MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 17, 1999

FROM: Medical Team Leader (MTL)
Division of Gastrointestinal and Coagulation Drug Products, (HFD-180)

SUBJECT: LOTRONEX™ (alosetron hydrochloride; GR68755), NDA 21-107: Secondary, Multidisciplinary Review and Recommendations for Regulatory Action

TO: Director
Office of Drug Evaluation III, HFD-103

THROUGH: Director, Division of Gastrointestinal and Coagulation Drug Products, (HFD-180)

SYNOPSIS

From this secondary review, a recommendation for Regulatory Action is formulated on the basis of a multidisciplinary approach which considers the contribution of each and all primary reviewers involved with NDA 21,107, LOTRONEX™, alosetron hydrochloride, GR68755.

GlaxoWellcome (the applicant, sponsor) proposes oral tablets, administered twice-a-day for up to 12 weeks, with or without food, for treating irritable bowel syndrome (IBS) in women over 17 years of age whose predominant bowel symptom is diarrhea, either alone or as part of an alternating pattern. Alosetron is a 5-hydroxytryptamine Type 3 (5-HT_3) receptor antagonist. Three 5-HT_3 receptor antagonists are currently approved for the prevention/treatment of emesis induced by cancer chemotherapy or preoperatively: ondansetron (ZOFRAN®), granisetron (KYTRIL®) and dolasetron (ANZEMET®). For the approved indications, the 5-HT_3 R. Ant. are used short-term but are generally perceived as safe (and effective). Adverse events most often reported with these approved 5-HT_3R Ant. are headache and constipation. It is, of course understood, that the proposed indication "treatment or IBS," requires the use of alosetron for longer periods of time (3 months) and this makes it necessary a very detailed review of the safety information provided by the sponsor.

As summarized in Section I, IBS is a common problem, usually diagnosed by exclusion, that affects more women than men. In this era of managed care, in the case of IBS, a minimal evaluation and a therapeutic trial, rather than extensive investigation, is emphasized.

In Section II, a summary of the evidence presented by the sponsor is given. All questions regarding Chemistry and raised by M. Ysern, have been promptly addressed by the sponsor. No issues of concern have been identified by Dr. K. Zhang, the Pharm/Tox reviewer. Transient decreases in acute hearing were observed in RH rats and beagle dogs after 12-month oral administration of >1000 fold the recommended dose of alosetron; but no effect on hearing was noted after 102-week administration of the drug to Wistar rats. Alosetron did not have secondary effects on the cardiovascular system or electrophysiologic effects on the heart. The human PK/PD data appear incomplete. The Clinical/Statistical data consisted of two Phase II dose-ranging trials that showed that efficacy was preferentially observed in females and that 1 mg b.i.d. is the optimal clinical dose. After an end-of-Phase II meeting with the Division, the sponsor elected to include only women in Phase III trials. The main evidence of efficacy consists of two adequate and well-designed 12-week trials comparing alosetron 1 mg b.i.d. to placebo. The primary endpoint of efficacy in these principal trials was adequate relief of IBS pain and discomfort, an adequate endpoint of evaluation. Secondary endpoints of efficacy included changes in stool consistence, stool frequency, urgency, % days with incomplete evacuation and bloating. The weekly data were captured electronically, thus providing more accurate information than the use of the customary unreliable diaries. The procedures to assess safety were adequate.

In section III the justification for accelerated review of this application is summarized. NDA 21-107 was granted accelerated review because of the lack of effective treatment for IBS. At present, there is no "gold standard" treatment for IBS, especially for non-constipated females with IBS. No agent has been shown to be of proven benefit in the treatment of the patient's most bothersome symptoms of abdominal pain, urgency and increased stool frequency. Alosetron appears to be suitable to meet this need.

As summarized in Section IV, reviews started in July, 1999. The review of the clinical data of efficacy was performed by Dr. Prizont. The safety review was performed by Dr. Senior. The NDA was presented to the GI Advisory Committee Meeting on November 16, 1999.

Summary Review of the evidence presented by the sponsor is given in Section V. The primary endpoint of efficacy, adequate relief of IBS pain and discomfort, showed 10 to 15% therapeutic gain as well as similar improvement of stool frequency, stool consistency and urgency in one trial. All these findings were replicated in the other critical trial. At the time of randomization into the trials, the female patients did not fulfill the definition of diarrhea. Efficacy was shown in the ITT and "diarrhea prominent"- IBS group. However, alosetron was not differentiated from placebo in the diarrhea/constipation alternating group. This information will be incorporated into the alosetron labeling.

The major AE was constipation, occurring in 26% to 30% of patients at the alosetron dose of 1 mg b.i.d., significantly greater than the 5% of patients on placebo. The constipation was dose-related and was the most frequent cause for patients to withdraw

from the trials. In his safety review as well as his presentation to the GI Advisory Committee, Dr. Senior addressed further characterization of constipation and this information should be incorporated into the labeling. There were no changes of concern in laboratory values, except for mild but transient transaminitis and mild elevation of bilirubin without overt jaundice experienced by one patient. Again, this information should, conservatively, be incorporated into the labeling.

Four alosetron-treated patients, each participating in a separate randomized clinical trial, experienced episodes of ischemic/infectious colitis. The ischemic colitis cases in the alosetron safety database are discussed next in detail in this review[1] with the clinical summaries and pathology assessment.[2] A strong case is made that, although ad hoc histologic interpretation can provide significant information, it should **never replace the careful clinical judgment**. All four patients had a clinical syndrome of ischemic colitis and this clinical impression was **consistently confirmed** by endoscopic examinations. This ischemic colitis may coexist or predispose to, or even be the consequence of, some form of E. coli infection. There is no clear cut evidence for a causal relationship between alosetron treatment and the development of this colitis, which appears to be acute and self-limiting. In an IBS patient with diarrhea and bloody stools, the most important question is whether the clinical picture represents the first episode of chronic inflammatory bowel disease (ulcerative colitis or Crohn's disease) or acute self-limited colitis (acute infectious-type colitis, often caused by Campylobacter, Salmonella, or Shigella). All four cases of colitis resolved without sequelae. There were no instances of necrosis/perforation that may necessitate colectomy. On the other hand, the direct or indirect contribution of alosetron use to the complex clinical/endoscopic/ histopathological picture in these four patients cannot be eliminated with certainty, since none was seen among those patients taking placebo. The occurrence of colitis should be carefully and conservatively addressed in the labeling.

This reviewer agrees with Dr. Kavangh, the Biopharm. Reviewer. Further PK and PD studies and evaluations, effects on motility of the colon, whole gastrointestinal tract, stomach, esophageal motility, effects on lower esophageal sphincter pressure, of the 1mg b.i.d. proposed dose should be carried out.

The status and expected contribution to the formulation of a Regulatory Action on NDA 21-107 of the clinical Report of Study 3003 are carefully considered in Section VI.

Recommendations for Regulatory Action are provided in Section VII of this review. Therapeutic gain was clearly demonstrated by alosetron using the primary and three of the five secondary efficacy endpoints of evaluation. The therapeutic gain in comparison to placebo is not very great, but clear cut differentiation from this negative comparator was shown and the results of one principal trial were clearly replicated in the other. Some of the encountered AEs, such as constipation and headaches were expected since they

[1] [T.T. Nostrant, et al. Histopathology differentiates acute self-limited colitis from ulcerative colitis. Gastroenterology 92:318-328 (1978)]

[2] [C.M. Surawicz and L. Belic, Rectal biopsy helps distinguish acute self-limited colitis from idiopathic inflammatory bowel disease. Gastroenterology 86:104-113 (1984)].

have been observed with the three approved 5-HT_3 receptor antagonists. With alosetron however, there appears to be more (and worse) constipation and less headache than with the other 5-HT_3 receptor antagonists. The three adverse events of concern, constipation, ischemic/infections colitis and possible liver injury can be - carefully and conservatively-addressed in the labeling . AEs/Evaluations of Special interest which were discussed in detail in this review included preliminary special studies as well as audiometry testing and EKG changes. In humans, no significant differences in either pure tone audiometry results or development of tinnitus between alosetron and comparators were shown. Alosetron treatment did not cause significant EKG abnormalities.

All things considered, alosetron appears to be effective and well tolerated. Since there are no major issues that remain unresolved, this reviewer recommends approval of alosetron for the proposed indication.

It is strongly recommended that commitments to promptly initiate Phase IV PK/PD evaluations and Clinical studies (see separate memorandum by MTL and Division Director), be obtained before approval. These trials should be designed to: a) prospectively characterize unexplained rectal bleeding as possible ischemic colitis, in a large number of IBS patients being administered alosetron at the proposed dose and regimen and b) better characterize the regimen.

MULTIDISCIPLINARY, SECONDARY REVIEW
OF NDA 21-107 (ALOTRONEX™; alosetron
Hydrochloride, GR68755)

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I. BACKGROUND/INTRODUCTION:

The 5-HT_3 subtype receptors have been implicated in the mechanisms controlling gastrointestinal function especially motility and sensation[3]. The drug which is the subject of the present multidisciplinary review is alosetron (also known as GR68755), proposed brand name LOTRONEX™. Alosetron belongs to a class of compounds known as 5-hydroxy-tryptamine type 3 (5-HT_3) receptor antagonists (5-HT_3RAnt). Three drugs of this type (ondansetron, granisetron and dolasetron) have been approved for the prevention of nausea or vomiting induced by either cancer chemotherapy or surgical anesthesia and operative procedures[4]. In addition, the 5-HT_3 receptors on visceral afferent neurons are thought to be implicated in the underlying pathophysiology of irritable bowel syndrome (IBS)[5] and other gastrointestinal disorders such as functional dyspepsia and non-cardiac chest pain. For example, ondansetron has been shown to delay colonic transit in healthy volunteers [S. Gore et al. Aliment. Pharmacol. Ther. 4: 139-144 (1990); N.J. Talley et al. Dig. Dis. Sci. 35: 477-480 (1990)] while granisetron has been shown to increase the volume threshold for perception of pain during rectal distention [A. Prior, N.W. Read Aliment. Pharmacol. Ther. 7: 175-180 (1993)]. 5-HT_3 receptors are also involved in the mediation of cutaneous vasodilatation with subsequent erythema and flare in response to intradermal 5-HT and several 5-HT_3 antagonists have been shown to inhibit this response[6]. Because of these and other properties, the 5-HT_3 R Ant have been anticipated to be of benefit in the treatment of non-constipated IBS patients[7].

IBS is the most common functional gastrointestinal disorder seen by general physicians. IBS is characterized by a number of clinical features and probably comprises a cluster of different conditions. Although the most frequent symptom reported by IBS patients is abdominal pain, for a number of patients, bowel disturbances are the most prominent symptoms[8]. During the last 12 years, epidemiological, physiological, and psychological data have emerged to improve our understanding of this disorder, which is now believed to result from dysregulation of intestinal motor, sensory, and CNS function (brain-gut dysfunction)[9]. IBS has been defined using symptom-based criteria (the Manning criteria, the Rome criteria) as "a combination of chronic or

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[3] [N.J. Tally 5-Hydroxytryptamine agonists and antagonists in the modulation of gastrointestinal motility and sensation. Aliment. Pharmacol. Ther. 6: 273-289 (1990)].

[4] The brand names of the approved drugs are ZOFRAN® (GlaxoWellcome), KYTRIL® (SmithKline Beecham) and ANZEMET® (Merrell Dow), respectively.

[5] [E.A. Mayer, H.E. Raybould. Role of visceral afferent mechanisms in functional bowel disorders. Gastroenterology 99: 1688-1704 (1990)].

[6] [J.R. Fozard, Neuropharma 23: 1473 (1984)]
[N.A. Minton. Br. J. Clin. Pharmacol. 37: 525-530 (1994)]
[J. M. Orwin, J.R. Fozard. Eur. J. Clin. Pharmacol. 20: 209-212 (1986)]

[7] [American Gastroenterological Association Medical Position Statement: Irritable Bowel Syndrome. Gastroenterology 112: 2118-2119 (1997)]

[8] [M. Delvaux, J. Frexinos. A European Approach to Irritable Bowel Syndrome Management. Can. J. Gastroenterol. 13 Suppl. A:85A-88A (1999)]

[9] [Irritable Bowel Syndrome: A Technical Review for Practice Guideline Development, AGA Patient Care Committee Bowel Syndrome: A Technical Review for Practice Guideline Development, AGA Patient Care Committee, Gastroenterology 112: 2120-2137 (1997)]
[D.A. Drossman Review article: an integrated approach to the irritable bowel syndrome. Aliment. Pharmacol. Ther. 13 Suppl.2:3-14 (1999)]

recurrent g.i. symptoms not explained by structural or biochemical abnormalities", which is "attributed to the intestines and associated with symptoms of pain and disturbed defecation and/or symptoms of bloated and distension". IBS affects 14% to 24% of women and 5% to 19% of men. For more than half of IBS patients the first presentation of symptoms to a physician is between the ages of 30 and 50 years[10] and prevalence decreases beyond age 60[11]. The symptoms of IBS wax and wane. Although the duration of exacerbations and remissions has not been adequately studied; instead of, **randomized clinical trials of 12-week duration** are usually recommended. Although consensus has not been reached, research to date indicates that symptoms of IBS are generated by quantitative differences in motor reactivity of the gut and increased sensitivity to stimuli (distension) or spontaneous contractions. However, the types of motility patterns seen in the colon and small intestine in patients with IBS are qualitatively similar to the contractions seen in healthy controls and there is no consensus on the patterns of motility responsible for diarrhea or constipation. In patients with IBS, factors such as meals, balloon inflation, cholecystokinin and psychological stress, lead to an exaggerated intestinal motor response[12]. There is increased sensitivity to painful distentions in the small bowel and colon. There is also increased sensitivity to normal intestinal function (e.g. spontaneous migrating motor complexes); as well as an increased or unusual area of somatic referral of visceral pain. Because the mechanisms of central interpretation of afferent signals are not known, it is also not known whether psychological or neurophysiological mechanisms work singly or together in the perception of incoming signals.

Other factors such as inflammation and motor activity play an important role in the development of IBS but the role of autonomic dysfunction in IBS requires further evaluation. An evolving theory is that chronic GI symptoms result from an alteration of the integration of intestinal motor, sensory, autonomic, and CNS activity, These domains interact through circuits at all levels of the brain-gut axis[13], which provide the linkage between visceral afferent sensation and intestinal motor function, and both can be modified by higher cortical centers. The numerous neurotransmitters found in brain and gut are the messengers that regulate these activities. The enkephalins, substance P, calcitonin gene-related polypeptide, nitric oxide, **5-HT**, cholecystokinin, and others have varied and integrated effects on pain control, GI motility, emotional behavior, and immunity[14].

