Alosetron increased colonic compliance to painful increase in pressure or volume distention, increased basal water and electrolyte absorption, and slowed colonic transit time.

Comment: Although not exclusively a safety matter, the gastrointestinal effects of alosetron on other parts of the tract—esophagus, stomach, small bowel—are important to understand, beyond the effects on slowing colonic motility.

The results of the studies done to establish the pharmacodynamic effects of alosetron did not define very well the motility effects of the dose of 1 mg b.i.d. to be used in women with IBS. Many of the studies done to determine gastric emptying, small bowel and colonic motility and transit times, were carried in men, or at much higher doses. It is clear that the sponsor had not yet discovered that women were more responsive than men, and that a dose of 1 mg b.i.d. was at least as good if not better than higher doses in reducing the pain or discomfort associated with IBS. The summary of clinical pharmacology studies (Section 8.1, Volume 1, pages 243-332) lists 31 completed and 3 ongoing studies, but information on women with non-constipated IBS on doses of 1 mg b.i.d. is very sparse and does not permit comprehensive understanding of the drug's pharmacodynamic profile at the regimen requested in the proposed labeling.

When the list of studies summarized on pages 244-8 of Volume 1 is examined, it appears that in only one study, S3BB2011, were the pharmacodynamic effects of alosetron on the gastrointestinal transit time and rectal sensitivity measured in a few women at dose of 1 mg b.id. The study was carried out from April 1997 to May 1998 at Mayo Clinic by Dr. M. Camilleri. A total of 26 patients with IBS were enrolled, 10 each to alosetron doses of 1 and 4 mg alosetron b.i.d. and 6 to placebo b.i.d. Of the 26, 7 were men and 19 women, but the summary does not state how many women were randomized to the 1 mg b.i.d. dose of alosetron (see Clinical Pharmacology review by Dr. R. Kavanagh for details). Gastric emptying and small bowel transit times were estimated by [redacted] labeled with [redacted] and colonic transit time was measured by [redacted] before dosing and after 27 days on study drug. All but one patient completed the study, but there were not enough data in the study to show any significant differences in alosetron-treated patients compared to placebo-treated patients on small bowel or colonic transit times, or on rectal sensitivity in IBS patients (Volume 1, pages 268-70).

It is suggested that the pharmacodynamic effects of the projected clinical dose and regimen of 1 mg alosetron b.i.d. for at least 4 weeks should be reinvestigated in the target group of patients to be treated, women with non-constipated forms of IBS. These restudies should be of sufficient size to show significant effects if there are any, based on the preliminary data from the package of submitted studies. A great many studies were done, but unfortunately they were planned and executed before the sponsor discovered the appropriate gender and dose, so that no conclusions can be drawn with any confidence about pharmacodynamic effects of alosetron in the patients to be treated at the dose to be used.

The general conclusions about pharmacodynamic effects (Volume 1, pages 329-30) may be true as stated, but need to be confirmed using the appropriate gender and dose. As stated they include:

- *Alosetron significantly increases colonic transit time, especially left colon transit, and probably has little consistent effect on gastric emptying or small bowel transit.*
- *Alosetron significantly increases colonic compliance in patients with IBS, but has not been proved to affect rectal sensitivity.*
- *Alosetron did not affect bloating in IBS patients.*

B. Clinical pharmacology of other -setrons in humans

Ondansetron (ZOFRAN®, GlaxoWellcome) was approved in 1991, initially as a sterile I.V. solution for prevention of nausea and vomiting associated with courses of cancer chemotherapy, many agents for which are highly emetogenic, including high-dose cisplatin. It was also approved for prevention of postoperative nausea or vomiting in patients in whom it is likely or in whom these adverse events must be avoided, and for use to prevent further nausea/vomiting in those who have already experienced it postoperatively. An oral solution and tablets were subsequently approved for those same indications, and for prevention of nausea and vomiting associated with radiotherapy in patients receiving total body irradiation, high single doses or daily fractional radiation doses to the abdomen.

The recommended oral dose of ondansetron is 8 mg twice daily (every 12 hours), beginning at least 30 minutes before the start of emetogenic chemotherapy and continuing for 1 to 2 days after completion of the chemotherapy. For prevention of postoperative nausea/vomiting, the oral dose is 16 mg ondansetron given an hour before induction of anesthesia as a single dose, and for prevention of radiation-induced nausea/vomiting, the recommended dose is 8 mg given 1-2 hours before radiotherapy and every 8 hours until 1 to 2 days after completion of radiotherapy. In U. S. studies, headache, fatigue/malaise, and constipation were seen significantly more often after ondansetron 8 mg b.i.d. or t.i.d. than after placebo (published labeling).

