

APPENDIX 8

Trial A3002. Stool Frequency

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Protocol: S38A3002
Population: ITT (Diarrhea-Predominant)

Table D-7.47
Lower GI Parameters: Number of Times Per Day Stool Passed
Monthly Change from Baseline: LDCF

Measurement	Statistic	Placebo (N=221)	Alosetron 1 mg BID (N=237)	P-value
Change in Times per Day Stool Passed Month 1	n	221	237	
	Mean	-0.35	-0.84	<0.001**
	SD	0.89	0.96	
	Median	-0.23	-0.73	
	Max.			
Month 2	n	221	237	
	Mean	-0.36	-0.90	<0.001**
	SD	1.04	1.01	
	Median	-0.24	-0.74	
	Max.			
Month 3	n	221	237	
	Mean	-0.36	-0.88	<0.001**
	SD	1.08	1.04	
	Median	-0.28	-0.73	
	Max.			

* Significant at the 0.050 level; ** significant at the 0.010 level.
Note: LDCF = last observation carried forward.
Note: P-value is the result of the van Elteren method of the Wilcoxon rank-sum test with stratification for cluster.

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Protocol: S3BA3002
Population: ITT (Alternat Ing)

Table A-7.47
Lower GI Parameters: Number of Times Per Day Stool Passed
Monthly Change from Baseline: LOCF

Measurement	Statistic	Placebo (N=95)	Alosetron 1 mg BID (N=85)	P-value
Change in Times per Day Stool Passed Month 1	n	95	85	<0.001**
	Mean	-0.13	-0.65	
	SD	0.61	0.82	
	Median	-0.06	-0.51	
	Min. Max.			
Month 2	n	95	85	<0.001**
	Mean	-0.23	-0.73	
	SD	0.78	0.87	
	Median	-0.17	-0.64	
	Min. Max.			
Month 3	n	95	85	<0.001**
	Mean	-0.19	-0.67	
	SD	0.90	0.90	
	Median	-0.15	-0.57	
	Min. Max.			

* Significant at the 0.050 level; ** significant at the 0.010 level.

Note: LOCF = last observation carried forward.

Note: P-value is the result of the van Elteren method of the Wilcoxon rank-sum test with stratification for cluster.

Source: AL050500DEV: [S3BA3002.TAB] LIB. TBSACD JACO_ITT_PASSED_CHG_SAS/QUINTILES (US)/01APR99/06:37

C20
Levine

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

NDA: 21-107

OCT 25 1999

APPLICANT: GlaxoWellcome, Five Moore Drive, P.O. Box 13398
Research Triangle Park, North Carolina 27709

DATE OF SUBMISSION: 29 June 1999

DRUG: Alosetron hydrochloride (LOTRONEX™, GR68755) tablets 1 mg

ADMINISTRATION: The applicant proposes to administer oral tablets, twice daily for up to 12 weeks, with or without food, for treating non-constipated women over 17 years of age with irritable bowel syndrome (IBS)

INDICATIONS: Reduction in pain or discomfort of irritable bowel syndrome with diarrhea predominance

MATERIAL REVIEWED: Application, clinical sections of the 336 volumes, with focus on the safety data: integrated summary of safety, safety aspects of reports, and data concerning individual patients from the principal clinical studies; pertinent other information and literature references.

REVIEWER: John R. Senior, M.D./ 22 October 1999

Brief Summary of Key Safety Issues Identified in this Review

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

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

An uncommon but serious adverse event was occurrence of ischemic colitis in three Caucasian women 33, 41, and 48 years of age, manifested by crampy abdominal pain and rectal bleeding,

