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 10^6M.

- 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).

APPEARS THIS WAY
ON ORIGINAL

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 • ↓ 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.

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
NDA 21-107

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 mg b.i.d. 1
- 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**.

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