The diagnosis of IBS is a **diagnosis of exclusion**. Now a days, the preferred approach is identification of IBS using positive symptom criteria (ex. the Rome criteria) and a limited diagnostic screen[15]. Additional diagnostic studies depend on the predominant symptom subgroup, namely constipation, diarrhea, alternating diarrhea/constipation, or pain/gas/bloating.

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[10] [R.F. Harvey, et al. Prognosis in the irritable bowel syndrome: a five-year prospective study Lancet i:963-965 (1987)]
[11] [L. Kay J. Intern. Med. 236: 23-30 (1994)]
[12] [D. Kumar, D.L. Wingate. Lancet 2: 973-977 (1985)]
[J.E. Kellow et al. Gut 29: (1236-1243 (1988)]
[J.E. Kellow et al. Gastroenterology 98: 1208-1218 (1990)]
[13] [E.A. Mayer, H.E. Raybould Gastroenterology 99: 1688-1704 (1990)]
[14] [E.A. Mayer, G.F. Gebhart. Basic and clinical aspects of visceral hyperalgesia. Gastroenterology 107: 271-293 (1994)]
[15] [D.A. Drossman. Diagnosing and treating patients with refractory gastrointestinal disorders. Ann. Intern. Med. 123: 688-697 (1995)]

In this era of managed care, a minimal evaluation and a therapeutic trial, rather than extensive investigation, is preferred[16].

The specific indication for which Glaxo Wellcome is seeking approval is:

> "LOTRONEX™ is indicated for the treatment of Irritable Bowel Syndrome (IBS) in female patients whose predominant bowel symptom is diarrhea, either alone or as part of an alternating stool pattern."

II. SUMMARY OF THE EVIDENCE PRESENTED BY THE SPONSOR

In support of their request for the approval of the marketing of LOTRONEX™, Glaxo Wellcome has submitted information on chemistry, pharmacology/toxicology, pharmacokinetics/pharmacodynamics and clinical/statistics. A succinct appraisal of these materials follows.

Non-clinical findings and relevance to clinical studies

- Mutagenicity and carcinogenicity studies in mice and rats revealed no evidence of genotoxicity or neoplasia following 2-year exposure to alosetron.

- In animal studies, transient decreases in hearing acuity were observed in RH rats and beagle dogs after 12-month oral administration of high dose (ca. 1000-fold the recommended dose) alosetron. These changes were not permanent and reversed within one month of cessation of alosetron treatment. No effect on hearing was noted after 102-week administration of alosetron to Wistar rats.

- [During the review of the safety data from clinical studies, special attention was put on the occurrence of hearing-related adverse events that may have been noted during alosetron treatment; see review of the 120 day SU of NDA 21-107].

- High dose alosetron administered in studies of rats and rabbits did no seem to produce significant adverse effects on reproductive function, fertility, or embryofetal toxicity. [However, the available clinical information on the use of this drug in pregnancy in IBS patients is minimal].

Human Pharmacokinetic/Phamacodynamic Data

This information appears incomplete.

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[16] [M. Camilleri, C.M. Prather. The irritable bowel syndrome: mechanisms and a practical approach to management. Ann. Intern. Med. 116: 1001-1008 (1992)]
[D.A. Drossman, W.G. Thompson. The irritable bowel syndrome: review and a graduated, multicompoaint treatment approach. Ann. Intern. Med. 116: 1009-1016 (1992)]

- Because alosetron is metabolized by a variety of liver enzymes, the sponsor proposes (and this seems reasonable) that alosetron metabolism is unlikely to be significantly affected by inhibition or induction of any one enzyme. Alosetron does not appear to induce the cytochrome P_{450} metabolizing enzyme system of the liver to a great extent. *In vitro* and *in vivo* drug-drug interaction studies appear to indicate little potential for clinically significant drug interactions by alosetron.
  [Alosetron interaction studies were conducted with cisapride, theophylline and oral contraceptives. These evaluations revealed no evidence of interaction. Assessment of EKG changes during alosetron treatment and concomitantly with cisapride also revealed no significant effects].

Clinical/Statistical Data

The efficacy and safety of alosetron has been evaluated in 3,670 patients and healthy volunteers enrolled in a total of 52 completed studies worldwide. This includes 1810 patients with IBS who received alosetron monotherapy. In the main, the clinical/statistical data consist of the following.

a) Two Phase II dose-ranging trials: S3BP12 [n=467; conducted in Europe and Canada] and S3BA2001 [n=370; conducted in the US (n=315) and Europe and Canada (n=55)]. In essence, data from these two trials showed:

   - Efficacy was preferentially observed in females, as compared to males. This differential gender effect was not readily explained by PK differences.

   - 1 mg BID is the optimal clinical dose.

At an end-of-phase II meeting with members of the Division, two options for Phase III trial designs (both testing 1 mg BID in studies of 12-week duration) were discussed.

i) inclusion of both men and women with stratified analysis by gender
or
ii) inclusion of women only.

Since female patients comprise the largest subgroup of IBS sufferers and Phase II results had demonstrated efficacy and an optimal clinical dose in this population, the sponsor made the decision to pursue the option of progressing to Phase III trials enrolling females only.

b) Two critical Phase III trials: S3BA3001 (n=626) and S3BA3002 (n=647)
   [It is important to note that studies to further explore possible physiologic mechanisms responsible for the observed differences in gender effect are underway. Also initiated is an additional, large dose-ranging efficacy trial in males (study S3B20023)].

- Both critical studies used an identical protocol, with a very useful design and were 2-arm, multicenter, double-blind, randomized (4 patients per permuted block), US trials. The treatment groups consisted of either alosetron (1 mg BID) or placebo BID. A 2-week

screening phase was followed by a 12-week double-blind treatment period and a 4-week post-treatment follow-up period for a total duration of 18 weeks.

- Key inclusion criteria were:

  i) an average abdominal pain/discomfort score between 1.0 and 3.3 during the screening phase[17] and

  ii) an average stool consistency score of at least 2.5[18].

- The **primary clinical endpoint** was the patient's weekly response in a diary to the question: "In the past 7 days, have you had adequate relief of your Irritable Bowel Syndrome pain and discomfort (YES/NO)?" The primary analysis[19] compared the number of **"monthly responders"** (patients who indicated "adequate relief" for at least 2 weeks out of the month). Thus a patient could be a responder for any of months 1, 2, or 3.

- In one of the Phase III trials (**3002**), Glaxo Wellcome concluded that efficacy on the primary endpoint was demonstrated only in the subgroup of women with the diarrhea-predominant type "(D-IBS)" but not in the alternating diarrhea/ constipation "(A-IBS)" or the constipation-predominant types of IBS "(C-IBS)". The sponsor subsequently performed post hoc analyses (not formulated before unbinding the data) on the D-IBS and A-IBS subgroups in the other critical study (**3001**).

- **Secondary endpoints** included a daily pain severity score,[20] proportion of pain-free days,[21] and evaluations of Lower GI functions such as number of times stool passed/ day and stool consistency using the scale mentioned above in connection with the inclusion criteria. Sense of urgency, bloating, and sense of incomplete evacuation were also evaluated using daily reports of 'Yes/No' to the presence of each symptom. Sponsor's **Amendment 2** contained a "step-down" (closed testing) plan for secondary endpoints where the order of endpoints to be tested would be 1) stool consistency, 2) sense of urgency, 3) stool frequency, 4) sense of incomplete evacuation, and 5) bloating, in that order. **The primary time point for these analyses was to be the change from baseline at month 1, "and if significance is demonstrated for this interval, change from baseline will then be interpreted for each week in the interval..." As mentioned in the FDA statistical**

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[17] where 1= mild, 2=moderate, 3=intense, and 4=severe

[18] where 1=very hard, 2=hard, 3=formed, 4=loose, and 5=watery

[19] For the **primary analysis**, Last Observation Carried Forward **(LOCF)** was used whereby months with all missing weeks of adequate relief were replaced by the number of weeks with relief in the previous non-missing month. Since there were 3 months of evaluation, the sponsor proposed a multiple endpoint adjustment using O'Brien's global testing approach. If the global test was significant at the 0.05 level, Koch and Gansky's strategy was used: viz., each month was analyzed separately for treatment effect at the 0.05 level using the CMH test using geographic clusters as strata. In addition to monthly responders, a full trial responder was defined as anyone who completed the study and reported adequate relief for at least 6 of the study's 12 weeks.

[20] Where 0=no pain, 1=mild, 2=moderate, 3=intense, and 4=severe.

[21] **Pain-free Days** would be analyzed by defining a "monthly responder to be one who reported at least 50% pain/discomfort-free days in a month with a least 14 daily pain assessments".

review, the protocol did not specify how comparisons of pain scores would control Type I error.

- The protocols (n=300 patients per group) predicated a 15% therapeutic gain of alosetron (55% responders) over placebo (40% responders), resulting in 90% power at the 0.05 level.

c) One long-term safety study: S3BA3003 (n=859, 637 women and 222 men). This study was begun on 30 September 1997; enrollment was completed in November, 1999. This trial was 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 about 600 females and 160 males with non-constipation-predominant IBS at 250 centers, derived mainly from patients who had completed pivotal 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. At the time this study was designed, the principal safety concerns[22] were reflected in the special measurements to be made of EKGs, 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).

III. JUSTIFICATION FOR ACCELERATED REVIEW

Glaxo Wellcome requested and was granted, accelerated review of NDA 21-107. In granting this request, the Division considered that, in comparison to existing therapies, alosetron represents a significant therapeutic advance (with an apparently acceptable safety profile) as a first line monotherapy for the significant population of female patients with non-constipating IBS.

As previously mentioned, one of the major obstacles to demonstrate drug efficacy in IBS is the **high placebo response rate** in these patients. This placebo response could be as high as 60%[23] or even higher. [30% to 88%, according to the AGA (Gastroenterology 112: 2120-2137 (1997)]. Strictly speaking, only a few agents in the US are labeled for the treatment of IBS or symptoms of IBS. Most are described as **"adjunctive treatment"** while others, such as LIBRAX (a combination of the antidepressant Librium with the anticholinergic clidinium bromide) have the qualifier that they are **"possibly effective."** This reflects the market introduction of these products prior to establishment of the current regulatory standards for providing substantial evidence of effectiveness. Among the approved drugs is LOPERAMIDE (IMODIUM; and

[22] The reasons cited for special concerns about EKGs and PTAs were the history of EKG QT prolongation by certain agents affecting serotonin receptors (especially cisapride, a 5-HT_4 agonist) and the above mentioned findings in rats of decreased ear twitch reflex response to noise (Preyer test) and in dogs (BAER test).

[23] [G.F. Longstreth et al. Ann. Intern. Med. 95: 53 (1981)]
[R.F. Harvey et al. 1: 1278 (1973)]

probably other opioid agonists), belladona alkaloids and synthetic substitutes. An example of this type of drug is DONNATAL, a drug combination that provides natural belladona alkaloids in a specific fixed ratio, combined with phenobarbital to provide peripheral anticholinergic/antispasmodic action and mild sedation. This combination is classified as "possibly effective". Another example is the long line of LEVSIN products (Tablets, Elixir, Drops, Injection, LEBSID Extended-release Tablets, LEVSINEX TIMECAPS). One of the difficulties when using IBS drugs that contain an anticholinergic agent as one of the primary active ingredients is the numerous adverse events that are associated with their use. These evens include constipation, bloating, abdominal pain, and numerous CNS-related adverse events.

In literature reviews dealing with the subject of therapy of IBS, the use of fiber (12g per day in patients with constipation-predominant IBS) is always mentioned. Then drugs, both approved and those not yet approved for this indication by the FDA, are usually listed according to their pharmacologic effect (anticholinergics, drugs that inhibit contractile colonic motor activity, those that modulate g.i. transit and visceral perception, psychotropic substances and psychological treatment)[24]. In his recent review article, M. Camilleri [25] concludes that current therapies targeted on the predominant symptoms of IBS (meaning diarrhea, constipation or abdominal pain/bloating) are "moderately successful". Marvin M. Schuster[26] states: **"given the many visceral afferent innervations-and the even greater complexity introduced by the dynamic interaction of these factors (both of which remain poorly understood)- it is easy to see why no effective treatment for IBS has yet evolved."**

It was therefore concluded that, in spite of IBS being an important clinical entity (see Section I of this review), there is no "gold standard" treatment for this condition. No commercially available agent in the United States has been shown to have proven efficacy in the treatment of IBS. Specifically, in non-constipated female IBS patients, no agent has been shown to be of proven benefit in the treatment of the patient's most bothersome symptoms of abdominal pain, urgency and increased stool frequency. Alosetron appears to be suitable to meet this need.

In summary, antidiarrheals are effective in increasing stool firmness and decreasing stool frequency but do not have a significant effect on a) relieving abdominal pain; b) pain thresholds nor c) decrease rectal pain sensitivity[27]. The neuromodulatory and analgesic properties of antidepressants may aid in the relief of IBS symptoms; but only a few trials have specifically evaluated the efficacy of tricyclic antidepressants in IBS. According to Francis and Whorwell[28] tricyclic antidepressants have not demonstrated consistent improvement in abdominal pain, bowel functions or other IBS symptoms. In addition, tricyclic antidepressants are frequently poorly tolerated, causing weight gain, dry mouth, constipation, sexual disfunction and cognitive

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[24] [F. Pace et al. Therapy of Irritable Bowel syndrome-An Overview. Digestion 56: 433-442 (1995)]
[25] [M. Camilleri. Review article: clinical evidence to support current therapies of irritable bowel syndrome. Aliment. Pharmacol. Ther. 13 Suppl. 2: 48-53 (1999)].
[26] [M.M. Schuster. Chapter 13. Pharmacologic Therapy of Irritable Bowel Syndrome. Gastroint. Pharmacol. Ther. G. Friedmant et al. (eds.). Lippincott-Raven Publishers, Philadelphia pp. 127-131 (1997)]
[27] [W.E. Whitehead. Effects of Loperamide on Pain Thresholds in Healthy Subjects. Gastroenterology 116:A1102 (1999)]
[28] [Brain and Irritable Bowel Syndrome:Time for Reappraisal. Lancet 344: 39-40 (1994)]

impairment[29]. Recent evaluations reveal that the antidepressant amitriptyline[30] improves somatic pain while it does not significantly change visceral noniception.