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

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

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

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

1. How the frequent adverse effect of constipation should be interpreted, studied further, and labeled for instructions to physicians as to a regimen of administration to obtain benefits of abdominal pain reduction in IBS without causing excessive or symptomatic constipation.
2. Whether alosetron truly does cause ischemic colitis in some patients with IBS, and if so at what incidence rate, in patients with what predisposing factors and whether ischemic colitis can be proved to have occurred, and can be predicted by surrogate markers, mechanism of effect, whether milder "formes frustres" syndromes occur that may not be diagnosed as ischemic colitis, and whether severe cases of bowel infarction/gangrene may occur in some patients and be life-threatening or require resection.
3. Whether the single case of ALT, AST and bilirubin elevation seen in S3BA3001 was truly caused by alosetron, and what should be done about it (looking for more cases), assuming that this represents 1 in about 1266 patients exposed to alosetron for up to 12 weeks..
4. Should a prospective, large (3000-5000 patient cohort, observed and reported monthly on treatment) but simple study be required post-marketing as a condition of approval, looking for

ischemic colitis by symptoms of unexplained rectal bleeding with abdominal pain or constipation (and monitoring ALTs) during clinical use? Should a control group be treated with an approved anti-diarrheal agent such as loperamide (Imodium, Janssen)? This could provide a denominator and reliable numerators for better estimation of the true risks of ischemic colitis (and also of drug-induced hepatotoxicity), and perhaps better ways to predict and avoid the problems.

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

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

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

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

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I. Introduction

A. Approach to the review and conventions used

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

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

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

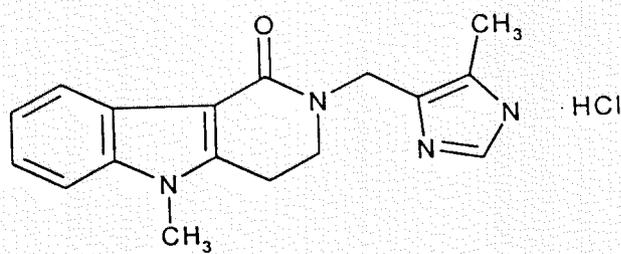
Sections of the review are numbered and paginated as shown in the Table of Contents. These correspond in general with the "Guideline for the Format and Content of the Clinical and Statistical Sections of an Application," published in July 1988 by the Center for Drug Evaluation and Research of the Food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

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

B. Description of the drug and drug product

Alosetron is a compound synthesized as a serotonin (5-hydroxytryptamine) receptor-type 3 (5HT₃) antagonist, several earlier variants of which (ondansetron, granisetron, dolasetron) have been studied and approved for the treatment or prevention of nausea and vomiting caused by cancer chemotherapy or by surgical anesthesia and operative procedures. Alosetron, while structurally very similar, uniquely has been studied by the applicant for the treatment of the symptoms of irritable bowel syndrome (IBS).

Alosetron is 5-methyl-2-(5-methyl-1H-imidazol-4-yl methyl)-2,3,4,5-tetrahydro-pyrido [4,3-b] indol-1-one, hydrochloride:



alosetron
(GR68755C)

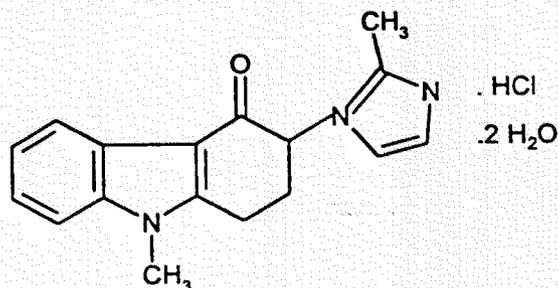
$C_{17}H_{18}N_4O \cdot HCl$
m.w. 330.8

The compound has no chiral centers, and no stereoisomers. The suffix C indicates the salt form (hydrochloride); suffix X, the free base. As prepared, it is a white-to-beige crystalline powder with melting point 276°C, and is not hygroscopic. The salt form is somewhat soluble in distilled water (61 mg/mL) and in saturated aqueous solution has a pH of 3.3, but is less soluble in saline (28 mg/mL) and much less so in pH 6 phosphate buffer (0.3 mg/mL). Its pKa is 6.95, but secondary pKa values were not provided (Vol. 1, page 74).