Principal Adverse Events in U.S. Trials of Ondansetron for Three Days

	Placebo n = 262	Ondansetron 8 mg b.i.d. n = 242	p value vs placebo	Ondansetron 8 mg t.i.d n = 415	p value vs placebo
Headache	34 (13%)	58 (24%)	< 0.002	113 (27%)	< 0.001
Malaise/fatigue	6 (2%)	32 (13%)	< 0.001	37 (9%)	< 0.001
Constipation	1 (<1%)	22 (9%)	< 0.001	26 (6%)	< 0.001
Diarrhea	10 (4%)	15 (6%)	N.S.	16 (4%)	N.S.
Dizziness	12 (5%)	13 (5%)	N.S.	18 (4%)	N.S.
Abdominal pain	1 (<1%)	3 (1%)	N.S.	13 (3%)	< 0.03
Dry mouth	1 (<1%)	5 (2%)	N.S.	6 (1%)	N.S.
Weakness	1 (<1%)	0	N.S.	7 (2%)	N.S.

Comment: Data are not available to compare ondansetron doses to the proposed 1 mg b.i.d. dose of alosetron for treatment of IBS. They are used, for different clinical problems and in different regimens, ondansetron for relatively short-term use and alosetron for long-term use in a chronic condition, IBS. Relative dose-effect comparisons between ondansetron and alosetron have not been done. However, both agents have been compared and are effective in reducing vomiting in ferrets given cisplatin (Rudd, et al., 1994).

Constipation is a notable and significant adverse side effect of ondansetron treatment; multidose administration includes slowing of colon transit in normal volunteers. About 1 to 2% of patients showed transient increases in serum transaminase of idiosyncratic nature, but symptomatic hepatic disease or liver failure could not be clearly attributed. Rare cases of anaphylaxis, angina pectoris, bronchospasm, electrocardiographic changes, grand mal seizures, hypokalemia, rash, tachycardia, and vascular occlusive events also have been reported.

Ondansetron tablets have an absolute bioavailability of 48 to 75%, more in women than men, and more in the elderly than in the young adults. Peak plasma concentrations of about 25 ng/mL are seen after single oral doses of 8 mg tablets, again higher in women than men and in the elderly, and the Tmax is about 2 hours, half-time for plasma clearance about 3 hours, somewhat slower in females, especially elderly females. Ondansetron is extensively metabolized by hepatic cytochrome systems, and only about 5% of an administered dose appears in the urine unchanged. Hydroxylation of the indole ring, followed by glucuronidation or sulfate conjugation, is the major pathway of its metabolism.

Comment: These pharmacokinetic characteristics of ondansetron are fairly similar to those of alosetron, summarized above. There are no comparable data for 1 mg b.i.d. dosing, however, and very little experience in experience in using ondansetron for treatment of IBS. Therefore, little information is available about the safety of long-term ondansetron administration. However, search of Medline for [irritable bowel syndrome AND ondansetron] does reveal a few papers describing a case report from Australia (Evans, 1993), a few small trials reporting partial success in the U.K. (Maxton, et al., 1996; Goldberg, et al., 1996) or failure at Mayo Clinic (Steadman, et al., 1992; Hammer, et al., 1993), but little new information from them about safety of ondansetron given over extended periods of time. There have been proposals in review articles speculating on its possible use in IBS and the need for controlled trials (Lamars, 1991; Talley, 1992; Wilde and Markham, 1996; Farthing, 1998), which if done might provide safety data.

2. **Granisetron,** (KYTRIL®, SmithKline Beecham), was approved in 1993 as an intravenous formulation and later as oral tablets, for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin. In the U.S. the recommended intravenous dose is 0.01 mg/kg body weight once only 30 minutes before chemotherapy is started and before each dose of chemotherapy. The recommended oral dose for adults is either 2 mg an hour before chemotherapy, or 1 mg an hour before chemotherapy and 1 mg at 12 hours later. Continued treatment, beyond the first day, was not found to be useful. After a single oral dose of 1 mg of granisetron hydrochloride, peak plasma levels in healthy volunteers average about 3.6 ng/mL, with a plasma half-time of 6.2 hours; in patients with cancer and in elderly people without cancer the half-time for clearance is longer, about 9.0 hours (after I.V. dosing). The effects of gender on pharmacokinetics of oral granisetron were not studied, but no differences in AUC after I.V. administration were seen between men and women. Renal functional impairment did not affect clearance of granisetron (only 11% of an administered dose is excreted unchanged in the urine over 24 hours in human subjects), but hepatic impairment due to neoplastic involvement did reduce the clearance rate by half. Granisetron is metabolized via N-demethylation and aromatic ring oxidation by hepatic cytochrome enzymes of the P-450 3A subfamily, but does not either induce or inhibit any of them, although there have been no definitive drug-drug interaction studies performed. The compound and some of the metabolites that may have 5-HT3 receptor antagonist activity may bind to rat tissues such as eye and adipose tissues for several days.

