alosetron on endothelial cells.]

d. Patients Reporting "Unexplained" Rectal Bleeding

This section is added here for completness but, in reality, this information does not substantially modify the overall evaluation of and conclusion on colitis.

This database was generated by the sponsor at the request of the Division on October 8, 1999. The cases were reviewed and events that lasted more than 24-48 h and were not associated with constipation were analyzed further. This information was reviewed by Dr. L. Goldkind, a Medical Officer in our Division. Particular attention was paid to cases where diarrhea and bleeding were both reported.

Several cases of bleeding were identified based on the computer generated reports from the sponsor for further inquiry including review of the investigators primary source documents.

Subject 4595: This patient was diagnosed during the study as having crohn's Disease over 5 weeks into the study. In addition she developed mild elevation in transaminases and bilirubin. She underwent an ERCP to evaluate the LFT abnormalities and developed pulmonary edema. The primary source documents were not available to this reviewer. It is unclear whether the initial diagnosis at entry was incorrect and the patient had CD all along (which may have been related to the LFTs) or whether she may have developed a treatment related inflammatory bowel disorder as well as LFT elevations associated with the drug. Careful review of the primary source documents and follow-up information on the patients condition after exit from the study would help clarify the event.

Dr. L. Goldkind speculated that if the patient had resolution of her CD symptoms and signs off drug and had no recurrence, a drug related phenomenon may need to be considered. **Records pending.**

Subject 4761: A placebo treated patient with diarrhea (duration unspecified) followed six weeks later by blood in stool, lightheadedness, near syncope dehydration and vomiting all within a week of one another. **Records pending**.

Subject 8245: Another placebo treated patient with a report of bloody diarrhea for 11 days. **Records pending.**

Subject 8419: An alosetron treated patient with bloody stool and hemorrhoids 4/2/98 lasting 3 days, campylobacter infection reported 6/9/98-6/26/98 and again 9/1-9/10/98 and slight microscopic colitis of undetermined duration on 5/7/98 (multiple somatic complaints as well). **Records pending.**

Subject 10206: Watery bloody stool reported 12/3/98 5-10 episodes over 24 h and then stopped. MD diagnosed possible infectious colitis clinically. Colonoscopy not done for 4 weeks at which time poor prep precluded adequate exam of colonic mucosa. Small polyp identified at 10-15 cm and a 0.5 cm rectal at the anal verge. Biopsy report: acute ulcerative proctitis with epithelial inflammatory and reparative atypia. The description included the comment: "An ischemic process is raised because of the presence of fibrin thrombi within capillary spaces but appropriate clinical correlation is needed."

Dr. L. Goldkind's comment: "Solitary rectal ulcer disease is demographically found in constipated patients (as was this patient prior to the onset of her bloody diarrhea). This entity is differentiated from other forms of colonic ulcers by the clear demarcation of disease limited to a 'solitary rectal ulcer'. Unfortunately, the endoscopist stated that the colonic mucosa was not seen due an exceeding poor prep. Therefore it is unclear if the condition was truly limited to a solitary rectal ulcer, or was there other colonic mucosal pathology obscured by the poor prep. Although some histologic features highlight solitary rectal ulcer disease, the current pathology report does not allow for reasonably certain interpretation. Fibrosis noted in the report is suggestive of solitary rectal ulcer rather than acute proctitis however.

"This case cannot be well interpreted. It is worthy of considering as a question in the database but should not be considered as a probable case of colitis."

C. Pharmacokinetics/Pharmacodynamics

The Office of Clinical Pharmacology and Biopharmaceutical Evaluation II (OCPB/DPE-2) has reviewed NDA 21-107 and has concluded that the overall Human Pharmacokinetic Section requires additional studies. This reviewer agrees with this conclusion. In addition, as pointed out during the presentation to the members of the Advisory Committee during the November 16, 1999 meeting, additional pharmacodynamic evaluations are also needed. These PK/PD studies would be acceptable as a Phase IV commitment. The specific edited comments to be sent to the sponsor are excerpted below, taken from Dr. R. Kavangh Clinical Pharmacology and Biopharmaceutics Review.

1. Due to the minimal difference in the to-be-marketed formulation compared with the clinical trial formulation, the bioequivalence requirement comparing LOTRONEX™ prepared in a 'commercial' batch to Lotronex™ clinical trial batches is waived.

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Phase IV commitments (see separate memorandum by this reviewer) should also be agreed upon before approval.

In this reviewer's opinion no major issues remain unresolved. If it concurs with the Division's assessment of the efficacy and safety of alosetron, we recommend the Office to approve alosetron.

December 10, 1999

/S/

Hugo E. Gallo-Torres, M.D., Ph.D.
Medical Team Leader

cc:
NDA 21=107
HFD-180
HFD-180/LTalarico /S/ 12-10-99
HFD-180/SAurecchia
HFD-180/HGallo-Torres
HFD-103/Dr. F. Houn
HFD-103/Dr. V. Raczkowski
HFD-180/R.Prizont
HFD-180/JSenior
HFD-870/DLee/RKavanagh
HFD-715/PFlyer/DHoberman
HFD-181/PLevine
HFD-180/JChoudary
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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."**

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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.

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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