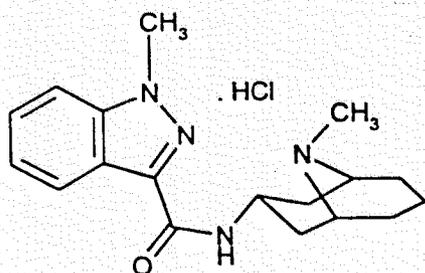
Tablets made up as studied in the pivotal trial and to be marketed are oval-shaped and coated with blue film. They contain 1.124 mg of the hydrochloride salt of alosetron, to provide 1.00 mg of the free base, along with anhydrous lactose *The amount of lactose in these tablets, is too small to induce diarrheal effects in lactase-deficient people.*, microcrystalline cellulose pregelatinised starch, and magnesium stearate. The coating film is _____ to make a total tablet weight of 155 mg (Volume 1, page 84). For further details, please see the chemistry review (Dr. Maria Ysem).

In searching for adverse events induced by alosetron, it may be of interest to compare the previously approved members of this drug class of 5HT₃ blocking agents, which have been in clinical use for some years, and for which safety information in clinical use is available. This first compound of the group was ondansetron, synthesized by the same sponsor (Glaxo) and patented in 1986, now marketed as ZOFRAN® by GlaxoWellcome. This was followed quickly by two more compounds with similar pharmacologic effects: granisetron (SmithKline Beecham, 1986, KYTRIL®) and dolasetron (MerrellDow, 1988, ANZEMET®). Their chemical structures are shown below, for comparison; their effects will be considered in the pharmacology section and clinical safety section.

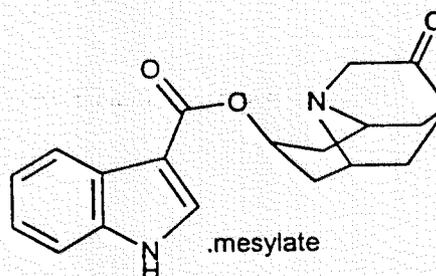
C. Background of previous NDAs approved for similar products



ondansetron
GlaxoWellcome ZOFRAN®

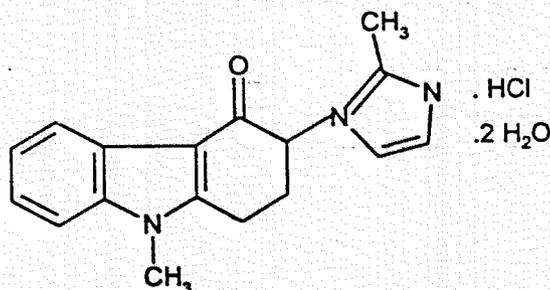


granisetron
SmithKline Beecham KYTRIL®

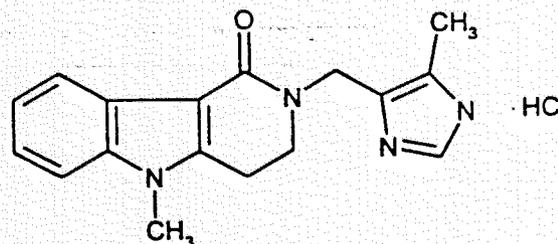


dolasetron
MerrellDowHoechst ANZEMET®

It is apparent that ondansetron is structurally most similar to alosetron, with both having identical methyl-indole structures on the left (as shown below), but alosetron has an attached piperidinone ring instead of cyclohexanone, and a slightly different methylimidazole linkage.



ondansetron



alosepron

The two other compounds differ from the Glaxo compounds in having the azabicyclo or quinolizino structures instead of the methylimidazole side chains.

Ondansetron was approved for clinical use first as an intravenous product in January 1991 (NDA 20-007) and later as tablets for oral use in December 1992 (NDA 20-103). Granisetron was then approved as a parenteral product in December 1993 (NDA 20-923) and subsequently in tablet form in March 1995 (NDA 20-305). Dolasetron was approved in both parenteral and oral formulations in September 1997 (NDAs 20-623 and 20-624). These three approved compounds, particularly the first two, have been quite widely used for prevention of nausea/vomiting that may be expected from cancer chemotherapy regimens. Ondansetron and dolasetron are approved for preventing nausea/vomiting from the effects of anesthesia and surgical procedures. Consequently, considerable safety information has accumulated from both the controlled studies done prior to approval and from post-marketing experience in the years since approval.