Comment: Granisetron is not approved for prophylaxis of postoperative nausea and vomiting, but nevertheless is widely used for that purpose. Its dose in mg/day is much closer to that proposed for alosetron, but it has a considerably longer half-time for clearance. However, there were no

data provided on exactly which hepatic cytochrome enzyme system metabolizes granisetron, or precisely what metabolites are formed. The major metabolizing system appears to be CYP 3A4, as evidenced by the effects of ketoconazole, a powerful 3A4 inhibitor. An important observation possibly pertinent to this application is that ***single and multiple oral doses of granisetron slowed colonic transit in normal volunteers,*** *although single I.V. infusions of 50 or 200 μg/kg had no effect on orocecal transit time.*

Adverse reactions to granisetron observed in controlled trials of about 3700 people include headache, constipation, weakness, diarrhea, abdominal pain, leukopenia, anorexia, serum transaminase elevations in 5-6% of patients, fever, dizziness, insomnia, anemia, alopecia. No cases of lengthened QT interval or cardiac arrythmias are reported in the labeling. In most of these cases, no placebo comparisons were available, but in controlled trials for which control data in patients receiving placebo, the following adverse events were observed:

Principal Adverse Events in Clinical Trials of Granisetron for up to 14 Days

	Placebo n = 185	Granisetron 1 mg b.i.d. n = 978	p value vs placebo	Ondansetron 2 mg/day n = 1450	p value vs placebo
Headache	22 (12%)	205 (21%)	< 0.005	290 (20%)	< 0.01
Constipation	15 (8%)	176 (18%)	< 0.001	203 (14%)	< 0.03
Weakness	7 (4%)	137 (14%)	< 0.001	261 (18 %)	< 0.001
Diarrhea	7 (4%)	78 (8%)	< 0.05	131 (9%)	< 0.02
Abdominal pain	6 (3%)	59 (6%)	N.S.	58 (4%)	N.S.
Dyspepsia	7 (4%)	39 (4%)	N.S.	87 (6%)	N.S.

Comment: Again headache was a prominent adverse effect, along with weakness or asthenia, but both constipation and diarrhea were reported to occur significantly more often than associated with placebo administration. Also included in the labeling are mentions (under Adverse Reactions) of occasional but not uncommon elevations of serum activities of ALT and AST to more than twice the ULN in 6 and 5% of patients taking oral KYTRIL, compared to 9% and 2% in patients taking comparators (not specified). Rare instances of hypotension were also noted during controlled trials.

3. **Dolasetron** (ANZEMET®, Hoechst Marion Roussel) was approved in 1997 for prevention of nausea and vomiting both after chemotherapy and postoperatively, in both oral tablet and intravenous formulations. The recommended dose intravenously is 1.8 mg/kg given 30 minutes before chemotherapy, or 12.5 mg as a single dose 15 minutes before cessation of anesthesia or as soon as nausea or vomiting are reported by the patient. The oral dose is 100 mg given an hour before chemotherapy or 2 hours before surgical procedures.

Dolasetron is well absorbed (75% absolute bioavailability) and very rapidly metabolized by the ubiquitous enzyme carbonyl reductase to hydrodolasetron, with subsequent hepatic CYP 2D6 catalysis of hydroxylation and N-oxidation by CYP 3A- enzymes and flavine monooxygenase. Glucuronides and N-oxide metabolites also are found. The hydrodolasetron exerts the principal pharmacodynamic effects on $5HT_3$-receptor antagonism, and 61% of the administered dolasetron

dose appears in urine as unchanged hydrodolasetron. Its plasma Cmax occurs at about 1 hour, and clearance half-time is 8.1 hours. About two thirds of the administered dose is accounted for by renal excretion into the urine, and the other third into the feces. Absorption is not affected by food, and metabolism is the same in men and women. No dose adjustment is recommended for patients with renal or hepatic functional impairment, nor for elderly patients.

