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Safety Profile of Tegaserod, a 5-HT_4 Receptor Agonist, for the Treatment of Irritable Bowel Syndrome

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Contents

Abstract

This article reviews the safety and tolerability profile of tegaserod, a novel selective partial agonist of the serotonin 5-HT_4 receptor. Tegaserod was recently approved for the treatment of women with irritable bowel syndrome (IBS) with constipation.

Tegaserod exhibits rapid absorption from the small intestine, and is excreted unchanged in the faeces and as metabolites in the urine. Meal ingestion decreases its bioavailability. There is little effect of age or gender on pharmacokinetics, although plasma levels may be slightly higher in the elderly. Tegaserod has no effect on plasma levels of other drugs metabolised by cytochrome P450 enzyme systems.

Gastrointestinal symptoms are the most common adverse effects of tegaserod therapy. In data pooled from phase III randomised controlled trials (RCTs) in IBS with constipation patients, diarrhoea was reported by 8.8% of patients treated with tegaserod 6mg twice daily versus 3.8% of patients receiving placebo. Similar rates have been observed in international post-US marketing RCTs. In most patients, tegaserod-induced diarrhoea was mild and transient. In RCTs, it did not elicit fluid or electrolyte disturbances, and fewer than 3% of IBS patients discontinued tegaserod due to diarrhoea. Since its release, rare cases of more severe diarrhoea and ischaemic colitis have been reported. The incidence of other gastrointestinal symptoms (e.g. abdominal pain, nausea, and flatulence) has been similar among tegaserod-treated patients and placebo-treated patients. Pooled analysis of phase III RCTs and post-US marketing RCTs have not demonstrated significant differences between tegaserod-treated patients and placebo-treated patients in the incidence of abdominal-pelvic surgery. There is no convincing evidence that rebound gastrointestinal symptoms occur upon termination of tegaserod therapy.

Pooled analysis of phase III RCTs demonstrated an increase in the incidence of headaches among tegaserod-treated patients (6mg twice daily) compared with placebo-treated patients (15% vs 12.3%, respectively, $p < 0.05$), although post-US marketing RCTs have not observed this increase. Other extra-gastrointestinal adverse events occur with similar frequency among tegaserod-treated patients and placebo-treated patients. Tegaserod-treated patients in RCTs have not demonstrated significant prolongation of the QTc interval or cardiac arrhythmias compared with placebo-treated patients. Supra-therapeutic doses in healthy volunteers did not effect electrocardiographic parameters. Laboratory parameters are mostly unaffected by tegaserod, although several individuals have exhibited increased eosinophil counts.

In summary, tegaserod exhibits a favourable safety and tolerability profile in IBS patients based on data from clinical trials. Diarrhoea is the most common adverse event associated with tegaserod use. Continued post-US marketing surveillance will further define the safety and tolerability profile of tegaserod.

1. Clinical Utility of Tegaserod

Tegaserod (Zelnorm®)[1] is an aminoguanidine indole which acts as a selective partial agonist on serotonin 5-HT_4 receptors, exhibiting a potency one-fifth that of endogenous serotonin.[1] The drug exerts motor stimulatory effects in the gastrointestinal tract resulting in enhanced propulsion in several gut regions. In healthy human volunteers, tegaserod accelerates gastric emptying, colonic filling, and colonic transit.[2] Small intestinal transit times are shortened by 30% and 37% with oral and intravenous administration, respectively. In irritable bowel syndrome (IBS) patients with constipation, the drug increases colonic filling of an ingested radionuclide marker at 6 hours from 46.4 ± 1.9 to 70.4 ± 1.3%, signifying promotion of small bowel propulsion.[3] Tegaserod also exhibits effects on visceral afferent

1 The use of trade names is for product identification purposes only and does not imply endorsement.

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function, blunting the somatic reflex to colonic distension.[4] Because of these effects on colonic motor and sensory function, tegaserod is promoted as a treatment for IBS with constipation.

Randomised controlled trials (RCTs) demonstrate that tegaserod is effective for treatment of IBS with constipation in women.[5] In a 12-week, international, placebo-controlled, double-blind RCT of 881 IBS patients with constipation, tegaserod 6mg twice daily significantly reduced global IBS symptoms and improved individual symptoms of abdominal discomfort, infrequent defecation, hard stools, and bloating.[6] In this study, 50% of patients given tegaserod reported responses at the end of 12 weeks versus 36.6% of placebo-treated patients ($p < 0.05$). Another 12-week, placebo-controlled, double-blind RCT of 1519 women with IBS with constipation in the US also found that tegaserod produced significant improvement in global IBS symptoms and individual IBS symptoms with tegaserod 6mg twice daily compared with placebo.[7] Response rates in this investigation were 43.5% with tegaserod versus 38.8% with placebo ($p < 0.05$). International post-US marketing RCTs (i.e. RCTs completed after marketing of tegaserod in the US in August 2002) confirm its efficacy for global IBS symptom improvement, abdominal discomfort, bloating and constipation across a geographically and ethnically diverse range of populations.[8-11] However, the small number of men enrolled in these RCTs precludes a precise estimate of tegaserod efficacy in male IBS patients. Recent studies in patients with chronic constipation, not secondary to IBS, noted increases in stool frequency and improvements in other constipation symptoms, suggesting that other colonic dysmotility syndromes may respond to this agent.[12,13]

Any treatment for IBS should demonstrate a favourable efficacy and tolerability/safety profile. In this article, we present a summary of safety and tolerability data from RCTs in patients with IBS and chronic constipation. Supplementary safety and tolerability data from pharmacokinetic studies, drug interaction data, and open-label trials of IBS patients and healthy volunteers are also included.