Comparisons of the pharmacologic effects and characteristics of these compounds, and of the clinical safety information available about them, will be found in the sections below in which those issues will be discussed for alosetron tablets, the drug product that is the subject of the data submitted.

D. Labeling requested

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

LOTRONEX® (alosetron hydrochloride) Tablets, 1 mg, for oral administration are indicated for **“the treatment of irritable bowel syndrome (IBS) in female patients with diarrhea predominance.”** The recommended dose for adult women at least 18 years of age is **“1 mg taken orally twice daily with or without food.”**

The claim for safety _____ appears moot, since the primary indication _____, and efficacy has not been established _____ However, a new protocol for _____ was just submitted on 29 September 1999, and will be reviewed separately.

II. Clinical Pharmacology

A. Clinical pharmacology of alosetron in humans

Alosetron, as the hydrochloride salt in LOTRONEX® 1 mg tablets, was administered as batch #T97/108A to the 633/1273 women of the two critical studies, S3BA3001 and -3002, and is the formulation to be marketed if approved. A series of 26 studies of the bioavailability, bioequivalence, pharmacokinetics and drug interactions, using a variety of doses and formulations, had been carried out by the applicant in North America and Europe over the period from 1989 to 1996. Both intravenous and oral formulations were investigated, single and repeated doses, in healthy subjects and selected volunteer patients.

In summary, it was found that absorption of alosetron after oral dosing was rapid but incomplete, with absolute bioavailability of about 60%, not altered by gender or age. Administration with food (high fat breakfast) caused delay and reduction in absorption that was statistically significant but was thought to be clinically unimportant. Plasma concentrations increased proportionally to ingested dose, up to 8 mg, and they were 30-50% higher in women than in men, because of slower clearance in females, and to some extent in the elderly. Absorbed alosetron was 82% protein-bound in plasma, and the volume of distribution was 65-95 L, about 1.5-2.0 times the total body water volume. Individual variability in absorption of alosetron from oral tablets ranged from 40 to 80% in various studies, far greater than the up to 5% variability in dissolution of sequential batches of tablets.

Comment: The clinical importance of the differences in alosetron plasma levels among individual patients is unclear, and data are available only for groups of patients taking various doses. To what extent individuals may need dosing or regimen adjustments to preserve effectiveness and yet avoid constipating side effects has not been established.

Alosetron is predominantly transformed metabolically by a wide variety of hepatic cytochrome enzyme systems (CYP 2C9, 30%; 3A4, 18%; 1A2, 10%; and non-CYP processes, 11%). At least 13 metabolites were detected in urine, mainly as the glucuronide conjugate of the 6-hydroxy metabolite, a bis-hydroxy metabolite, but not glucuronide or sulfate conjugates of intact alosetron. Although the 6-hydroxy metabolite showed some 5HT₃ receptor binding affinity, it was not detectable in plasma. Alosetron had no discernable effect on induction or inhibition of CYP 2D6, 3A4, 2C9, or 2C19, but very high concentrations 100-fold higher than peak plasma levels after therapeutic doses showed some inhibition of 1A2 (60%) and 2E1 (50%). However, *in vivo* metabolism of probe substrates showed no alosetron effects on activity of CYP 2E1 (on the hydroxylation of chlorzoxazone), 3A4 (hydroxylation of dapsone), or 2C19 (hydroxylation of mephenytoin), but there was 30% inhibition of 1A2 (demethylation of caffeine) and of dapsone N-acetylation. However, it was later shown that there was no inhibition of the 1A2 metabolism of theophylline. Alosetron appeared to have no effect on cisapride metabolism (mainly CYP 3A4), nor on metabolism of ethinyl estradiol/levonorgestrol or haloperidol.