Dolasetron administration causes dose-related electrocardiographic (ECG) effects in normal volunteers, mainly QRS widening, QT prolongation, and patients have been affected similarly in clinical trials. The drug labeling includes a warning that these ECG abnormalities occur, are related to the concentration of active metabolite hydrodolasetron, and changes may persist for up to 24 hours. However, cardiac arrhythmias or heart block have rarely been reported. Nevertheless, it is advised to take caution in using dolasetron in patients with preexisting QT prolongation, hypokalemia or hypomagnesemia, taking diuretics, using antiarrhythmia drugs or anthracycline therapy. Constipation, abdominal pain, dyspepsia and rare pancreatitis have been reported, as well as rash, thrombocytopenia, prolonged prothrombin time and PTT, anemia, hematuria, facial edema, urticaria, myalgia, arthralgia, taste perversion, vision abnormalities, flushing, vertigo, paresthesia, tremor, agitation, sleep disorder, and other events rarely. In controlled trials of preventing nausea or vomiting, the adverse event profile showed:

Adverse Events in Placebo-Controlled Dolasetron Trials

	ANZEMET 100 mg n = 228	Placebo n = 231	p value
Headache	16 (7.0%)	11 (4.8%)	N.S.
Hypotension	12 (5.3%)	15 (6.5%)	N.S.
Dizziness	10 (4.4%)	0	< 0.003
Fever	8 (3.5%)	7 (3.0%)	N.S.
Pruritus	7 (3.1%)	8 (3.5%)	N.S.
Oliguria	6 (2.6%)	3 (1.3%)	N.S.
Hypertension	5 (2.2%)	7 (3.0%)	N.S.
Tachycardia	5 (2.2%)	2 (0.9%)	N.S.

Comment: Dizziness was noted to occur significantly more often in dolasetron-treated patients than in those receiving placebo, but no warning or precaution about it is present in the labeling. Because of its very rapid reduction by carbonyl reductases, dolasetron is effectively a pro-drug; the derivative hydrodolasteron is the principal active agent that antagonizes the $5HT_3$-receptor to inhibit peripheral vagal and central area postrema receptors. It is not stated in the labeling just which of the two carbonyl groups is reduced by the "ubiquitous carbonyl reductases" nor exactly which cytochrome isozyme produces exactly which metabolite. This may be important because of the dose-related QTc prolongation. Other drugs (such as found for cimetidine) could inhibit the cytochrome system that metabolizes hydrodolasetron, thereby raising the plasma levels of hydrodolasetron to possibly dangerous or arrhythmogenic levels, but clinically apparent arrhythmias so far have only rarely been reported, according to the current labeling. It is also notable that the structures of both dolasetron and hydrodolasetron are quite different from that of alosetron, which does not appear to have the property of dose-related QTc prolongation. Although it is of interest to compare the safety profile of other $5HT_3$-receptor antagonists, it is also important to bear in mind differences between them.

C. Pre/non-clinical pharmacology of alosetron in animals

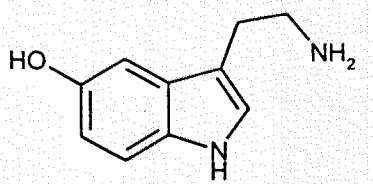
Alosetron is rapidly absorbed and extensively metabolized after oral administration to mice, rats, rabbits, and dogs. In pregnant rats and rabbits alosetron crosses the placenta and in lactating rats related metabolites are excreted in the milk, so there is potential to affect fetal and infant functions. Pharmacodynamically, 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 has a highly selective and potent antagonist at 5-HT3 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, but there was no carcinogenicity. Intravenous 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. 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.

B. Background on 5-HT receptor agonists and antagonists

Comment: Because the mechanism of alosetron's pharmacodynamic action is to block the specialized receptors for serotonin, an emerging science, this background section reviewing what has been learned recently about them is provided here. Much of the material is taken from the current Goodman and Gilman text (9th Edition, 1996), chapter by Sanders-Bush and Mayer.

Serotonin (5-hydroxytryptamine, 5-HT, or 3-(β-aminoethyl)-5-hydroxyindole) is produced by nuclear 5-hydroxylation of the amino acid L-tryptophane, catalyzed by the enzyme tryptophane hydroxylase. The 5-hydroxy-L-tryptophane side-chain is decarboxylated by L-aromatic amino acid decarboxylase, a widely distributed enzyme that uses pyridoxine as a cofactor and acts rapidly. In brain, 5-hydroxytrytophane is undetectable by currently available tools and does not seem to be a determinant of 5-HT levels. Tryptophane hydroxylase is a mixed function oxidase that requires molecular oxygen and tetrahydropteridine as cofactor, and is rate-limiting in the production of 5-HT. It is found in the central nervous system and in peripheral nerve endings that regulate smooth muscle in the cardiovascular and gastrointestinal systems.



serotonin, 5-HT (5-hydroxytryptamine)

Serotonin acts as a neurotransmitter in the central nervous system, a regulator of cardiovascular and gastrointestinal smooth muscle and of platelet functions. The principal route of 5-HT metabolism is via monoamine oxidase (MAO) to 5-hydroxyindole acetic aldehyde, from which it is oxidized to 5-hydroxyindole acetic acid, which is excreted into the urine, which can be used to measure 5-HT turnover, or a small amount may be reduced to 5-hydroxytryptophol. An alternate pathway is by N-acetylation of the side chain, followed by O-methylation to melatonin. There is also a transporter mechanism for 5-HT, a Na^+-dependent carrier mediated process, located in the outer membrane of serotonergic axon terminals, where it takes up and terminates the action of the 5-HT in synapses; the transporter is also present in the outer membrane of platelets, which lack the enzymes to synthesize 5-HT, but can concentrate and store it within secretory granules.