IV. REVIEW PLAN

On the basis of considerations discussed in detail under Section III. above, the GlaxoWellcome application on alosetron (NDA 21-107) **received a priority review classification**. A 6-month Review Plan was instituted (Appendix 1). The reviewers and the dates of reviews are listed in Table 1.

TABLE 1
NDA 21-107: Reviewers

Discipline	Reviewer
Chemistry	Dr. M. Ysern (November 18, 1999)
Pharmacology/Toxicology	Dr. Ke Zhang (November 4, 1999)
Pharmacokinetics/Pharmacodynamics	Dr. R. Kavanagh (December 3 , 1999
Efficacy	Dr. R. Prizont (November 4, 1999)
Safety	Dr. J. Senior (October 25, 1999)
Review of → Safety Update	Dr. J. Senior (December , 1999)
Secondary (Multidisciplinary) Review	Dr. H. Gallo-Torres, (This memorandum)

Throughout the NDA evaluation, contemporaneous communication to sponsor and prompt reply by GlaxoWellcome of reviewer questions (Appendix 2), mainly related to safety concerns have been place. This interaction has greatly facilitated timely completion of reviews and adequate preparation for presentations to the Gastrointestinal Advisory Committee Meeting scheduled for November 16, 1999.

[29] [AGA Medical Position Statement: Irritable Bowel Syndrome. Gastroenterology 112: 2119 (1997)]
[30] [A.B. Gorelick et al. Differential Effects of Amitriptyline on Perception of Somatic and Visceral stimulation in Healthy Humans. Amer. J. Physiol. 275: G460-G466 (1998)].

V. SUMMARY REVIEW OF THE EVIDENCE

A. Efficacy (Studies 3001 and 3002)

1. Baseline Characteristics (Table 2)

- There were no imbalances in important baseline characteristics between alosetron (ALOS) and placebo (PL).

- In all 4 randomixed groups (between the 2 trials), the mean baseline parameters of evaluation were:

Pain score	2.0
Stool consistency	3.4
Stool frequency	2.7/day
Sense of urgency	69% days/week
Abdominal bloating	77% days/week
Incomplete evacuation	70% days/week

Thus the study population did not have diarrhea at randomization, either by definition of stool consistency (diarrhea would be 4=loose stools, 5=watery stools) or frequency (diarrhea would be ≥3 bowel movements per day).

2. Number of Patients in Analyzed Study Populations

Study Population	3001		3002	
	PL	ALOS 1 mg BID	PL	ALOS 1 mg BID
ITT	317	309	323	324
"Diarrhea Predominant"	222	224	221	237
Alternating Pattern	87	82	95	85

Source: Tables 3 and 4, Statistical Review and Evaluation by Dr. D. Hoberman

TABLE 2

Patient Baseline Characteristics in Principal Clinical Trials

I. Demographics				
	3001		3002	
	PL [n=317]	ALOS [n=309]	PL [n=323	ALOS [n=324]
Age (Mean)	45.3	46.5	45/7	46.5
Race				
- White	87%	88%	03%	92%
Mensturation				
- Yes	41%	42%	40%	41%
Fiber Use				
- Yes	46%	45%	46%	44%
- No	54%	55%	54%	57%
II. IBS				
Time since onset of symptoms (mean years)	10.7	12.4	9.6	11.1
IBS subtype "Diarrhea-Predominant"	70%	72%	68%	73%
Alternating	27%	27%	29%	26%
Pain/Discomfort score	1.97	1.93	1.90	1.95
% Pain/Discomfort free days	12.7	13.0	14.8	14.3
% Days urgency	69.3	69.8	69.3	67.0
Stool frequency	2.71	2.75	2.77	2.71
Stool consistency	3.46	3.42	3.40	3.42

3. Dropouts (Table 3)

- Both trials suffered from a substantial number of patients who exited prematurely, ca. 25% in each trial. The FDA statistician carried out a detailed examination of the numbers and timing of dropouts in each study arm. According to the FDA statistician, this approach is expected to help in the assessment of constraints in drawing conclusions about efficacy.

- A substantial number of dropouts occurred within the first 4 weeks (Table 3). Patients who were assigned to ALOS felt they could not continue in the trial due to AEs (partly constipation); it is to be noted what PL patients left for a variety of reasons. Dropouts tended to taper off after 4 weeks. The reason for the substantial number of "Withdrawn Consents" in the PL group in study 3001 has not been determined. To assess the extent to which dropouts contributed to the achievement of adequate relief response, Dr. Hoberman tabulated the number of dropouts achieving adequate relief in each group:

In Study 3001, there were a total of 40 dropouts who happen to be monthly responders for adequate relief for at least one month during the trial, 18 (PL) and 22 (ALOS). Of the 22 (ALOS) dropouts, 9 did so due to AEs.

In Study 3002, there were a total of 38 dropouts who happen to be monthly responders for adequate relief for at least one month during the trial, 16 (PL) and 22 (ALOS). Of the 22 (ALOS) dropouts, 7 did so due to AEs.

TABLE 3
NDA 21-107

DROPOUTS IN PRINCIPAL CLINICAL TRIALS

		3001 [n=616]			3002 [n=647]		
		Week			Week		
		4[a]	8	11	4	8	11
Adverse Event	PL	8	7	6	10	2	1
	ALOS	36	11	1	36	10	3
Consent Withdrawn	PL	16	8	1	6	1	0
	ALOS	4	1	1	7	0	0
Lack of Efficacy	PL	3	4	0	8	5	1
	ALOS	4	2	1	4	1	1
Lost to Follow-up	PL	4	4	2	5	1	1
	ALOS	4	1	0	6	1	2
Protocol Violation	PL	0	0	0	0	1	1
	ALOS	0	1	0	1	0	0
Other	PL	5	0	1	1	0	1
	ALOS	1	1	2	0	1	0
Misc[b]	PL	0	0	6	0	1	13
	ALOS	1	0	10	2	0	14
Total		86	40	31	86	24	38

Source: Statistical Review, pages 3 and 4.
a) These columns (W4, W8, etc.) refer to separate epochs during which patients dropped out.
This "miscellaneous" category is Dr. Hoberman's. It accounts for patients that were not evaluated for the primary efficacy endpoint but were not accounted for by the sponsor.

- The FDA statistician noted that of all the reasons for withdrawal, the only one which is specific enough to likely affect the comparison of the two arms is "adverse events" dropouts which are not random. Dr. Haberman showed that patients who dropped out on ALOS did not contribute more adequate relief responses than PL dropouts. As already mentioned, the bulk of non-random dropouts occurred within the first 4 weeks of the trial,

thus leaving the remaining cohort relatively free of non-random dropouts. Since there were non-random dropouts, it is not possible to estimate a "true" treatment difference at any particular time. However, using all the data in the trial, one can ask the global question; "Is there convincing evidence that the distribution of responses on the drug is different from that on PL, given the pattern of dropouts?" Dr. Hoberman further noted that if the pattern and number of dropouts is judged not to have overwhelmingly determined the result of the treatment comparison, then a statistical analysis is often reasonable. Similar results of analyses using the 75% of the initial cohorts who completed the trial are useful as a way to check that the dropouts did not unduly affect the evidence which will lead to an inference concerning the activity of the drug. In summary, **dropouts did not seem to influence efficacy results.**

4. **Electronic Data Capturing (EDC)**

Using the EDC method the patients phoned in daily to a central database and responded to automated questions by pressing appropriate keys on a touch phone pad. The symptom data entered by patients was time and date stamped. Once the patient data had been entered, the database was secured and not accessible to modification. The patients were asked questions about pain and discomfort and bowel function.

This EDC approach, used in the gathering of Phase II and III data, represents a significant advantage over the traditional paper diary cards. Inherent problems with the latter included uncertainty about when the data were recorded by the patient and the possibility of retrospective changes (recall bias).

The usefulness of the EDC can be summarized as follows:

	Phase II Results	Phase III Results
Time system was operational	98%	>99%
Phone calls completed by patients	82%	85%

5. **Results of Primary Efficacy Analyses (Tables 4 and 5)**

The primary efficacy endpoint was adequate relief of IBS pain and discomfort, captured when the following question was asked of patients.

"In the past seven days have you had adequate relief of your irritable bowel syndrome pain and discomfort?"

In both the ITT and "Diarrhea Predominant" (but not in the Alternating Pattern) study populations, patients on ALOS treatment reported significantly more months with adequate relief

in IBS pain and discomfort[31] as compared to patients receiving PL, in both 3001 and 3002. In Study 3002, the difference at Month 2 in the ITT population was N.S.

- On page 5 of Dr. Hoberman's review, he points out that the sponsor's LOCF strategy for filling in data on 'adequate relief' monthly responders for the purpose of an all patients-randomized analysis could be misleading because it reports percentages of patients who were responders at month 3 who were not in the trial at that time. As an alternative, he analyzed the *patterns* of response over the 3 months. Like the sponsor' LOCF analysis, this approach incorporates all patients, but **does not carry forward the last response evaluation of a dropout**. The CMH test using modified ridit scores (essentially a Wilcoxon Rank Sum test) yielded a p-value of <0.001 in 3001 and 0.008 in 3002. This indicated that the ALOS groups had a more favorable adequate relief profile than the PL groups. Dr. Hoberman further notes that the difference between the two distributions appears to be due to the fact that more patients were ***never*** responders in the PL group, while more patients responded at all 3 months in the ALOS group. Using Dr. Hoberman's approach, there was no statistical evidence of interaction between treatment and either baseline pain, pre-study symptom duration, or geographical cluster. The results for the "Diarrhea Predominant" IBS subgroup were similar.

[31] Definition of Primary Endpoint
- ≥2 weeks/month with adequate relief
- For months with incomplete data, missing weeks were imputed as no relief
- LOCF for months with all weeks missing

TABLE 4
NDA 21-107

Study 3001: Monthly Relief of IBS Pain/Discomfort: LOCF

Measurement (Month)	Statistic	PL [n=317]	ALOS 1 mg BID [n=309]	Therapeutic Gain[a]	p-value[b]
I. ITT Population					
1	n (%) (95% CI)	126 (40%) (34.4%, 45.1%)	154 (50%) (44.3%, 55.4%)	10.1% (2.3%, 17.8%)	0.010
2	n (%) (95% CI)	137 (43%) (37.8%, 48.7%)	176 (57%) (51.4%, 62.5%)	13.7% (6.0%, 21.5%)	<0.001
3	n (%) (95% CI)	130 (41%) (35.6%, 46.4%)	179 (58%) (52.4%, 63.4%)	16.9% (9.2%, 24.6%)	<0.001
II. "Diarrhea Predominant" Population					
		[n=222]	[n=224]		
1	n (%) (95% CI)	87 (39%) (32.8%, 45.6%)	112 (50%) (43.5%, 56.5%)	10.8% (1.6%, 20.0%)	0.022
2	n (%) (95% CI)	96 (43%) (36.7%, 49.8%)	129 (58%) (51.1%, 64.1%)	14.3% (5.2%, 23.5%)	0.003
3	n (%) (95% CI)	92 (41%) (35.0%, 47.9%)	135 (60%) (53.9%, 66.7%)	18.8% (9.7%, 27.9%)	<0.001
III. Alternating Pattern Population					
		[n=87]	[n=82]		
1	n (%) (95% CI)	35 (41%) (31.0%, 51.7%)	40 (49%) (38.0%, 59.6%)	7.4% (-7.6%, 22.4%)	N.S.
2	n (%) (95% CI)	38 (44%) (33.3%, 54.1%)	45 (55%) (44.1%, 65.6%)	11.2% (-3.8%, 26.2%)	N.S.
3	n (%) (95% CI)	37 (43%) (32.1%, 52.9%)	42 (51%) (40.4%, 62.0%)	8.7% (-6.3%, 23.7%)	N.S.

Source: Table 3a, 3b and 3c in Dr. Hoberman's Statistical Review and Evaluation, with major modifications.

NOTE: A subject was defined as a responder if she reported adequate relief of abdominal pain/discomfort for at least two of the four weeks during a month.

a) ALOS > PL
b) Mantel-Haenszel test with stratification for cluster

TABLE 5
NDA 21-107

Study 3002: Monthly Adequate Relief of IBS Pain/Discomfort: LOCF

Measurement (Month)	Statistic	PL [n-323]	ALOS 1 mg BID [n=324]	Therapeutic Gain[a]	p-value[b]
I. ITT Population					
1	n (%) (95% CI)	137 (42%) (37.0%, 47.8%)	169 (52%) (46.7%, 57.6%)	9.7% (2.1%, 17.4%)	0.019
2	n (%) (95% CI)	152 (47%) (41.6%, 52.5%)	176 (54%) (48.9%, 59.7%)	7.3% (-0.4%, 14.9%)	N.S.
3	n (%) (95% CI)	151 (47%) (41.3%, 52.2%)	183 (56%) (51.1%, 61.9%)	9.7% (2.1%, 17.4%)	0.015
II. "Diarrhea Predominant" Population					
		[n=221]	[n=237]		
1	n (%) (95% CI)	89 (40%) (33.8%, 46.7%)	139 (59%) (52.4%, 64.9%)	18.4% (9.4%, 27.4%)	<0.001
2	n (%) (95% CI)	104 (47%) (40.5%, 53.6%)	140 (59%) (52.8%, 65.3%)	12.0% (2.9%, 21.1%)	0.013
3	n (%) (95% CI)	100 (45%) (38.7%, 51.8%)	145 (61%) (55.0%, 67.4%)	15.9% (6.9%, 25.0%)	<0.001
III. Alternating Pattern Population					
		[n=95]	[n=85]		
1	n (%) (95% CI)	45 (47%) (37.3%, 57.4%)	29 (34%) (24.0%, 44.2%)	NONE (-27.5%, 1.0%)	N.S.
2	n (%) (95% CI)	46 (48%) (38.4%, 58.5%)	35 (41%) (30.7%, 51.6%)	NONE (-21.8%, 7.3%)	N.S.
3	n (%) (95% CI)	48 (51%) (40.5%, 60.6%)	36 (42%) (31.8%, 52.9%)	NONE (-22.7%, 6.4%)	N.S.