Many of the early pharmacokinetic studies were done using 4-mg (*cf.*, proposed dose 1 mg b.i.d.) and other doses, male or Japanese subjects. Perhaps the study closest to the actual intended use was done under Protocol S3BB1011 (summarized in Volume 1, pages 218-20) in which 30 healthy men and women were given 1 mg oral tablets of alosetron b.i.d. for a month, along with a

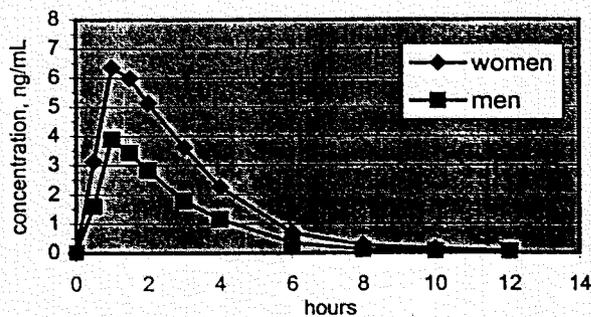
“cocktail” of four probe substances 8 days before the alosetron and one day after the month on alosetron, for estimation of alosetron effects on metabolism of those drugs. The study was carried out at one center (Aziz Laurent, M.D., at Austin TX) 26 September-17 December 1997, also to measure the pharmacokinetics of alosetron in healthy adult men and women. During the 29½ days of alosetron administration, without other drugs at the same time, the following data were obtained (Vol.1, page 219):

Alosetron (1 mg q 12 hr) Pharmacokinetic Parameters (S3BB1011)

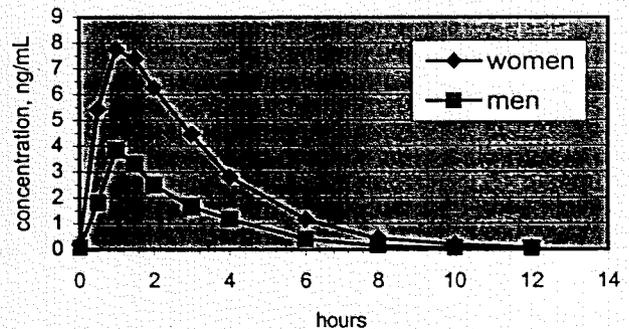
	Day 1	Day 8	Day 15	Day 22	Day 29
C _{max} , ng/mL	5.03 (4.13-6.13)	5.28 (4.43-6.30)	5.33 (4.44-6.40)	5.64 (4.69-6.78)	5.54 (4.76-6.45)
T _{max} , hr	1.00 (0.5-2.0)	1.00 (0.5-3.0)	1.00 (0.5-3.0)	1.00 (0.5-4.0)	1.00 (0.5-2.0)
AUC ₀₋₁₂	14.66 (11.80-18.23)	15.50 (12.83-18.74)	16.49 (13.50-20.15)	17.08 (14.05-20.77)	17.08 (14.45-20.19)
T _{1/2} , hr	1.41 (1.30-1.54)	1.48 (1.37-1.61)	1.53 (1.40-1.68)	1.53 (1.41-1.65)	1.51 (1.40-1.62)
C ₁₂ , ng/mL	0.19 (0.13-0.26)	0.20 (0.15-0.51)	0.25 (0.18-0.34)	0.23 (0.17-0.31)	0.24 (0.18-0.32)

Note: Geometric means (95% confidence intervals), except T_{max}: median (range); Day AUC 0-∞.