Receptors for 5-HT are found in many species of animals and even in plants such as fruits and nuts. A complex set of receptor subtypes have evolved and are now just being clearly sorted out by cDNA cloning and expression (Sanders-Bush and Mayer, 1996). In brief, four subfamilies of receptors with defined functions have been identified, 5-HT_1 to 5-HT_4, and three more are being investigated 5-HT_5 to 5-HT_7. Several of them have further subtypes, such as 5-HT_{1A}, 5-HT_{5B}, etc. The 5-HT_3 receptor uniquely differs from the others in not being G-protein coupled but is a ligand-gated ion channel for Na^+ and K^+ movements, and its effect is to speed depolarization of neurons, whereas 5-HT_{2A} and 5-HT_4 receptors decrease K^+ conductance and slow depolarization.

In the gastrointestinal tract, the enterochromaffin cells in the mucosa are the site of synthesis and most of the storage of 5-HT in the body and the source of circulating 5-HT. The 5-HT released by vagal or mechanical stimulation or by other mechanisms may enhance or inhibit motility via at least 6 subtypes of receptors in the gut smooth muscle. Release of enteric 5-HT occurs in response to acetylcholine, noradrenergic nerve stimulation, increased intraluminal pressure, and pH reduction (Gershon, 1991). The stimulatory response occurs at nerve endings on longitudinal and circular smooth muscle (5-HT_4), at postsynaptic enteric ganglia cells (5-HT_3 and 5-HT_{1P}), and by direct effects on muscle cells (5-HT_{2A} in intestine and 5-HT_{2B} in stomach fundus). In the esophagus, action at 5-HT_4 receptors causes species-specific relaxation or contraction. Abundant 5-HT_3 receptors on vagal and other afferent neurons and on enterochromaffin cells play an important role in emesis (Grunberg and Hesketh, 1993). Ondansetron and the later –setrons are relatively specific 5-HT_3 receptor antagonists, while cisapride is a 5-HT_4 receptor agonist, with quite different pharmacodynamic and clinical effects and side effects. The 5-HT_3 receptors are located on parasympathetic terminals in the gastrointestinal tract, including vagal and splanchnic afferents, and in the area postrema and nucleus tractus solitarii of the brain. Extensive pharmacological evidence in tissues and intact animals suggests that there are multiple components of 5-HT_3 receptors. Activation of 5-HT_3 receptors causes a rapidly desensitizing depolarization mediated by the gating of cations. Antagonists of 5-HT_3 receptors act to reduce or block those effects of 5-HT at those sites.

Visceral hypersensitivity seems to play an important role in the symptomatology of IBS. Serotonin, acting via 5-HT_3 and 5-HT_4 receptors, may be critical in modulation of gastrointestinal functions by facilitating the release of acetylcholine. It stimulates cholinergic transmission in the enteric nervous system. Blocking 5-HT_3 receptors on afferent vagal fibers and enteric neurons is postulated to attenuate both motility and sensory responses; 5-HT_3 receptor antagonists have been reported to inhibit gastric motility (Wilmer, et al., 1993) as well as colonic motility. This may explain in part some of the effects of ondansetron and like drugs on reducing emesis after chemotherapy or post-operatively. It was not shown that symptoms of gastric retention arose in the normal subjects. In an earlier study, Akkermans *et al.* (1988) did show that gastric half-emptying time of a solid meal in normal subjects was reduced about 20% by I.V. doses of 10 or 20 mg of tropisetron, another experimental 5-HT_3 receptor antagonist (ICS 205-390, Sandoz).

It is of interest to note the actions of the 5-HT_4 receptor agonists such as cisapride, a pro-kinetic agent. These compounds have effects on stimulating human cardiac atrial myocyte 5-HT_4 receptors that may initiate atrial arrhythmias (Pino, et al., 1998) and prolong the duration of guinea pig papillary muscle action potential and QT intervals (Kii, et al., 1997), as well as produce positive inotropy and tachycardia or arrhythmias (Hegde and Eglen, 1996). These effects are to be differentiated from those of the 5-HT_3 receptors that are found on afferent vagal fibers (Saxena, 1989; Saxena and Villalon, 1991). Stimulation of those vagal 5-HT_3 receptors may cause the Bezold-Jarisch reflex (bradycardia and hypotension), but this effect is blocked by antagonists such as tropisetron (Berthold, et al., 1989) and granisetron (Pires, et al., 1998), which like alosetron are 5-HT_3 receptor antagonists.