Source: Table 4a, 4b and 4c in Dr. Hoberman's Statistical Review and Evaluation, with major modifications.
NOTE: A subject was defined as a responder if she reported adequate relief of abdominal pain/discomfort for at least two of the four weeks during a month.
a) ALOS > PL
b) Mantel-Haenszel test with stratification for cluster

- In summary, the difference between the treatment arms' efficacy lays in the number of patients that responded for all 3 months.[32]

6. Results of Secondary Efficacy Analyses (Table 6)

In both trials, statistically significant differences favoring ALOS over PL were seen for **urgency, stool frequency and stool consistency,** but not for other secondary endpoints evaluated. On page 9-10 of his review, Dr. Hoberman notes that p-values below **0.01** were **maintained**

[32] The number of patients who discontinued prematurely that were adequate relief responders for 3 months was 2 in the placebo arm and 3 in the alosetron arm. In study 3002, the numbers were also 2 and 3, respectively.

through 3 months [the p was <0.05 at each of the 12 weeks analyzed for urgency, stool frequency and consistency].

TABLE 6
NDA 21-107

Response Using Secondary Efficacy Endpoints

ITT POPULATION

	3001	3002
I. Pain		
ALOS	47%	49%
PL	38%	45%
II. Stool Frequency[a]		
ALOS	20%	24%
PL	11%	11%
III. Stool Consistency[b]		
ALOS	10%	13%
PL	3%	5%
IV. Stool Urgency[c]		
ALOS	49%	48%
PL	35%	34%

Source: Table on page 10 of Dr. Hoberman's Statistical Review, with major modifications.

This represents an attempt by the statistician to give some sense of "clinically interpretable" result. Listed in this Table is the proportion of patients in each treatment group who experienced at least a 50% change from baseline as of the last observed value for each patient. If the patient did not have an adequate relief evaluation at week 6 (half-way through the trial) then she was treated as a "non-responder".

a) In response to the question: **"Have you felt or experienced a sense of urgency today?**
b) In response to the requests **"please enter the number of times you have passed stool today"**
c) In response to the request:s **" please rate the consistency of your stool today"**

7. Other

In his review, Dr. Hoberman addressed two additional statistical issues. The first examined the question of to what extent do "hard stools" contribute to efficacy assessments. He noted that the results could be construed to suggest that hardening of the stool was not the predominant determinant of patients adequate relief from week to week. The second assessed whether the relief attributed to ALOS was not confined to menstrual pain. Results of studies in both principal trials indicated that, on average, patients had adequate responses for more weeks on ALOS than on PL, regardless of whether the weeks of evaluation overlapped weeks of menstruation during the trial(s).

B. Safety

1. Preclinical Evaluations

As summarized in Table 7, the target organs in acute and chronic toxicity studies in rats and dogs were the thymus,[33] CNS[34] and the liver[35]. Decreased hearing acuity in M and F animals was seen in 12-month oral toxicity studies in rats and dogs. The results of a 29-day special toxicity study on the hearing in dogs revealed no treatment related effects on hearing threshold. The increased hearing threshold in the 1-year toxicity studies in rats and dogs was not observed in the shorter term studies (up to 6 months).

Also, in special toxicity studies, GR 68 755 suspension (50% w/w) produced no skin irritant reaction. Single application of 10 mg GR 68755 to the rabbit eye produced slight corneal, and moderate iridal and conjunctival reactions. The compound had no contact sensitizing potential in guinea pigs. In oral carcinogenicity studies in rats and mice, no treatment related clinical signs of toxicity were observed. ALOS did not have tumorigenic potential.

- In a segment I fertility and reproductive performance study in rats, the fertility and mating performance were not adversely affected. In two segment II teratology studies in rats and rabbits, respectively, ALOS was not theratogenic. In a segment III perinatal and postnatal reproductive study in rats, reproductive performance of F_1 generation was not adversely affected at doses up to high dose (40/30 mg/h/d).

- Because some 5-HT_4 receptor antagonists such as cisapride have been shown to delay cardiac repolarization and prolong the QT_c interval, the sponsor was asked to evaluate possible heart conduction effects in animal models. Telemetry studies in guinea pigs and dogs, evaluation in the Purkinje fiber and in *in vitro* models for I_{Kr}, demonstrated that alosetron does not alter heart electrophysiologic parameters.

- Similarly, because of the cases of ischemic colitis found among patients treated with alosetron (and none with PL) the sponsor investigated the effects of the drug on the mesenteric artery tone isolated from guinea pigs and dogs. Alosetron did not alter the resting tone nor the response to the nerve stimulating the isolated inferior mesentenic arteries from the guinea pig and dog at concentrations up to 10^{6}M.

- Furthermore, the sponsor **re-evaluated** the histopathological data from the toxicity studies in animals. This re-evaluation included the 2-year oral carcinogenicity studies in mice and rats, 1-month oral toxicity study in rats, 1-month, 6-month, and 12-month oral toxicity studies in dogs. No significant treatment related histopathological changes in the intestinal tract were found.

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[33] (thymic involution)

[34] (subdued behavior, bulging eyes/partly closed eyes, "croaking", open mouth, ataxia, labored respiration, noisy breathing, piloerection, prostration tremor and reduction of body temperature)

[35] (increased AP and Alanine Aminotransferase activity and histopathological changes including multiple basophilic foci, clear cell foci, and fine, minimal fatty vacuolation of periacinar hepatocytes)

In summary, alosetron is rapidly absorbed and extensively metabolized after oral administration to mice, rats, rabbits, and dogs. In pregnant rats and rabbits alosetron crosses the placenta and, in lactating rats, related metabolites are excreted in the milk, so **there is potential to affect fetal and infant functions**. Pharmaco- dynamically, alosetron is active in animal models of anxiety, psychosis, cognitive impairment, drug withdrawal, and emesis. However, the drug does not cause adverse cardiovascular or respiratory effects, nor adverse pharmacodynamic effects in conscious normal animals at doses within the range proposed for human administration, adjusted for body size. Alosetron is a highly selective and potent antagonist of 5-HT_3 receptors. It showed anxiolytic effects, and muted withdrawal effects from diazepam, alcohol, nicotine, and cocaine, without producing withdrawal effects on its own.

At doses over 1000 times the expected relative human dose, hepatic foci of basophilic infiltrates were noted in female rats in 6 and 12-month studies at 40 mg/Kg/day. However, there was no carcinogenicity. I.V. administration in Cynomolgus monkeys showed no cardiovascular effects at doses up to 1 mg/Kg, except for a single ventricular ectopic beat and small increase in QT interval, believed not to be drug-related. The reported increased hearing threshold in the 1-year toxicity studies in rats and dogs was not observed in the shorter term studies (up to 6 months). Data from extensive toxicological assessments show that alosetron is well tolerated in all species studied. **The reported preclinical adverse event profile has not raised concerns of undue risk in humans.**

In conclusion, adequate preclinical studies have been conducted and upon recommendation of the Pharm/Tox reviewer, relevant findings of the pre-clinical studies should be incorporated in the labeling (pages 108 through 110 of Dr. Zhang's review of November 4, 1999).

TABLE 7
NDA 21-107

Alosetron: Toxicity Studies in Animals

I. RATS					
I.V. 1 Month	**Oral 34/35d**	**Oral 6 mo.**	**Oral 12 mo.**	**Oral 3 mo.**	**Oral Carcinogenicity**
(0, 1, 3.5 and 12.25 mg/Kg/d) • CNS	(0, 1, 8, 40 [days 1-5]/64 mg/Kg/d) • The high dose was lethal • Partial thymus involution shown histo-pathologically	(0, 1, 8 and 20 [Days 1-4]/40 [Days 5-7]/64 [Days 8-54-55]/40 [Days 55/56 onwards] mg/Kg/d • CNS and • Liver	(0, 1, 6.5, and 20/40 mg/Kg/d) • CNS • Liver • 1 hearing acuity in M + F animals	(0, 10, 20 and 40 mg/Kg/d) (in diet) • Useful to select 40 mg/Kg/d as the max tolerated dose in rat carcinogenicity studies	(0, 1, 6.5 and 40 mg/Kg/d) • Treatment had no significant effect of intercurrent mortality rates • ALOS did not have tumorigenic potential
II. DOGS					
I.V. 1 mo.	**Oral 35d**	**Oral 6 mo.**	**Oral 12 mo.**		
(0, 1, 3.5 and 12.25 mg/Kg/d) • CNS	(0, 1, 5.5, and 30 mg/Kg/d) • High dose was lethal • CNS • Thymus	(0, 1, 5.5, and 20 [Days 1-3]/ 30 [Days 4-8]/ 25 [Day 9 onwards mg/Kg/d) • High dose was lethal • CNS • Liver	(0, 1, 5 and 20 [Days 1-3]/25 [Day 4 onwards] mg/Kg/d) • High dose was lethal • CNS		
III. MICE					
Oral 13 wks.	**Oral Carcinogenicity 94/95 wks in M 104/105 wks in F**				
(0, 20, 30 and 40 mg/Kg/d) • Useful to select 30 mg/Kg (via drinking water) as the max. tolerated dose in mouse carginogenicity studies	(0, 0, 1, 5.5 and 30 mg/Kg/d) • No treatment related clinical signs of toxicity • ALOS did not have tumorigenic potential				

MTL's Table.

2. Safety Studies in Humans

a. Primary Safety Database (Table 8)

Five Phase II, III and long-term studies provided the most pertinent safety data on 1 mg b.i.d for 12 weeks, the proposed dose of alosetron. Of the five studies listed in Table 8, three (P12, 2001 and 3003) enrolled both men and women. The other two (principal efficacy Phase III trials 3001 and 3002) enrolled only women. The primary safety database identified by the sponsor comprised 1263 patients (184 M, 1079 W) who received ALOS, and 834 (54 M, 780 W) who received PL for up to 12 weeks in the first four clinical trials listed in Table 8.

TABLE 8
NDA 21-107

Primary Safety Database

	(mg, b.i.d.)	(men/women)
I. Phase II, Dose Ranging		
• S3BP12	0.1, 0.5, 2	127/335
• S3BA2001	1, 2, 4, 8	111/258
II. Phase III, Proposed Dose		
• S3BA3001	1 (principal efficacy)	0/626
• S3BA3002	1 (principal efficacy)	0/647
III. Long-Term Safety		
• S3BA3003	1 (year-long study)	221/507
Total		459/2373
NOTE: Maximum daily doses up to 16 mg b.i.d. have been administered to healthy subjects and have been well tolerated.		

b. Serious Adverse Events (and Deaths) in Phase II/III 12-week Trials

As summarized in Table 9, the proportion of patients experiencing any serious AE while receiving ALOS (0.1 and up to 8 mg b.i.d.) was similar to placebo.

TABLE 9
NDA 21-107

Serious Adverse Events in Phase II/III 12-week Trials

		ALOSETRON mg BID					
	PL [n=834]	0.1 [n=115]	0.5 [n=116]	1 [n=702]	2 [n=187]	4 [n=75]	8 [n=60]
Any Serious AE	14 [2%]	1 [<1%]	3 [3%]	17 [2%]	7 [4%]	2 [3%]	2 [3%]

- There were no deaths in Study S3BP12, S3BA2001, and 3002.
- There was one death that occurred before Study 3001, of patient #4129, a 42-y old Caucasian woman. She was severely depressed and committed suicide by shooting herself in the heart during the screening phase before randomization. She took no test medication and was not included in the ITT.
- Two (2) of the 542 patients who had taken ALOS in study 3003 up to February 1999 died of sudden cardiac events; none of the 175 on placebo died. Data from this study are not included in Table 9. Both deaths were attributed to heart and vascular disease that long preceded the entry of the two (T.G.G., #11950 and S.C.H, #10209) patients into the trial. Clinical summaries are provided on page 44 of Dr. Senior's review.
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c. Adverse Events Causing Premature Withdrawal (Table 10)

In each of these clinical trials, significantly more g.i. events and specific constipation occurred with ALOS than PL, with dose response when more than one dose level was tested. No significant increase in headaches, arrhythmias or AEs in other systems was seen.

TABLE 10
NDA 21-107
Adverse Events Causing Premature Withdrawals

I. Study S3BP12

	PL BID [n=117]	ALOS (mg BID) 0.1 [n=115]	0.5 [n=116]	2.0 [n=114]
Withdrawn prematurely	33 (28.2%)	33 (28.7%)	41 (35.3%)	32 (28.1%)
Any AE	8 (6.8%)	12 (10.4%)	23 (19.8%)	18 (14.9%)
Gastrointestinal event	**5 (4.3%)**	**8 (7.0%)**	**17 (14.7%)**	**14 (12.3%)**
constipation	**2 (1.7%)**	**3 (2.6%)**	**8 (6.9%)**	**9 (7.9%)**

II. Study S3BA2001

	PL BID [n=80]	ALOS (mg BID) 1 [n=70]	2 [n=73]	4 [n=75]	8 [n=68]
Withdrawn prematurely	12 (15.0%)	15 (21.4%)	22 (30.1%)	20 (26.7%)	20 (29.4%)
Any AE	5 (6.3%)	8 (11.4%)	18 (24.7%)	11 (13.3%)	17 (25.0%)
Gastrointestinal event	**4 (5.0%)**	**7 (10.0%)**	**17 (23.3%)**	**9 (12.0%)**	**16 (23.5%)**
constipation	**2 (2.5%)**	**7 (10.0%)**	**12 (16.4%)**	**8 (10.7%)**	**13 (19.1%)**

iii. Studies S3BA3001 and 3002

	3001			3002		
	PL BID [n=316]	ALOS 1 mg BID [n=309]	p-value	PL BID [n=321]	ALOS 1 mg BID [n=322]	p-value
Withdrawn prematurely	71 (22.5%)	72 (23.3%)	N.S.	53 (16.5%)	79 (24.5%)	**0.013**
Any AE	**21 (6.7%)**	**48 (15.5%)**	**<0.0005**	**14 (6.7%)**	**49 (15.2%)**	**<0.0001**
Gastrointestinal event	**13 (4.1%)**	**45 (14.6%)**	**<<0.0001**	**11 (3.4%)**	**43 (13.4%)**	**<<0.0001**
constipation	**5 (1.6%)**	**32 (10.4%)**	**<<0.0001**	**1 (0.3%)**	**33 (10.2%)**	**<<0.0001**
all other events	8 (2.5%)	13 (4.2%)	N.S.	16 (5.0%)	18 (5.6%)	N.S.
Neurological event	2 (0.6%)	3 (1.0%)	N.S.	1 (0.3%)	1 (0.3%)	N.S.
headache	1 (1.3%)	2 (2.9%)	N.S.	0 (0.3%)	1 (0.3%)	N.S.
Cardiovascular event	1 (0.3%)	0	N.S.	0	0	N.S.
arrhythmias	0	0	N.S.	0	0	N.S.
Malaise or fatigue	2 (0.6%)	4 (1.3%)	N.S.	0 (0.6%)	1 (0.3%)	N.S.
All other system AEs	11 (3.5%)	8 (2.6%)	N.S.	3 (0.9%)	9 (2.8%)	N.S.