**Median Plasma Alosetron, ng/mL
After 1 mg Oral Dose, Day 1**



Median Plasma Alosetron, ng/mL After 1 mg Oral Dose, Day 29



*Comment: In this study it was evident that there was **no accumulation of plasma alosetron** over time, with approximately 8 half-lives between doses on average, and trough levels less than 4% of peak levels seen at about an hour after oral dosing. Considerable differences in alosetron pharmacokinetics were seen between the 15 men and 15 women in the study, not accounted for by the differences in body weight (men: median 79.5 kg, range 59.5-97.0; women: 69.8 kg, range 50.5-78.5). However, the women were somewhat older (median age 38.5 years, range 21-50) than the men (median age 27.7 years, range 18-46), and 6 of the women but only 1 of the men were of Hispanic ethnicity (Volume 55, pages 1-46, 66, 67-71, 91-93). Women showed higher peak plasma levels than the men, out of proportion to their relative body weights, suggesting a gender-related difference in the amount absorbed or the rate of metabolism/clearance of the drug.*

Effect of Alosetron (1 mg b.i.d., 1 month) on Other Drug Metabolism

Metabolite/Drug Enzyme	gender, number -8:30	pre-alosetron Day -8	post-alosetron Day 30	post/pre ratio	p value* (pairs)
DMX/caffeine (CYP 1A2)	M, 12:15	1.75 (1.06-2.87)	1.28 (0.89-1.85)	0.731	0.001 (20)
	F, 8:15	1.39 (0.81-2.35)	0.82 (0.57-1.18)	0.590	
MAD/dapsone (NAT)	M, 9:10	0.45 (0.33-0.61)	0.30 (0.21-0.41)	0.667	<0.001 (19)
	F, 12:14	0.60 (0.45-0.79)	0.43 (0.32-0.58)	0.717	
6HC/chlorzoxazone (CYP 2E1)	M, 14:14	0.42 (0.30-0.60)	0.43 (0.34-0.55)	1.024	N.S. (21)
	F, 7:9	0.23 (0.14-0.37)	0.29 (0.22-0.39)	1.261	
DHA/dapsone (CYP 3A4)	M, 15:14	0.75 (0.69-0.82)	0.72 (0.65-0.79)	0.960	N.S. (24)
	F, 11:14	0.67 (0.61-0.74)	0.75 (0.68-0.82)	1.119	
4HM/mephenytoin (CYP 2C19)	M, 14:14	26.6 (19.0-37.2)	29.0 (22.0-38.1)	1.090	N.S. (29)
	F, 15:15	21.6 (15.6-29.9)	21.3 (16.3-27.7)	0.986	

Note: Data on plasma metabolite concentrations as geometric means (95% confidence intervals), of number of subjects before (-8) and after (30) alosetron period; p values on paired differences; M, male; F, female.

Comment: These findings showed no statistically significant effects on the hydroxylation of chlorzoxazone, dapsone, or mephenytoin (CYPs 2E1, 3A4, 2E19), but significant reductions in the demethylation of caffeine (CYP 1A2) and acetylation of dapsone (NAT), in both sexes. However, it was later shown that there was no inhibition of the 1A2 metabolism of theophylline. Alosetron had no effect on cisapride metabolism (mainly CYP 3A4). In the report for S3BB1011, it was noted that the 6 Hispanic women showed AUC 30% greater than the 9 White women, but the single Hispanic male was not different than the 13 White and 1 Black males.

A previous study (S3B102), done in Austin Tx by Dr. T. Hunt from January-August 1991, had compared pharmacokinetics in 24 healthy young men (ages 19-40) with sets of 12 elderly men (ages 65-82) and elderly women (ages 65-78). It showed that women cleared alosetron more slowly and elderly people showed longer half-times, but there was no significant accumulation of drug after 27½ days on 2 mg of oral alosetron every 12 hours (Note: twice the proposed clinical dose). The higher AUC, Cmax, and T½ values for the elderly, and particularly for the elderly women, suggested reduction in either first pass metabolism or metabolic capacity to account for the lessened metabolic clearance and increased bioavailability of the GR68755C (alosetron hydrochloride) used. Data were summarized in Volume 1, pages 221-2, and provided in more detail in Volume 58, pages 1-41):