Comment: It has been noted by Talley (1992) that some 5-HT_3 receptor antagonists also have 5-HT_4 receptor agonist activity; this is true for renzapride and zacopride, but not for ondansetron, granisetron, tropisetron. Animal data provided (Volume 1, pages 60, 62) indicate that alosetron has no (4 log_{10}s less affinity) 5-HT_4 receptor agonist activity that might be a problem in initiating cisapride-like effects on the heart, and is a potent blocker of vagal 5-HT_3 receptor activity.

III. Clinical Study Safety Results

A. Primary Safety Database

The proposed dose of alosetron is 1 mg b.i.d. for 12 weeks in adult women with non-constipated IBS. The studies that provide the most pertinent safety data on this regimen comprise the three U.S. studies S3BA2001, a dose-ranging study involving both men and women, and two identical phase III studies, S3BA3001 AND S3BA3002 that involved only women. In addition, the U.K. study S3B-P12 of men and women on 2 mg alosetron b.i.d. for 12 weeks is of interest for comparison of the effects of the higher dose. Partial results are also available for the U.S. study S3BA3003 of men and women on 1 mg b.i.d. for a year.

Long-Term, Placebo-Controlled Alosetron Studies

Study started-ended	Sites	P M/F	A 0.1 M/F	A 0.5 M/F	A 1.0 M/F	A 2.0 M/F	A 4.0 M/F	A 8.0 M/F	*Total M/F*	Duration
S3B-P12 Jul'93-Sep'94	43 Eur	33/84	38/77	31/85		25/89			127/ 335	12 weeks
S3BA2001 Oct'95-Dec'96	71 U.S.	21/59			18/54	23/51	21/54	28/40	111/ 258	12 weeks
S3BA3001 Sep'97-Dec'98	112 U.S.	0/317			0/309				0/626	12 weeks
S3BA3002 Sep'97-Oct'98	120 U.S.	0/323			0/324				0/647	12 weeks
Subtotal, 12-week studies		54/ 783	38/ 77	31/ 85	18/ 687	48/ 140	21/ 54	28/ 40	238/ 1866	
S3BA3003* Nov'97-Feb'99	131 U.S.	46/ 129			175/ 378				221/ 507	12 months

*Note: Doses b.i.d.: P, placebo; A 0.1 to 8.0, alosetron 0.1 to 8.0 mg. M/F, males, females; *, partial report as of 26 Feb'99 on 728 of 859 patients entered by 25 Sep'98.*

The "primary safety database" identified by the applicant comprised 1263 patients (184 men, 1079 women) who received alosetron, and 834 (54 men, 780 women) who received placebo for up to 12 weeks in the four clinical studies listed above. Studies S3BP12 and S3BA2001, were dose-ranging studies (from 0.1 to 8.0 mg b.i.d.) that included some men; studies (S3BA3001 and S3BA3002) were done in women only, comparing alosetron 1 mg to placebo b.i.d.

Table 8.10: Demographic Characteristics of Patients in the Primary Safety Database (Studies S3BP12, S3BA2001, S3BA3001 and S3BA3002) ***[Vol. 1, page 402]***

	Placebo n = 834	A 0.1 n = 115	A 0.5 n = 116	A 1.0 n = 702	A 2.0 n = 187	A 4.0 n = 75	A 8.0 n = 68	Total A n= 1263
Gender: M/F % M/F	54/780 6/94%	38/77 3/67%	31/85 27/73%	18/684 3/97%	48/139 26/74%	21/54 28/72%	28/40 41/59%	184/1079 15/85%
Age: m ± sd (range)	45 ± 0.5 (18-63)	42 ± 1.2 (18-70)	45 ± 1.3 (18-74)	46 ± 0.5 (18-82)	44 ± 1.0 (18-77)	44 ± 1.4 (20-71)	45 ± 1.4 (20-93)	45 ± 1.1 (18-93)
Race: w/b/o % w/b/o	763/51/20 91/6/2%	112/2/1 97/2/1%	113/2/1 97/2/1%	635/28/39 90/28/39%	177/6/4 95/3/2%	72/2/1 97/2/1%	63/0/5 99/0/7%	1172/40/51 93/3/4%

Note: Note: Doses b.i.d.: Placebo; A 0.1 to 8.0, alosetron 0.1 to 8.0 mg; M/F, numbers of males, females; m ± sd, mean ± standard deviation; w/b/o, white/black/other.