IV. Study S3BA3003

	PL BID [n=175]	ALOS 1 mg BID [n=542]	p-value
Withdrawn prematurely	61 (35%)	237 (43%)	N.S.
Any AE	**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 events*	19 (10.9%)	59 (10.7%)	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: For studies P12 and 2001 events other than those occurring in the g.i. tract, are not depicted.

* Some patients had more than one AE

d. Adverse Events in Phase II/III, 12-week Trials (Table 11)

The main significant difference between test medication and PL was in adverse g.i. events, particularly the highly significant and clearly dose-related increase in **constipation**. Nausea, abdominal discomfort and pain and headaches were not a problem.

TABLE 11
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Adverse Events: General
(Phase II/III 12-week trials)

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

e. Adverse Events/Evaluations of Special Interest

a) Preliminary Special Studies

GlaxoWellcome conducted 21 trials (Volume 209, page 38, 43-4) of single doses of ALOS given to 710 healthy volunteers outside the U.S., from 1989 to 1992. These were PK studies, including food interaction, bioequivalence, and PD evaluations, including intradermal serotonin-induced flare response, gastrointestinal transit time, water absorption, visceral sensitivity, gastric acidity, cardiovascular effects, and drug interactions. All of these studies were included in the integrated database provided by the sponsor. The main adverse effect noted was **headache** after either I.V. or oral alosetron (sponsor's Volume 209, pages 72-73), but there were no serious effects. Dr. Senior noted that no cases of unexplained rectal bleeding, or suspected **ischemic colitis** were reported in these studies, most of which were short-term or single-dose studies, and many were done in healthy young men rather than in middle-aged women with IBS. In addition, such events were not specifically looked for.

Also studies[36] were done in Japan to investigate single-dose ALOS PK in Japanese subjects (Studies AS-01 and AS-03), and in France to investigate the PKs of alosetron in renally impaired persons (S3BB1010). There were no additional adverse effects in the two Japanese studies, and there were no significant effects on plasma uptake or clearance of 1-mg oral doses of ALOS in

[36] These studies were not included in the integrated safety database.

moderate (creatinine clearance 30-60 mL/min) or severe (10-<30 mL/min) renal impairment, compared to healthy subjects (sponsor's Volume 209, page 123).

In summary, studies in both IBS patients and healthy volunteers showed ALOS to be constipating, at the proposed dose of 1 mg b.i.d. to be recommended for treatment of IBS in women. Headache, variably seen in some of the healthy volunteers, was not seen in ALOS-treated more than PL-treated patients with IBS in the controlled studies.

b) Audiometry Testing

Because of the findings in pre-clinical evaluations, special assessments of hearing acuity and tinnitus were done in long-term study S3BA3003 (sponsor's Tables 7.16 and 7.17, volume 205, pages 145 and 146). No significant differences in either pure tone audiometry results or development of tinnitus between treatment groups were shown.

c) Effects on Cardiac Conduction in Humans

Phase I studies targeted EKGs at and around C_{max}. Studies of alosetron and cisapride combination were conducted. In long-term safety studies, EKG were carried out at baseline (pre-drug) and after 2 months. It was concluded that **alosetron had no effect on cardiac conduction.**

d) Further Analyses of EKG Changes

The sponsor provided an expert appraisal by Dr. Julie Fetters (April 10, 1999); this assessment was based on review of 723 patients in S3BA3003, randomized 3:1 to ALOS or PL. Of these 723 patients, 232 had pre-study abnormalities that persisted, but were not worsened by ALOS; 83 had pre-study abnormalities that disappeared after 2 months on study, another 362 showed no abnormalities before or after study drug, and 46 patients developed new abnormalities.

- In the group of patients that developed new abnormalities, 33 ALOS-treated patients developed the following: 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 MI in 1, right axis deviation in 1, incomplete RBBB in 1.

- Among 13 PL-treated patients, bradycardia occurred in 6, incomplete RBBB in 3, and increased QTc interval, sinus tachycardia,MI, and rare premature beats in one of each of these patients.

- Among the 232 patients with pre-study abnormalities, sinus bradycardia was the most prevalent abnormality in both the ALOS-treated and PL-treated patients, and the only clinically significant change was atrial flutter in 1 patient on PL. 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.

From the above information, Dr. Fetters concluded that ALOS treatment does not cause significant EKG abnormalities. This reviewer agrees with this conclusion.

e) Further Characterization of Constipation

The subject of constipation was one of the safety issues discussed by GlaxoWellcome as well as by Dr. J. Senior at the G.I. Advisory Committee Meeting of November 16, 1999. Highlights of these presentations are given below.

- In Phase II studies, 13% to 29% of the patients experienced constipation with doses of ALOS 0.5 mg b.i.d. or higher; this was higher than the 3% to 6% observed with PL. Most patients had only one episode, but with a dose of ALOS of 0.5 b.i.d. or higher, 7% to 19% of the patients withdrew because of constipation, compared to 2% to 2.5% of those given PL.

- In Phase III trials (Table 12) there were highly significant differences between ALOS 1 mg b.i.d. and PL on three constipation parameters examined. This included new onset of constipation while on test medication, treatment interrupted because of constipation and proportion of patients withdrawn from trials 3001 and 3002 because of constipation.

TABLE 12
NDA 21-107

Constipation in Principal (Phase III)
Efficacy Studies 3001 and 3002

	PL BID 638 women	ALOS 1 mg BID 631 women	p
Constipation, new onset while on study drug	31 (4.9%)	176 (27.9%)	<<0.001
Treatment interrupted, because of constipation	25 (3.9%)	86 (13.6%)	<.001
Withdrawn from study, because of constipation	6 (0.9%)	65 (10.3%)	<<0.001

Source: Dr. Senior's November 16, 1999 Advisory Committee Slide No. 10

- Findings in study 3003 reconfirmed those mentioned repeatedly above in the other studies. Very significant differences were found between treatment groups in the relative numbers of patients withdrawn from the trial because of AEs; these were due almost entirely to g.i. events and particularly if not entirely to constipation.

f) Changes in Laboratory Values, Including Transaminases and Bilirubin

This information arises from 12-week Phase II/III trials where CBC and Chemistry Panels were obtained at baseline and month 1, 2, 3 and from the long-term safety study 3003. In the latter, the CBC and Chemistry Panel were obtained at baseline and at month 2, 4, 6, 8, 10 and 12. A summary of results is given below.

- There were no clinically relevant changes in any hematologic or chemistry parameter during ALOS treatment up to 12 months.
- Because of a case of hepatitis (see below), an in-depth review of LFTs was undertaken. Similar frequency for elevation (>2-fold) in LFTs was observed for ALOS- and PL-treated groups.
- There were no serious AEs of hepatitis or elevated LFTs.

CASE OF HEPATITIS (Table 13)
(Patient No. 4595, Study S3BA3001)

- A 33y old WF was enrolled into study 3001 on 2/9/98 and randomized to ALOS 1 mg b.i.d.
- Upon study enrollment the subject's LFTs were WNL (Table 13).
- She had a previous history of asthma, depression and hypothyroidism.
- Concomitant medications during the trial included: synthroid, estrogen, albuterol, norfloxacin (2/27 → 3/19/98), prednisone taper (4/16/98), omeprazole, zafirlukast, and sulfasalazine (5/22/98).
- Following 4 weeks of ALOS treatment, the patient experienced rectal bleeding (3/30/98 through 4/1/98). On the basis of endoscopic evaluations, **Crohn's disease** was diagnosed (4/7/98 → not resolved).
- The patient was noted to have mild cholestasis and transaminitis (3/20/98 through 4/22/98), with AEs of elevated bilirubin (4/17/98 through 5/1/98) and elevated LFTs (4/17 through 5/1/98) but NO JAUNDICE.
- Pt. No. 4595 was withdrawn from the trial on 5/1/98.
- All LFTs had fully normalized by 5/1/98.

TABLE 13
NDA 21-107

Serial Hepatotoxicity Tests for Patient #4595 (Study 3001)

Test (NR) Date (1998)	ALT 6-34 IU/L	AST 9-34 IU/L	AlkPhos 31-110 IU/L	Total Bili 0.2-1.2 mg/dL	Comment
09 Feb	21	26	103	0.5	screening
27 Feb					start drug
20 Mar	65	62	198	0.4	22nd Day
17 Apr	131	111	174	2.1	50th Day
20 Apr					stop drug
22 Apr	75	38	156	1.1	off 2 days
01 May	29	10	90	0.7	off 11 days
15 May					ERCP done

Note: NR, normal range; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AlkPhos, alkaline phosphatase; Bili. bilirubin; IU/L, international of enzyme activity per liter of serum.

- 15 days after ALOS discontinuation (5/15/98), an ERCP was performed, reportedly to evaluate the prior LFT abnormalities. During the ERCP the patient developed pulmonary edema as a reaction to general anesthesia. She was hospitalized. No additional LFTs were reported. Symptoms resolved and the patient was discharged 8 days later. In the investigator's opinion the event (the sponsor is not clear to what event reference is being made) was unrelated to test medication.

Additional Comments

This case was reviewed by Dr. Senior at the November 16, 1999 GI Advisory Committee meeting. He invoked the postulate by Dr. Hyman J. Zimmerman (a recently deceased respected hepatologist) that

> . . . "if drug-induced hepatocellular injury, shown by elevated ALT values, is accompanied by jaundice, acute liver failure may be expected in 10-15% of patients so affected."

Upon detailed examination of the above ennumerated facts, this reviewer does not agree that the above statement applies to this case. This patient did not have jaundice, only elevation of serum bilirubin (from 0.5 to 2.1 mg/dl) and the latest value (on 4/17/98) was only twice the upper limit of normal (1.2 mg/dl). Moreover, although there was transaminitis, the elevations of liver enzymes (131 for ALT and 111 mg/dl for AST on 4/17/98) were not marked. In addition, the case was confounded by the use of several concomitant medications and the diagnosis of Crohn's disease, which in itself may be accompanied by perihepatitis, PSC, etc. In summary, although there is not much concern about the single case of mild hepatitis arising in apparent temporal relationship to alosetron administration, this information should, conservatively, be incorporated in the labeling.

g) COLITIS

i) Introductory Remarks

- COLITIS (inflammation of the colon) could be of the following types:

  - Bacterial[a]
  - Collagenous
  - Cystica Profunda
  - Diversion
  - Drug Induced[b]
  - **Ischemic (including drug-induced)**[c]
  - Lymphocytic
  - Neutropenic
  - Pseudomembranous **(due to C. difficile)**
  - From Radiation Therapy
  - In Typhlitis
  - Ulcerative
  - Crohn's

a) Bacterial infections of the colon include thyphoid fever, shigellosis, cholera, clostridium difficile, traveler's diarrhea, giardiasis, amebiasis, diarrhea caused by *campylobacter jejuni* (and camp. coli), intestinal salmonellosis, cryptosporidiosis and **enterohemorrhige E. Coli.**
b) In antibiotic therapy; in gold therapy
c) Includes oral contraceptives, vasopressin, ergotamine, cocaine, dextroamphetamine, neuroleptics, tricyclic antidepressants, digitalis

NOTE: Of the many existing forms of colitis listed above, the sponsor has invoked the ischemic type and that associated with E. coli 0157:H7 as an explanation for the histopathological features in biopsies from the 4 cases of colitis reported in apparent association with alosetron but not with PL. In an attempt to further characterize these colitis cases, the MTL gives next a very detailed description of ischemic colitis, followed by a more succinct reference to the colitis induced by enterohemorrhagic E. coli.

ii Ischemic Colitis (IC)

- This form of colitis is due to a lack of arterial blood to the colon.

Incidence and Epidemiology

- As with all forms of visceral ischemia, IC occurs primarily in middle-aged and elderly persons. The overall incidence is unknown because many cases resolve spontaneously and are unrecognized. Ischemic injury to the colon usually occurs in associated with aortic by surgery or acute systemic hypotension.

Etiology and Pathogenesis

- The same adaptive mechanisms protecting the small intestine from ischemic injury are operative in the colon. Autoregulation, capillary recruitment, increased oxygen extraction, and colateral flow all help maintain the oxygen supply in the setting of compromised arterial inflow.

- The cecum, right colon and transverse colon are served primarily by tributaries of the superior mesenteric artery, whereas the left colon receives flow from tributaries of the inferior mesenteric artery.

  - The Splenic Flexure is in the watershed region of the superior and inferior mesenteric arteries and is the colonic site most susceptible to ischemic insult.

  - The rectum is well protected by an overlapping vascular supply from tributaries of the inferior mesenteric artery and the internal iliac artery.

- In contrast to acute mesenteric ischemia, spontaneous occlusion of the inferior mesenteric is an uncommon cause of ischemic colitis.

- Most cases are caused by SYSTEMIC HYPOPERFUSION or SURGICAL DISRUPTION OF BLOOD FLOW in the inferior mesenteric artery after AORTIC SURGERY. System hypoperfusion is often accompanied by ANGIOTENSIN-MEDIATED VASOCONSTRICTION, Similar to the pathophysiologic events of NONOCCLUSIVE MESENTERIC ISCHEMIA.

Clinical Features

- Many cases of mild IC are not recognized because patients are unable to report symptoms in the immediate postoperative period or in the setting of a critical illness that compromises splanchnic blood flow.

- The most common presentation is crampy lower abdominal pain, nausea, vomiting and bloody diarrhea several hours to days after an episode of **hemodynamic instability**.

  - The low-flow state is transient and not recognized in many patients.

  - A small percentage of patients with chronic colonic ischemia present with obstructive symptoms caused by a segmental ischemic stricture.

  - 'Physical findings of acute IC are nonspecific and include fever, abdominal tenderness and occult or overt rectal blood.

- Patients with medication-induced colonic ischemia present with

  - abdominal pain (possibly with rebound tenderness and guarding)
  - bloody or nonbloody diarrhea
  - tenesmus
  - nausea
  - vomiting
  - and fever

  Leukocytosis may be present.