Plasma Alosetron After 2 mg Twice Daily, Study S3B102

	Young Males		Elderly Males		Elderly Females	
	Day 2	Day 28	Day 2	Day 28	Day 2	Day 28
Cmax, ng/mL	8.6 ± 5.0	12.4 ± 6.7 ‡	11.6 ± 4.2	13.0 ± 5.1	18.7 ± 5.7*	18.9 ± 5.6*
Tmax, hr	1.8 ± 0.4	1.7 ± 0.6	1.6 ± 0.7	2.1 ± 0.9	1.8 ± 0.6	1.6 ± 0.6
AUC ₀₋₁₂ , ng-hr/mL	22.6 ± 14.8	39.4 ± 22.9 ‡	39.1 ± 18.2	47.4 ± 19.9	62.4 ± 23.7*	66.9 ± 22.9*
T½, hr	1.4 ± 0.2	1.4 ± 0.2	1.8 ± 0.4 †	1.8 ± 0.3 †	1.6 ± 0.3	1.7 ± 0.3

Note: Arithmetic means ± standard deviations; ‡, significantly higher than Day 2; †, significantly higher than young males; *, significantly higher than elderly males.

The pharmacodynamic effects and side effects of alosetron were investigated in a series of 31 studies completed in 1989 to 1997 in North America, Europe, and Japan in both healthy volunteers and patients with IBS, tabulated in Volume 1, pages 244-8. These studies were designed to assess overall drug tolerance; effects on gastrointestinal transit times; visceral sensitivity; motility of esophagus, small bowel and colon; bloating; gastric acidity; absorption; and drug interactions.

In summary, single intravenous (I.V.) doses up to 10 mg and oral doses up to 16 mg were generally well tolerated by healthy male subjects, with only a few exceptions. In the early, single-dose, I.V. studies, headaches were noted by 3 healthy male subjects, but 2 of them had received placebo, and the other only 0.12 mg of alosetron. Headaches were not a notable problem in studies of oral alosetron in the pharmacokinetic, pharmacodynamic, or clinical trials. In the ascending dose-ranging study GHP:89:38, conducted in England in 1989, one healthy young man of 22 years of age showed tachycardia, T-wave inversion, and QTc prolongation to 476 msec 90 minutes after a 16-mg oral dose, at which time his alosetron level was measured at 152 ng/mL. He had previously received placebo and an 8-mg dose of alosetron. He was later seen for a special rechallenge study (GHP:90:05) and showed no abnormal response to another 16-mg single oral dose and placebo in February 1990, and showed no electrocardiographic findings on tracings taken every 15 minutes from 1 hour before to 4 hours after the alosetron; in this restudy, Holter monitoring of him showed clinically insignificant spontaneously occurring ectopic arrhythmias after both placebo and alosetron. The C_{max} after oral 16 mg of alosetron in the rechallenge study was 131 ng/mL at 120 minutes after ingestion of the four 4-mg tablets.

Comment: The single observation of prolonged QTc interval in the young man was noted but was not explained, nor did it recur upon rechallenge with the same dose, which produced a somewhat lower C_{max}, or upon further special studies, and no clinical arrhythmias were seen.

Pharmacodynamic Effects

Alosetron is 5-10 times more potent as a 5-HT₃ receptor antagonist than ondansetron (Volume 1, page 338). In its clinical pharmacology studies alosetron did not affect gastric emptying but slowed mouth to cecum transit in healthy men given 4 mg single oral doses (Study S3BH03), indicating increased small bowel transit time. In IBS patients given 1 or 4 mg of alosetron b.i.d. for 28 days, no significant effect was found on gastric emptying, small bowel transit time, or colon transit time, although the study was small and could detect with statistical significance only differences of at least 60% between alosetron and placebo groups (Study S3BB2011). No effect was seen of single doses of 4 mg alosetron on orocecal transit time, using the (Study C92-057). Using radio-opaque markers in healthy men, alosetron 2 mg b.i.d. for 8 days had no effect on orocecal transit time, but did slow colonic transit time by approximately 20% (Study S3BH05), and similar findings were obtained in patients with IBS, especially in the left colon (Study S3BH06).