Comment: As may be seen, the numbers of patients enrolled as tabulated above in the table entitled "Long-Term, Placebo-Controlled Alosetron Studies" *differs very slightly from the Table 8.10 in the applicant's summary (Volume 1, page 402) because not all of the patients randomized to study drug actually took medication. The above numbers are those taken from each individual study report from Volumes 200, 110, 138, 167, and 205. Safety aspects of the four individual studies of the designated primary database of patients studied for 12 weeks will be considered first.*

B. Dose-ranging studies in men and women

1. S3BP12: European 12-week, placebo-controlled, dose-ranging study (Vol.200)

This dose-ranging, exploratory study was carried out at 43 study centers outside the U.S. (United Kingdom, Sweden, Poland, Belgium, Holland, Canada, Denmark, Germany, France) from July 1993 to September 1994 in adult out-patients with IBS, by the then-provisional Rome criteria (Thompson, *et al.*, 1992), for at least 6 months and active over the 4 weeks before enrollment with pain or discomfort on at least 3 days each week, defining altered stool frequency by >3/day or <3/week. A total of 510 patients were enrolled into a two-week "run-in" period during which no medication was given but screening studies were done, resulting in exclusion of 43 who did not qualify or wished to withdraw and leaving 467 who were randomized, but 5 never took any study medication. The net number of 462 patients (127 men, 27%; 335 women, 73%) were considered the "safety" population, and the 454 who had at least one efficacy assessment after starting treatment were considered the "intent-to-treat" population. Patients were excluded if they had histories of severe constipation (less than 1 bowel movement/week or requiring laxatives or enemas, if they had organic or infectious gastrointestinal disorders, were taking drugs with effects on gastrointestinal motility or pain, or if they had other significant systemic diseases. The average age of the patients was 43 (range 18-74); 97% were Caucasian, 2% Black, 1% other. About a third of the patients reported diarrhea- predominant IBS, another third alternating, and a third constipation-predominant IBS. Patients were randomized to receive alosetron 0.1, 0.5, or 2.0 mg, or placebo b.i.d. for 12 weeks. Patients for whom there were no major protocol violations (principally taking drug >80% of days) were counted in the "per protocol" subset.

Distribution of Patients to b.i.d. Treatment in Study S3BP12

Population Sample	Placebo	Alosetron 0.1 mg	Alosetron 0.5 mg	Alosetron 2.0 mg	Total Patients Observed
"Safety"	117	115	116	114	462
"ITT"	117	113	111	113	454
Completed study	85	83	75	82	325
"Per protocol"	96	91	95	103	385

Efficacy results in brief showed the expected placebo response in about half the patients. Beneficial effects of alosetron were apparent mainly in those presenting with loose stool consistency of >3.5 to 5 on the scale of (0 = none, 1 = hard, 2 = firm, 3 = soft, 4 = loose, 5 = watery) in patients receiving the 2-mg b.i.d. dose. Effects on stool consistency were alosetron dose-related, associated with the patients' perceptions of diarrhea severity and firming of stools.

Deaths and Serious Adverse Events

There were no deaths during this study, but serious adverse events were seen in 10 patients:

Serious Adverse Events, Study S3BP12 *(Vol. 200, pages 78-80)*

Dose, mg b.i.d.	*Patient No.:age/sex/race*	*Clinical Problem After __ time on study drug*	*Investigator's Opinion*
Placebo	F0219: 32Mc	Bell's palsy @ 11 weeks	unrelated
Alosetron 0.1	F0786: 36Mc	Perianal abscess, fever @ 2 weeks	possibly related
Alosetron 0.5	F0117: 45Fc	Herniated lumber disc @ 2 weeks	unrelated
	F0783: 62Fc	Uterine prolapse @ 12 weeks	unrelated
	F1035: F42c	Ureteral stone @ 12 weeks	unrelated
Alosetron 2.0	F0140: F47c	Benign ovarian cyst @ 12 weeks	unrelated
	F0777: F47c	Chest urticaria @ 4 weeks	probably related
	F0817: M49c	Salmonella infection @ 10 weeks	unrelated
	F0910: F30c	IBS abdominal pain @ 3 days	probably related
	F1080: F60c	Breast cancer @ 1day	unrelated

Note: M, male; F, female; c, Caucasian.

With reference to the alosetron-treated patients with "probably related" serious adverse events (SAEs), reference to the copies of case report forms (CRFs) provided electronically on tape as portable document format (.pdf) files, additional details were noted. Case F0910, a 30-year-old woman with constipation-predominant IBS symptoms relieved by defecation had a history of long-standing asthma, depression, and insomnia. On the third day on alosetron 2 mg b.i.d. she reported severe and continuous abdominal pain and was hospitalized for investigation. Study drug was stopped immediately, and work-up showed no other intra-abdominal problem, so the final diagnosis was "flare-up of IBS" probably caused by alosetron. The other case thought by the investigator to be probably related to study drug (F0777) was an urticarial rash of the chest, upper trunk and arms after a 47-year-old woman had been on alosetron 2 mg b.i.d. for 30 days. She was hospitalized, study drug was stopped, and the urticarial rash subsided within 15 hours after single doses of betamethasone 6 mg and Loratadine 10 mg orally. The rash was attributed to the alosetron as an "allergic reaction," although she had also been taking Econazole for vaginitis and acetaminophen and aspirin for headache for 12 days and trimethoprim sulfa for urinary tract infection for 10 days before the urticaria appeared. The perianal abscess in patient F0786 flared up 17 days after he had started alosetron 0.1 mg b.i.d, and was assessed to be "possibly related."