Findings on Diagnostic Testing

- Diagnosis is suggested by negative findings for other causes of bloody diarrhea in the elderly population (i.e., Polyps, hemorrhoids, carcinoma, diverticulosis, and angiodysplasia) or feces contaminated by menstrual flow in younger women.

- The WCC may be elevated to ca. 20,000/mm^3.

- A flat plate x-ray may show

  Thickening of the Bowel Wall or "Thumbprinting"
  of the mucosa (this represents submucosal hemorrhage and edema).

- In contrast to mesenteric ischemia, angiography is rarely informative in IC because most spontaneous episodes are the result of systemic low-flow states rather than acute occlusion of the inf. mesenteric artery.

- Sigmoidoscopy may be very useful in confirming the diagnosis but in many instances it may reveal only bloody fluid.

- Because the systemic and splanchnic vascular supply overlap, the rectum usually is spared, and abnormal mucosa is first encountered in the rectosigmoid region.

- On colonoscopy, the mucosa is usually edematous and friable in the early stages of IC and frankly ulcerated and necrotic in the later states. Other colonoscopic findings include erythema and granularity.

- The distribution of injury is variable, but usually involves the **left colon**.

- Endoscopic Biopsy reveals nonspecific inflammation, and occasionally, a characteristic pattern of superficial epithelial sloughing and subepithelial hemorrhage.

Management and Course

- Most patients with IC improve with conservative measures that optimize cardiovascular function.
- Unlike for nonocclusive mesenteric ischemia, vasodilation agents have not proved useful in treating IC.
- Vasoconstricting agents and volume depletion should be avoided.
- If patients deteriorate clinically or demonstrate frank peritonitis, emergency surgical exploration is required and all necrotic segments should be resected.
- Similarly, patients with symptomatic colonic strictures should undergo elective resection.
- Revascularization is not indicated for IC.
- Although a small percentage of pts. succumb to complications of IC, survival is most often limited by the acute illness precipitating the compromised colonic perfusion.

Medications That Produce Colonic Ischemia

- Oral contraceptive use (10 days to 11y) is associated with mesenteric arterial and venous thrombosis, typically presenting as IC.
- Estrogen produces hypercoagulability, mesenteric vasospasm, and endothelial proliferation with subendothelial fibrosis.
- Vasopressin causes colonic ischemia by reducing blood flow whereas
- Cocaine and dextroamphetamine evoke intense mesenteric vasospasm.
- Ergot preparations produce colonic vasospasm, whereas Ergotamine suppositories can cause rectal ulcers with obliteration of small blood vessels, endothelial proliferation, and thickening of the vascular wall.
- IC has been reported after the use of neuroleptic and tricyclic antidepressants.
- Digitalis Preparations are associated with colonic ischemia, in part because of the underlying low-flow states (e.g. CHF) that produce **colonic hypoperfusion**.
- These agents produce mesenteric vasoconstriction in animal models however, and may directly contribute to consequent ischemia.

iii) Escherichia coli 015:H7-Associated Colitis[37]

- This syndrome was recognized in the early 70s before an etiology was found and reported under names such as evanescent colitis, transient ischemic colitis or transient hemorrhagic colitis. Since its description as a cause of hemorrhagic colitis (HC) in 1983, Escherichia coli (E. coli) 0157:H7 has been increasingly recognized as an important pathogen.

- E. coli serotype 0157:H7 was first isolated in 1982, when 47 persons in Michigan and Oregon developed bloody diarrhea after eating hamburgers contaminated with the organism. Retrospective contamination of more than 3000 E. coli cultures obtained between 1973 and 1982 has found only one isolation with serotype 0157:H7; it was from a 50-y-old woman who had had an episode of acute, self-limited, grossly bloody diarrhea in 1975. Since the initial reports, sporadic cases and outbreaks of E. coli 0157:H7 infection have increasingly been reported, and surveillance and prospective studies to identify and characterize disease associated with E. coli 0157:H7 have been started in the U.S. and abroad.

- Infection with E. coli 0157:H7 presents with a wide spectrum of clinical manifestations. These include asymptomatic carriage, only nonbloody diarrhea, severe abdominal cramps with little or no fever and watery diarrhea that often progresses to grossly bloody diarrhea. Extraintestinal involvement, including cardiac and neurologic manifestations, has been reported and infection can be associated with serious conditions such as the hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura. The disease can be fatal.

- Not only is E. coli 0157:H7 an important agent for hemorrhagic colitis, it is also one of the leading causes of bacterial diarrhea.

- Patients at extremes of age have an increased risk for infection and associated complications.

- Transmission of E. coli 0157:H7 is primarily food-borne. Undercooked meat is the most common culprit, and secondary person-to-person spread is also important.

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[37] [P.M. Griffin et al., Escherichia coli 0157:H7-Associated Colitis. A clinical and Histological Study of 11 cases. Gastroenterology 99:142-149 (1990)]
[K.J. Morris, G.G. Rao Conventional screening for enteropathologic Escherichia coli in the UK. Is it appropriate or necessary?, J. Hosp. Infect. 21:163-167 (1992)]
[C. Su and L.J. Brandt. Escherichia coli 0157:H7 Infection in Humans Ann. Intern. Med. 123:698-714 (1995)]
[R. Gonzalez et al. Age-specific prevalence of Escherichia coli with localized and aggregative adherence in Venezuelan infants with acute diarrhea. J. Clin. Microbiol. 35:1103-1107 (1997)]
[T.J. Baldwin The 18th C.L. Oakley Lecture. Pathogenicity of enteropathogenic Escherichia coli. J. Med. Microbiol. 47:283-293 (1998)]
[N. Porat et al. Prevalence of intestinal infections caused by diarrheagenic Escherichia coli in Bedouin infants and young children in Southern Israel. Pediatr. Infect. Dis. J. 17:482-488 (1998)]
N.T. Perna et al. Molecular evolution of a pathogenicity island from enterohemorrhagic Escherichia coli 0157:H7. Infect. Immun. 66:3810-3817 (1998)]
[C Su et al. The immunological diagnosis of E. Coli 0157:H7 Colitis: Possible Association with Colonic Ischemia. Amer. J. Gastroenterol. 93:1055-1059 (1998)]

- The organism produces at least two shiga-like toxins that differ antigenically, physicochemically, immunologically, and in their biological effects. These toxins are thought to have direct pathogenic significance in E. coli 0157:H7 infection.

- Direct stool detection or culture of E. coli 0157:H7 remains the preferred approach to its diagnosis. Thus, this infection is usually **diagnosed from a POSITIVE STOOL CULTURE, from the presence of Shiga-like toxins or both.** [Timely collection (within 7 days of illness onset) of a stool sample for culture is imperative for a high recovery rate]. **If infection is confirmed, it should be reported to public health officials.**

- Radiological and colonoscopic changes range from a normal appearance to mucosal and submucosal hyperemia, edema, erosions, ulceration, and hemorrhage; bowel wall thickening mainly affects the ascending and transverse colon.

- Microscopically, E. coli 0157:H7-associated colitis can resemble a combination of **colonic ischemia** and of infections and toxic injury similar to that seen in colostridium difficle-associated pseudomembranous colitis. Submucosal hemorrhage, edema, and fibrin exudation are the most prominent features; other less common lesions include ulceration, hemorrhage, capillary thrombi, and mild neutrophil infiltration of the mucosa.

- Currently, the diagnosis of infection with E. coli 0157:H7 is established by finding sorbitol nonfermenting colonies on MacConkey-sorbitol agar that react with 0157 and H7 antisera.

- Because the hemorrhagic colitis of E. coli 0157:H7 infection in older adults is frequently indistinguishable from COLONIC ISCHEMIA in its presentation, colonic ischemia is often the initial diagnosis until **the organism is detected by stool culture.**

- Because of the similarities between ischemic and hemorrhagic colitis (of E. coli infection), Su et al. [Amer. J. Gastroenterol. 93:1055-1059 (1998)], have proposed that, in a subset of elderly patients, colonic ischemia is associated with, and possibly precipitated by, the infection. Demonstration of such an association, however, is problematic, as a retrospective diagnosis using stool culture is not possible and identification of the organism is not routinely performed in most clinical microbiological laboratories.

- In an attempt to assess retrospectively the presence of the bacteria in patients with colitis, Su et al. [Locus cited] (1998)], developed an immunohistochemical approach to its diagnosis using histological sections from archival formalin-fixed, paraffin-embedded tissue and immunospecific antisera that readily detected the bacteria in known, culture-proven cases of colitis. To determine whether a relationship exists between infection with the bacteria and colonic ischemia, sections from cases of colonic ischemia as well as other forms of colitis (idiopathic IBD and antibiotic-associated pseudomembranous colitis) were then evaluated for the presence of the bacteria.

- Both cases (100%) of E. coli 0157:H7 colitis and 3 of 11 (27.3%) cases of IC stained positive by light microscopy. In one culture-proved case, electron microscopy demonstrated staining of bacillary structures; in 2 cases of colonic ischemia, extensive

deposits of chromagen material were present that were associated neither with inflammatory cells nor with bacterial forms.

- Su et al. concluded that immunoperoxidase staining of archival sections may be used to diagnose E. coli 0157:H7 infection: an etiological role for this organism is possible in some cases of colonic ischemia. In this study, with this staining procedure, the finding of the bacteria in several cases diagnosed clinically as colonic ischemia, is meaningful. In conclusion, in a subset of patients, **colonic ischemia may have an infectious etiology.**

iv) Ischemic Colitis in the Alosetron Safety Database

In his safety review, Dr. Senior called attention to a "syndrome of constipation, abdominal pain, and rectal bleeding not accounted for by known causes of rectal bleeding (hemorrhoids, menstrual bleeding)". He attributed the syndrome to **ischemic colitis**, which was diagnosed by colonoscopy, in all three patients, one in each of three controlled trials. To these, a fourth case was reported by the sponsor on November 12, just prior to November 16 meeting of the GI Advisory Committee.

GlaxoWellcome called our attention to the fact that Dr. Kay Washington (Vanderbilt University) had carried out histopathological evaluation of all four cases so far reported as ischemic colitis. In this section of my review I first reproduce the clinical summaries for the 3 cases described by Dr. Senior and the additional cases presented at the Advisory Committee meeting. I then highlight the similarities and dissimilarities between the cases from the clinical, colonoscopic and histopathological viewpoints, incorporating Dr. Washington's information where applicable. The aim of this approach is to further characterize these four colitis cases.

a. Clinical Summaries (Table 14)

NOTE: To facilitate comparisons, inclusion of Dr. Wshington's information and possible conclusions, the cases are identified as:

Pt. No.	Study No.	Case I.D.
2829	S3BA2001[a]	The 1996 case
7195	S#BA3002[b]	The 1998a case
15687	S3BA3001[c]	The 1998b case
34069	S3B30011[d]	The 1999 case

a) One of the two Phase II dose-ranging studies (PL vs 1, 2, 4 or 8 mg case ALOS b.i.d.)
b) and c) The two principal Phase III trials.
d) New trial

TABLE 14
NDA 21-107

Concise Clinical Summaries of the 4 Cases of Colitis in the Alosetron Safety Database

Patient #2829, Study S3BA2001
The 1996 Case

- 33 year-old Caucasian woman
- 2 mg bid alosetron for 2 days, starting 17 Jul 96
- severe abdominal pain, 30 watery stools that day
- nothing found on exam in E.R., Levsin given
- pain worse, peritoneal signs, admitted
- colonic mucosal erosions at 40-80 cm
- ischemic colitis diagnosed, withdrawn from study
- gradually recovered over the next 11 weeks

Patient #15687, Study S3BA3001
The 1998b Case

- 41-year-old Caucasian woman
- 1 mg bid alosetron for 54 days, starting 15 Jul 98
- abdominal pain, rectal bleeding; seen in E.R.
- did not respond to hyoscyamine; admitted
- severe segmental colitis[a]
- biopsy indicated ischemic colitis; withdrawn
- gradually recovered over subsequent weeks

Patient #7195. Study S3BA3002
The 1998a Case

- 48-year-old Caucasian woman
- 1 mg bid alosetron, for 39 days, starting 21 Jan 98
- rectal bleeding and crampy abdominal pain
- local doctor prescribed fluid and fiber
- did not respond, pain worse, admitted at 3 a.m.
- colonoscopy showed mucosal sloughing
- ischemic colitis not attributed to study drug
- withdrawn, no more episodes of rectal bleeding

Patient #34069. Study S3BA30011
The 1999 Case

- 61-year-old Caucasian woman
- 7 days of treatment with 1 mg bid alosetron
  - severe abdominal pain (10/28/99)
  - bloody diarrhea
  - WBC 19,700
- CT Scan (10/29/99)
- Mural thickening entire tranisverse colon, descending colon, hepatic flexure
- Changes were consistent with colitis but ischemic colitis was considered unlikely (IMAEt SMA)
- Colonoscopy (11/2/99)
  - Distal transverse to descending colon: patchy areas of edematous hyperemia adjacent to pale areas
  - Bx
  - D/C (11/03/99)

a) Reviewer's correction. Upon colonoscopy this patient (see Table 15) had segmental colitis involving the distal transverse, the descending colon, starting at 50 cm in the proximal sigmoid colon, not the right (ascending) or proximal transverse colon, as erroneously stated in the Safety Review.

b. Clinical Presentations: Similarities and Dissimilarities (Table 15)

The main reason for this comparison is an attempt to identifying a syndrome, common to all four cases regarding clinical presentation of these colitis cases [CONCLUSION: No syndrome was identified]. This conclusion is based on all pertinent information made available by the sponsor, including histopathological assessments carried out by Dr. Kay Washington (Vanderbilt University). The detailed discussion will consider at least three categories of diagnosis: a) clinical, which, of course includes results of x-ray and laboratory tests, b) endoscopic which included either a sigmoidoscopy and/or a total colonoscopy and finally c) a confirmation of the clinical-endoscopic diagnosis by evaluating histopathologic results of biopsy samples taken during the endoscopic procedure. Note that not all patients underwent subsequent colonoscopies/colonic biopsies. This reviewer is concerned, primarily, with information obtained at a time as close as possible to the initiation of the clinical adverse event (refer to Table 15).

- Clinically, the AE(s) occurred in relatively young female patients, as young as 33 years and early elderly (61y of age).

- It occurred in apparent temporal association with alosetron (but no association with placebo was reported) and began anywhere from 2 (the 1996 patient) to 54 days (the 1988b patient) after the starting of test medication.

- The AE was primarily characterized by **rectal bleeding** accompanied by abdominal pain of varying severity, at times (the 1996 patient) with concurrent peritoneal signs and sometimes (2 of the 4 patients) with leukocytosis, most (if by not all) times with diarrhea (NOT CONSTIPATION), and sometimes with fever.

- Information from radiological examinations is not very helpful in that these were not done in two of the four patients. In the 1996 patient, a flat plate of the abdomen revealed no evidence of free perforation. In the CT scan done in the 1999 patient, lots of information is reported, including mural thickening of the entire transverse colon, descending colon, hepatic flexure and all of this is compatible with colitis.

Up to now, all of this clinical information is compatible with the diagnosis made by each of the individual investigators: ISCHEMIC COLITIS. It cannot be concluded however, that they were induced by alosetron.

TABLE 15
NDA 21-107

Comparison of the Clinical, Key Laboratory, Endoscopic and Histopathologic Findings in Alosetron-treated Patients Developing Colitis in Randomized Clinical Trials

Case Age of Patient (years)	1996 (2 mg b.i.d.) 33	1998a (1 mg b.i.d.) 48	1998b (1 mg b.i.d.) 41	1999 (1 mg b.i.d.) 61
Time to AE (days)	2 (07/17/96)	9 (01/21/98)	54 (09/06/98)	7 (10/28/99)
Occurred during outbreak of E. coli infection	NO	NO	NO	NO
Abdominal pain	YES (severe)	YES (Crampy)	YES	YES (severe)
Peritoneal signs	YES	NO	NO	Not Reported
Fever	NO	YES	N0	NO
Rectal bleeding	YES (also Hemoccult +)	YES (Also hematochezia)	YES	YES
Diarrhea	YES	NO	YES	YES
Leukocytosis	NO (WBC 9,900)	YES (17,500)	NO(10,300)	YES (19,700)
Constipation	NO	YES	NO	NO
Stool Culture	96/24/96 • No enteric pathogens. identified, including salmonella, shigella, E. coli 0157:H7, yersinia or campylobacter • No C. difficile toxin detected	02/13/98 • No salmonella, shigella, yersinia, campylobacter or E. coli 0157 isolated. •Negative for C. difficile toxin	Not Reported	Not Reported • Negative for Ova and Parasites • Negative for Clostridium Difficile Toxin A
Hospitalization	YES	YES	YES	YES (?)
X-ray, CT scan	Flat plate of the abdomen revealed no evidence of free perforation	NOT DONE	NOT DONE	10/28/99 (Flat plate abdomen-upright) • Non-specific, non-obstructive bowel gas pattern • 10/29/99 (CT scan) mural thickening entire transverpe colon, descending colon, hepatic flexure, compatible with colitis
Immunohistochemistry for E. Coli 0157:H7				
(a) H&E	YES	YES	YES	YES
(b) Paraffin Embedded	YES	YES	NOT DONE	YES
Dr. Washington's Classification				
(a) H&E	-	Infectious	Infectious	+
(b) E. coli	-	+	Not Done	-

Withdrawn from trial Investigator's diagnosis Considered differential diagnosis	YES ISCHEMIC COLITIS Less likely, infectious vs IBD	YES ISCHEMIC COLITIS "Secondary causes for ischemic colitis will likely need to be evaluated"	YES ISCHEMIC COLITIS Crohn's disease or "self-limiting colitis.	YES (11/03/99) ISCHEMIC COLITIS CT scan: Infectious or Inflam. colitis is considered the most likely.
Diagnosis on discharge	Probable Ischemic colitis	Abdominal pain and hematochezia secondary to Ischemic colitis	LLQ pain and rectal bleeding secondary to apparent Ischemic Colitis	IC is felt to be unlikely given the involvement of multiple vascular territories (IMA and SMA) but cannot be completely excluded on the basis of this examination
Evolution Resolved without sequelae	Improved YES	Improved YES	Improved YES	Improved YES
MAIN SIGMOIDOSCOPIC/COLONOSCOPIC FINDINGS				
	07/22/96 • Normal mucosa from the rectum to ca. 40 cm • At 40 to 80 cm was edematous mucosa with scattered erosions and edema; the erosions had some friability with a small amount of white exudate → consistent with ISCHEMIC MUCOSAL TYPE INJURY	02/14/98 • Normal transverse and part of the proximal descending • At about 60 cm insertion, there were changes in the mucosa surface consistent with ISCHEMIC COLITIS • The mucosa was sloughing in some areas and ulcerating and was quite inflammed. • Involvement was down to 30 cm insertion in the mid-sigmoid colon. This area was quite painful to pass the scope through for the patient. • The distal sigmoid and rectum was not involved. • There was no active bleeding seen going on, except at the biopsy sites.	09/08/98 • Beginning at 50 cm in the proximal sigmoid colon there were streaks of erythema and erosions and this became progressively more impressive proximally so that in the descending colon there were extensive areas of shallow ulceration with erythematous irregular margins and skip areas. This involved the distal transverse colon and seemed to "peter out" in the mid-transverse colon where there were areas of simply of erosion and erythema and the proximal transverse colon appeared normal.	11/02/99 • Mucosal changes were noted from the descending colon to the distal transverse colon. • Patchy areas of edematous hyperemia adjacent to more pale areas. • Frequent diverticular orifices were noted in the sigmoid colon. • The differential diagnosis for the colonic inflammation includes IC

MAIN BIOPSY FINDINGS				
	07/23/96 • Regular and well ordered crypt architecture • Lamina propria contains the expected component of chronic inflam. cells • Small numbers of neutrophils within the lamina propria • Significant eosinophilic or granulomatous inflammation is not seen. • The subepithelial collagen table is not diffusely thickened • No evidence of a diffuse intraepithelial lymphocytosis. • Mild edema of the lamina propria along with focal fresh hemorrhage. → Diagnostic features of ISCHEMIC-MEDIATED, mucosal injury are not identified.	02/14/98 • The specimen consisted of 5 to 6 fragments, half of which were ischemic. • There was near full thickness ischemia of the mucosa in three of the fragments. → Final pathological diagnosis: ISCHEMIC COLITIS	09/08/98 • Biopsies were most consistent with ISCHEMIC COLITIS with coagulative necrosis that was superficial and inflammatory destruction of superficial crypts with normal architecture and spacing of the deeper crypts and no granulomas.	11/02/99 • The colonic biopsies were interpreted as ISCHEMIC COLITIS (unrelated to test medication, according to the investigator)

The endoscopic evaluations invariably confirm the initial clinical impression as they are consistent with ischemic mucosal type injury, with varying degrees of severity. The patients, who had been hospitalized because of the AE, were discharged with the following diagnosis that included ISCHEMIC COLITIS before results of histopathological examinations were available:

The 1996 patient: Probable ischemic colitis
The 1998a patient: Abdominal pain with hematochezia secondary to ischemic colitis
The 1998b patient: LLQ pain and rectal bleeding secondary to apparent ischemic colitis
The 1999 patient: ISCHEMIC COLITIS

According to this information, all four patients had clinical/endoscopically proven ischemic colitis. The subsequent question is whether the clinical/endoscopic diagnosis of ischemic colitis can be **confirmed** by the pathologist's evaluation of the biopsies taken during endoscopy. The results are not surprising; it is well known that, in some instances, the histopathological evaluation does not confirm the clinical/endoscopic diagnosis. The reasons for this are unknown but may include ascertainment bias and, most important, the fact that the histological features of ischemic vs other colitis are difficult to distinguish. Also, it is worth noting the differential diagnosis considered (see below). This reviewer wishes to emphasize that, whatever post hoc information from histopathologic evaluations may be obtained and added (Dr. Washington et al's imput), this does not negate the fact that clinically (and **this is the most important diagnosis)** these patients **all had ischemic colitis** as the main and most relevant component to explain the clinical picture. In summary (Table 15) the biopsies provided the information highlighted below.

i) The histopathological examination did not identify diagnostic features of ischemic-mediated mucosal injury in the 1996 patient.

ii) In the 1998a patient, the final pathological diagnosis was ischemic colitis.

iii) Biopsies were most consistent with ischemic colitis with concomitant coagulative necrosis in the 1988b patient

and

iv) The colonic biopsies were interpreted as ischemic colitis in the 1999 patient.

Thus, according to these facts, only in the 1996 patient there is a disconnect between the biopsy results and the clinical/ endoscopic diagnosis. In the other three cases, the biopsy data confirmed the clinical/endoscopic impression. Again, one cannot conclude that the cases of ischemic colitis were induced by alosetron.

Etiologically, the available information cannot negate that this IC may co-exist with some other form of colitis or that it may be due primarily or secondarily to some effect of the drug, in association with colitis of infectious origin. In other words, Dr. Washington's evaluations need to be put in the proper perspective.

In the sponsor's November 12, 1999 submission a Section entitled Ischemic Colitis Narrative, explains that Dr. Washington, and an independent reviewer, Dr. Lawrence Brandt, had reviewed the four cases of ischemic colitis occuring in 12-week studies with alosetron. Specifically, Dr. Washington performed histopathological evaluation and immunohistochemistry evaluation for E. coli 0157:H7. H&E preparations were available on all four cases and immunohistochemistry evaluation was done on three of the cases (see Table 15). These findings were presented at the November 16, 1999 GI Advisory Committee meeting and can be succinctly summarized as follows (refer to Table 15):

i) No pathology was present for case 2829 (the 1996 case).

ii) Two cases appear to represent infectious colitis with E. coli positivity on one specimen (the other specimen was not available as the hospital laboratory had lost the paraffin block). The statement is made that Dr. Washington will report to the AC identical appearance of H-E on slides from cases 7195 (the 1998a case) and 15687 (the 1988b case).

iii) Only case 34069 (the 1999 case) represented a histologic diagnosis of ischemic colitis.

Drs. Washington and Brandt concluded that there is no evidence to support a causal relationship between alosetron treatment and development of ischemic colitis. Although this reviewer does not entirely disagree with this statement, additional considerations need to be taken into account.

c. Comments on Dr. Washington's Approach

One cannot make a final diagnosis on the basis of histopathological information alone. It must again be noted that, according to the investigator(s)/consultant, who are the persons close to the experimental subjects (the patients experiencing the AEs), these patients all had a clinical/endoscopic diagnosis of ischemic colitis. The issue is: is this clinical/endoscopic diagnosis confirmed by the biopsy data? If not, what alternatives are there? Opportunities and constraints are highlighted below (refer to Table 15).

i) The 1996 case is already controversial, even before Dr. Washington's intervention, because diagnostic features of - upon biopsy examination - ischemic mucosal injury (suggested by the clinical presentation and confirmed on endoscopy) were not identified. Once again, this is an example (of many) where the biopsy findings do not necessarily confirm the clinical/endoscopic diagnosis.

ii) According to Dr. Washington, both the 1998a and 1998b appear to represent infectious colitis. However, neither case appeared to have occurred during an outbreak of E. coli infection. This is very important because physicians must report to public health authorities the occurrence of E. coli epidemics; this was neither done nor suspected. Moreover, in the 2/15/98 stool culture of the 1998a patient, no salmonella, shigella, yersenia, campylobacter or (more important) E. coli 0157 were isolated [a positive stool

culture does establish the definite diagnosis]. In the other patient (the 1998b case), stool culture was apparently done but not reported.

iii) It is also important to mention that Dr. Washington used an experimental, not yet validated procedure. Nonetheless, the main point of disagreement here is that, although histopathologically, ischemic and infectious components may co-exist, the local pathologist's readings of the biopsy specimens from both patients confirmed the diagnosis of ischemic colitis that had been suspected on the basis of clinical and endoscopic findings. As a matter of fact, in patient 1998b discharge summary (dated 9/10/98), Ronald P. Schwarz, M.D. makes the following comments:

". . . There were multiple shallow ulcers in appearance and distribution most consistent with ischemic colitis and Crohn's disease was in the differential. Biopsies, however, were most consistent with ischemic colitis with coagulative necrosis that was superficial and inflammatory destruction of superficial crypts with normal architecture and spacing of the deeper crypts and no granulomas.

"The patient's clinical course was also consistent with ischemic colitis in that she gradually and fairly rapidly improved with lessening of pain and cessation of bleeding. Therefore, no specific therapy was given. She was advanced to a regular diet and discharged. She underwent Doppler ultrasound of her mesenteric vessels to rule out any large vessel problem which was considered unlikely and this result is pending.

"It remains unclear whether her colitis was a side effect or complication of her study drug but this was considered less than likely, however, the patient does not have any obvious risk factors for ischemic colitis otherwise . . ."

iv) According to Dr. Washington, only the 1999 case represented a histologic diagnosis of ischemic colitis. This is in agreement with the pathologist's evaluation of the biopsies which, as pointed out above, confirmed the suspected clinical/endoscopic suspicion of ischemic colitis. However, results of stool culture for E. coli in this patient were not available. Moreover, from the CT scan, infectious inflammatory colitis is considered the most likely [NOTE: Admittedly, this may represent an over-reading of the CT scan]. According to this report, ischemic colitis was felt to be unlikely given the involvement of multiple vascular territories (inferior mesenteric artery=IMA and superior mesenteric artery=SMA, Table 15). It is said, however, that IC cannot be completely excluded on the basis of the CT scan examination.

v) It is of interest to bring out the issue of differential diagnoses considered in each case (Table 15):

1996 case:	"Less likely infectious vs IBD"
1998a case:	"Secondary causes for ischemic colitis will likely need to be evaluated"
1998b case:	"Crohn's disease or self-limiting colitis"
1999 case:	"Infectious or inflammatory is considered the most likely; ischemic colitis cannot be completely excluded"

Incidentally, it is not surprising for conditions such as Crohn's disease to be included in the differential diagnosis. This is because the modern approach to IBS, both clinically and during experimental trials in humans, emphasizes diagnosing the condition primarily on the basis of compatible signs and symptoms while depending less and less in the use of diagnostic devices. So, using this modern approach, some patients with organic disease of the gut may be misdiagnosed as having IBS. An example is patient #4595, in principal Phase III Study S3BA3001. This is the patient that experienced transaminitis and mild elevation of bilirubin [reviewed under V. B. 2.f) above]. Following four weeks of ALOS treatment, this patient experienced rectal bleeding (3/30/98 through 4/1/98). On endoscopy, Crohn's disease was diagnosed which, as of 4/17/98 had not resolved. The most likely possibility is that this patient had already Crohn's disease at the time of randomization into the trial.

vi) The reviewer's conclusion is that all four patients being considered had a clinical syndrome of ischemic colitis that was confirmed on endoscopy but not always supported by histopathological findings. This schemic colitis may coexist or even be the consequence of some form of E. coli infection. This infection is somewhat common. Marshall and his coworkers[38] from the Mayo Clinic, now routinely culture stool specimens for this organism. To determine the prevalence of E. coli 0157:H7-associated diarrhea in their patient population, they surveyed all submitted stool cultures for 6 months for this organism. Specimens were screened for non-sorbitol fermenting E. coli and confirmed by slide-agglutination and immobilization testing. Of 2,164 specimens, 10 yielded E. coli 0157:H7 by this approach [NOTE: This incidence seems similar to the one reported in the alosetron trials considered here]. It was the fourth most common bacterial stool pathogen found. These authors concluded that E. coli 0157:H7 causes sporadic infections in the Mayo Clinic patient population and should be considered in the differential diagnosis of acute hemorrhagic colitis.

vii) The MTL believes that there is no clear cut evidence for a causal relationship between alosetron treatment and the development of this colitis, which appears to be acute and possibly self-limiting. On the other hand, the direct or indirect contribution of alosetron use to this complex clinical/endoscopic/histopathological picture cannot be completely rule out. It is true that, as far as we know, all cases resolved without sequelae and there were no instances of necrosis/perforation that may necessitate colectomy.