Reasons Given for Patients' Premature Withdrawals

	Placebo BID n = 117	A 0.1 mg BID n = 115	A 0.5 mg BID n = 116	A 2.0 mg BID n = 114	Total n =462
Lack of efficacy	15 (12.8%)	11 (9.6%)	11 (9.5%)	11 (9.6%)	48 (10.4%)
Adverse event	5 (4.3%)	11 (9.6%)	21 (18.1%)	15 (13.2%)	52 (11.3%)
(plus some other reason)	3 (2.6%)	1 (1.0%)	2 (1.7%)	2 (1.8%)	8 (1.7%)
"Failed to return"	5 (4.3%)	4 (3.5%)	5 (4.3%)	4 (3.5%)	18 (3.9%)
"Other"	8 (6.8%)	7 (6.1%)	4 (3.4%)	2 (1.8%)	21 (4.5%)
total	33 (28.2%)	33 (28.7%)	41 (35.3%)	32 (28.1%)	139 (30.1%)

Note: BID, bis in die, twice daily; A, alosetron.

Comment: The real reasons that patients "fail to return" or give "other" reasons for dropping out of studies may be masked by these apparent or proffered reasons, and may conceal either lack of perceived efficacy or some perceived adverse effect not admitted to the investigator or his staff. In 8 of the cases, an amended report (6 May 1999; Volume 200: pages 4, 91) was provided to include patients who withdrew with adverse reactions but claimed some other reason as primary reason for their withdrawal. Lack of efficacy was cited more often in the placebo group, but the differences were not statistically significant from any of the alosetron groups. However, withdrawal primarily because of adverse events occurred significantly more often in groups treated with alosetron 0.5 mg b.i.d. ($p < 0.001$) and alosetron 2 mg b.i.d. ($p < 0.02$). If the adverse events as secondary reasons were included, differences were still notable: alosetron 0.5 mg b.i.d. ($p < 0.004$) and alosetron 2 mg b.i.d. ($p = 0.057$). A substantial number, 139 of 462 (30%) were withdrawn prematurely (Vol. 200, p 91 (Table 2):

Patients Withdrawn Prematurely for Adverse Events

Adverse Events Causing Premature Withdrawal, S3BP12

	Placebo BID n = 117	A 0.1 mg BID n = 115	A 0.5 mg BID n = 116	A 2.0 mg BID n = 114
Withdrawn prematurely	33 (28.2%)	33 (28.7%)	41 (35.3%)	32 (28.1%)
Any adverse event	8 (6.8%)	12 (10.4%)	23 (19.8%)	17 (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%)**
Neurological event	3 (2.6%)	2 (1.7%)	6 (5.2%)	1 (0.9%)
headache	2 (1.7%)	1 (0.9%)	4 (3.4%)	0
Cardiovascular event	0	2 (1.7%)	1 (0.9%)	0
arrhythmias	0	1 (0.9%)	1 (0.9%)	0

Comment: There were no significant differences in the total numbers withdrawn, but significantly more for gastrointestinal events alosetron 0.5 mg b.i.d. ($p < 0.01$) and alosetron 2 mg b.i.d. ($p < 0.03$) than for placebo, and constipation appeared to show a dose-related and significant increase over placebo. No significant increase in headaches or arrhythmias was seen. (Table 118, Volume 200, pages 267-9):

When the prior type of IBS was considered, along with the average stool consistency scores, the patients with prior constipation-predominant IBS by history were more likely to be withdrawn on treatment with the higher doses of alosetron because of adverse constipation effects. This was examined by review of the classifications given to the investigators by patients in the study as to whether they felt their IBS was constipation or diarrhea-predominant, or was of the alternating type. This historical background of perceived type did not always match the average reported stool consistency values recorded by patients during the baseline period before initiation of the study treatment.

Comment: Data from Table 119 (Volume 200, page 270) show that prior history of constipation-predominant IBS was not a factor in determining whether patients might have to withdraw from treatment if they were on placebo or the lowest dose of alosetron, but was very important if they were receiving either 0.5 or 2 mg b.i.d. of alosetron during the study.