One important reason not to entirely exonerate alosetron is that these four cases of ischemic colitis occurred exclusively among women that were taking the drug and none among the patients taking placebo. This is a hard to explain/accept coincidence. This reviewer agrees with Dr. Senior's recommendation 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 [see separate memorandum by the MTL and the Division's Director on this matter]. The study should be designed to be

[38] [W.F. Marshall et al. Results of a 6-month survey of stool cultures for Escherichia coli 0157:H7. Mayo Clinic Proc. 65:787-792 (1990)]

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.

2. Complete dissolution profiles of LOTRONEX™ in simulated intestinal fluid (pH 7.5) for various batches needs to be performed. Comparative dissolution profiles in water for

the same batches should be included in the submission. Until the results of these experiments are reviewed by the FDA, the interim dissolution specification should be Q=80% at 20 min.

3. Metabolism data for alosetron are conflicting or incomplete. Consequently, studies should be performed that address the following issues:

a. Metabolites detected in large amounts in Japanese subjects (N-desmethyl-alosetron) were not detected in the mass balance study performed in only two Caucasian males.

b. Radiolabeled mass balance studies indicate that circulating metabolite concentrations are approximately 10 fold greater than alosetron concentrations, yet ≥2/3 of the circulating radioactivity cannot be attributed to alosetron or specific identifiable metabolites based on data gleaned from various studies.

c. Insufficient information was provided about the contribution of metabolites to PD effect. For example, 6-hydroxy-alosetron is reported to be twice as potent as alosetron and is produced in large amounts presumably by the liver. It is largely eliminated in the urine, but is not detected in plasma. However, the limit of detection of 6-OH-alosetron is 6 fold greater than the Ki for $5HT_3$ receptors. Receptor affinities for free drug, protein binding, and circulating concentrations for metabolites including N-desmethyl-alosetron and glucuronide conjugates need to be examined. Circulating metabolite concentrations need to be determined in the range that might be clinically relevant.

d. It is not known which P_{450} isozymes produce which metabolites, nor was information provided on which isozymes are responsible for secondary metabolism. If inhibition of individual pathways were to occur, shunting of alosetron elimination to alternative pathways would occur. Under certain conditions, this could result in an increased formation and exposure to active metabolites. Consequently, isozymes and their formation products should be identified.

e. Multiple-dose metabolite kinetic data were not provided.

f. Metabolite kinetic data were not provided for women.

g. No data were provided on the potential for metabolites to cause inhibition of drug metabolism, nor were free concentrations identified in the alosetron *in vitro* drug interaction studies.

4. Due to LOTRONEX's *in vivo* inhibition of NAT2, *in vitro* interaction studies with NAT1 should be performed.

5. Since LOTRONEX™ is an indole, the potential to inhibit monoamine oxidases should be examined.

6. The effects of specific and nonspecific enzyme inducers on alosetron PKs and metabolite kinetics for active metabolites should be examined.

7. A study to examine the effect of LOTRONEX™ on gastrointestinal first-pass effect of drugs with low bioavailability due to inhibition of intestinal mucosal CYPIIIA4 should be performed.

In vitro Alosetron demonstrates moderate inhibition (18.6%) of midazolam metabolism by CYPIIIA4 pathways at alosetron concentrations (200 nM/L) only a few fold higher than the concentrations achieved in plasma with the proposed dosage regimen (10-25 ng/ml / ca. 30-75 nM/L). Localized concentrations of alosetron in the GI tract, after tablet dissolution, may be much higher than plasma alosetron concentrations (1 mg = 3.02 μMoles).

Clinically relevant PK interactions occur with orally administered cyclosporine and other compounds with high degrees of first pass metabolism by CYPIIIA4. These interactions are presumed to be primarily due to inhibition of GI mucosal CYPIIIA4 and that it is not necessary to have significant inhibition of hepatic CYPIIIA4. This assumption is based upon several studies, including one in anhepatic subjects during liver transplantation [Paine et al. CPT 1996.60:14-24]. In this study 43 $\pm$ 18% of a 2 mg po dose of midazolam was metabolized by only CYPIIIA4 during passage through the GI mucosa. When 1 mg is administered i.v. only 8 + 11% is metabolized during passage through the splanchic vascular bed (p=0.009). These data suggest that ca. 80% of the first pass effect of midazolam is due to metabolism by the intestinal mucosa.

8. A study in patients with hepatic insufficiency should be performed. The study should enroll sufficient subjects with various types and degrees of severity of hepatobiliary disease. The various types of hepatic disease should include conditions that might effect metabolism and diseases with alterations in bile acid secretion/ metabolism. In addition to alosetron kinetics, metabolite kinetic data should be examined.

9. There are a number of gastrointestinal symptoms associated with IBS and LOTRONEX™. Consequently, self-medication with antacids, magnesium containing laxatives, pH altering agents, etc. might be expected. Since LOTRONEX™ is an imidazole with a pKa of 6.95, the effect of alterations in g.i. pH on absorption and metabolite kinetics should be examined.

10. The sponsor should investigate the mechanism and clinical consequences of the effect of LOTRONEX™ on steroidogenesis.

The following comments are for informational purposes only and are intended to help the sponsor with future submissions. Consequently, a response from the sponsor is not needed.

1) The effect of renal insufficiency in subjects with creatinine clearances <30 ml/min was not adequately evaluated. Renal drug elimination and renal function are continuous variables and should be analyzed as such. Neither the effect of renal disease on nonrenal elimination and metabolite kinetics nor the effect of alterations in protein binding due to renal disease were examined. Creatinine clearance and renal clearance of drugs and metabolites should be presented normalized to body surface area, in addition to un-normalized data.

2) For assay validations, data points identifying outliers, should not be excluded from analysis. The intent of the validation is to obtain an estimate of the assay variability including outliers. Consequently, exclusion will give erroneous estimates of the assay variability. Inappropriate data exclusion may have occurred in assay validation (UCP/92/014).

3) The calculation for metabolite exposure compared to exposure for parent drug in the ^{14}C mass balance study was incorrect as specific activity was not accounted for. The correct ratio of AUC m/AUCp is 12.85.

VI. STATUS OF CLINICAL REPORT FOR STUDY 3003

[Also see page 5, 2) of the 30 November 1999 memorandum by Dr. J. Senior]

This section of this review addresses the issue of the information that will be available in the final report for Study S3BA3003 vs the information that has previously been submitted to the Division (already reviewed by Dr. Senior). Note that this year-long trial is an assessment of the safety of alosetron for periods longer than the 12 weeks of administration in the Phase III critical trials 3001 and 3002.

- The plan for submission of data from this trial was discussed with GlaxoWellcome at the April 15, 1999 pre-NDA meeting. As agreed, the original application was to be submitted with an interim report containing data from patients treated for at least 6 months and the safety update to include data on patients treated for 12 months.

- The original NDA indeed provided **the first interim report** for study 3003.

  At the time of the NDA submission, the study had enrolled 859 patients (637 females and 222 males). The database cut-off for the first interim report included safety data for 728 patients of whom, 553 received alosetron 1 mg b.i.d. Of the 553 patients, 411 were treated with alosetron 1 mg b.i.d. for at least 6 months and 19 were treated for at least 12 months.

- At the Division's request, the SU was submitted on September 24, 1999 (30 days earlier than the required 120 days).

At the time of the SU, **a second interim report** was provided for study S3BA3003. In this second interim report, **all 859 randomized patients**[39] were included in the report database (649 in the alosetron group and 210 in the placebo group). Safety data were provided for all 649 patients randomized to alosetron; 187 of these patients had completed one year of treatment (>365 days), and 415 patients (including the aforementioned 187 patients) had received at least 6 months of treatment.

- As of the second interim report, **all patients entered have been accounted for**[40] As of 23 of July, 1999 only 163 patients on alosetron and 51 on placebo were still in their last 2 months of study (the last patient entered 28 September 1998), so information on their exposure for 10 to 11.9 months was included. Most of the drop outs occurred in the first three months, and for alosetron-treated patients significantly more for constipation (not a novelty anymore since constipation has been exhaustively addressed by both the MO and this reviewer).

  - From the above clarifications, Dr. Senior concluded and this reviewer agrees that it is not expected that significant new findings will emerge from inspection of safety data or modify the safety profile established by analyses of the safety efficacy trials (3001 and 3002). There is already available almost complete report of 3003, the year-long trial.

VII. RECOMMENDATION FOR REGULATORY ACTION

Each of the involved review disciplines has recommended that LOTRONEX™ be approved. From this detailed multi-disciplinary, secondary review of the evidence, this reviewer concludes that alosetron is effective. Therapeutic gain (against PL) has been demonstrated using the primary efficacy endpoint and three of five secondary endpoints of evaluation. Although the therapeutic benefit with this drug (ca. 15%) is not very great, alosetron is undoubtedly differentiated from PL. Moreover, the results of one principal Phase III trial are clearly replicated in the other. These efficacy results are very convincing because, up to now, drugs tested for efficacy in IBS have shown inconsistent results. **In no other instance have replicative data like those observed with alosetron been reported.**

Alosetron is also safe and well-tolerated. Some of the encountered AEs, such as constipation and headache, have indeed been observed with other 5-HT_3 receptor antagonists and higher incidence of constipation are the logical consequence of longer exposures. The three adverse events of concern: constipation, ischemic/infectious colitis and possible liver injury should – carefully and conservatively – be incorporated into the labeling (to be addressed separately).

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[39] 637 women + 222 men = 859 (total enrolled)

[40] According to the information provided by the sponsor, the final report to be submitted at the end of February 1999 will include the complete safety data for all 649 patients randomized to alosetron with 323 of the alosetron-treated patients now having completing one year of exposure. Again, the final report will include no new patients. The higher number treated for 12 months is accounted for by additional exposure for 136 of the 415 patients reported in the second interim report. It is reiterated that **no new patients not included in the second interim report are to be presented.** Additional demographic subgroup analyses and data listings will also be provided in addition to the data presentations provided in the interim reports.

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 /S/ 12-10-99
HFD-180/LTalarico
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
HFD-180/LZhou
r d 12/6 99 jgw
r d 12/9 99 jgw
f t 12/9/99 jgw
f t 12/10/99 deg
N 21107911.1HG

APPENDIX 1

Alosetron NDA 21-107 Review Plan

Paul Levine, Project Manager

13 Weeks Total Review Time

Weeks		1999
	Letter Date of NDA	06/29
	Receipt of NDA	**06/30**
16	**Filing/Review Planning Meeeting**	**07/27**
	*** Team Meeting #1**	**08/26**
	*** Team Meeting #2**	**09/29**
	Statisti. Rev. of Carcinog. Study	09/13
	▸ **Clinical/Stat Meeting**	**10/04**
	▸ **pre-Industry Meeting**	**10/04**
	▸ ***90-Day Industry Meeting***	***10/06***
	REVIEWS TO TEAM LEADERS	**10/19**
1	▸ pre-AC meeting #1	10/25
1	*** Team Meeting #3**	**10/27**
	▸ pre-AC meeting #2	11/03
	REVIEWS COMPLETED	**11/05**
5 days	AC Package	11/09
	• *Reviews*	
	• Questions	
	▸ pre-AC meeting #3	11/10
1	(Division's AC Presentation Finalized)	
	ADVISORY COMMITTEE MEETING	**11/16**
2	Labeling Work and Action Package	11/19
	Division Level Sign-Off	**11/30**
1	**To Office for Sign-Off**	**12/07**
2	**Action Letter Issued**	**12/21**

GOAL DATE: December 31, 1999

APPENDIX 2

Alosetron NDA 21-107 SUBMISSIONS

		1999
	Letter Date of NDA	06/29
	Receipt of NDA	**06/30**
	FR (Firm's Response) - 7/7/99	
2	*FR - 7/20*	
	Filing/Review Planning Meeting	07/27
	FR - 8/23‡ *FR- 8/11* *FR-8/25*	
6	*FR - 8/24* *FR-8/26*	
	*** Team Meeting #1**	08/26
	FR - 8/30 *FR - 9/14* *FR - 9/21*	
	FR - 8/31 *FR - 9/15* *FR - 9/23*	
14	*FR - 9/3‡* *FR - 9/16‡* *FR - 9/27*	
	FR - 9/13 *FR - 9/20*	
	‡ = more than 1 submission	
	*** Team Meeting #2**	09/29
	FR - 10/1	
1		
	Clinical/Stat Meeting	10/04
	pre-Industry Meeting	10/04
1	*FR - 10/5*	
	90-Day Industry Meeting	10/06
	FR - 10/18	
1		
	REVIEWS TO TEAM LEADERS	10/19
	FR - 10/22	
1		
	pre-AC Meeting #1	10/25
1	*FR - 10/26 (Response to 90-Day Conference)*	
	*** Team Meeting #3**	**10/27**
	G-W's NDA Briefing Document	
	pre-AC meeting #2	11/03
	REVIEWS COMPLETED	11/05
	Package 11/09	
	• Reviews • Questions	
	pre-AC meeting #3	*11/10*
	(Division's AC Presentation Finalized)	

ADVISORY COMMITTEE MEETING 11/16