2. Pharmacokinetics of Tegaserod

2.1 Metabolism

Tegaserod is metabolised by a number of pathways. The first pathway is initiated by pH-dependent hydrolysis in the stomach followed by oxidation and conjugation to produce 5-methoxyindo-3-carboxylic acid glucuronide, also known as M29.0.[14] This metabolite possesses neither 5-HT_4 agonist properties nor prokinetic actions on the gastrointestinal tract. The second pathway involves direct glucuronidation to three N-glucuronide isomers, M43.2, M43.8 and M45.3.[14-16] The liver and small intestine both are capable of direct glucuronidation of tegaserod. In human liver microsomes, tegaserod is metabolised to O-desmethyltegaserod at a low rate, which is inhibited by quinidine.[15] O-methyltegaserod is also produced by cDNA-expressed cytochrome P450 (CYP) 2D6.

2.2 Absorption, Distribution and Clearance

Tegaserod is absorbed from the small intestine and two-thirds of the dose is excreted unchanged in the faeces with the remainder eliminated in the urine as the M29.0 metabolite.[14] The pharmacokinetics of tegaserod are linear in the dose range from 2–12mg.[14] Steady-state plasma levels are achieved within 8 days with repeated administration.[17] Absorption in healthy volunteers is rapid with a time to reach maximal concentration (t_{max}) of 0.8–1.3 hours and 11 ± 3% bioavailability.[18,19] The maximal plasma concentration is dose-dependent with maximal concentration (C_{max}) values of 0.7 ± 0.3, 2.7 ± 1.2, and 5.6 ± 2.9 μg/L with 2, 6, and 12mg doses, respectively.[18] The volume of distribution is 368 ±

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223L.[19] The cumulative absorption (area under the concentration time curve; AUC) ranges from 2.4 ± 1.3 to 20.4 ± 14.0 μg • h/mL for doses from 2 to 12mg.[18] Meal ingestion prolongs the t_{max} to 2 hours, decreases bioavailability to 5%, and lowers the AUC by half due to reductions in the extent of absorption.[19,20] Elimination half-lives ($t_{1/2}$) range from 5.8 ± 1.2 hours for the 2mg dose to 9.8 ± 3.2 hours for 12mg.[18] There is no effect of gender or age on either t_{max} or C_{max} values and no effect of gender on AUC.[21] AUC values are increased in the elderly, but this is not felt to be clinically relevant and no dose adjustment is recommended for older individuals. Pharmacokinetic parameters are similar in healthy volunteers and patients with IBS.[14] No dose adjustments are necessary for mild hepatic or renal impairment, although the drug is contraindicated in patients with moderate or severe liver or severe kidney disease.[14]

3. Drug Interactions

The metabolite M29.0 does not inhibit any CYP enzyme.[15] Tegaserod inhibits CYP1A2 and CYP2D6 with dissociation constant (K_i) values of 0.84 and 0.85 μmol/L, respectively.[15] These values are approximately 140-fold higher than plasma concentrations achieved with the 6mg dose, thus it is unlikely that dose adjustments will be needed for drugs metabolised by these enzymes (e.g. theophylline)[22] during concurrent therapy with tegaserod. In healthy volunteers, the AUC, C_{max}, and $t_{1/2}$ for theophylline were similar when the drug was given alone or in combination with tegaserod.[23] Furthermore, tegaserod had no effect on renal clearance of theophylline or conversion of theophylline to 1,3-dimethyluric acid or 3-methylxanthine. There was no increase in reported adverse effects when theophylline was taken with tegaserod. However, the t_{max} for theophylline is 2 hours shorter when the drug was taken with tegaserod and there was a 25.7% decrease in metabolism of theophylline to 1-methyluric acid after tegaserod.[23] These actions are believed to have limited impact on the overall pharmacokinetics of theophylline administration, thus dose modifications are not recommended. Likewise, no significant drug interactions have been observed when tegaserod was administered with dextromethorphan (a CYP2D6 substrate), warfarin, or oral contraceptives.[14]

Use of gastrointestinal prokinetic drugs could limit bioavailability of drugs absorbed in the small intestine by reducing contact time in the small intestine.[24,25] Indeed, both metoclopramide and cisapride decrease absorption of digoxin, a drug absorbed from the small intestine.[25,26] In similar studies, the t_{max} for digoxin peaked at 1.5 hours when digoxin was given alone versus 1.0 hours when digoxin was taken after 3 days of tegaserod (p = NS).[27] Furthermore, AUC and C_{max} values for digoxin were 11.9% and 15.0% lower when digoxin was taken after tegaserod ($p < 0.05$). Tegaserod therapy also lowers the distribution rate constant for digoxin by 40% and the steady-state digoxin trough concentration by 11.4%. These effects are consistent with a minor prokinetic effect on digoxin absorption, but are not considered clinically relevant. Only a small percentage of patients who use tegaserod and digoxin are likely to require changes in digoxin dosage and this should be detectable by routine monitoring of digoxin levels.[27]

4. Adverse Events Associated with Tegaserod

4.1 Overview of Studies

Adverse event data from eight randomised, double-blind, placebo-controlled studies of 4–12 weeks' duration[6-8,10,11,28-30] in IBS patients, an open-label study of 12 months' duration in IBS with constipation patients,[28,31] two randomised, double-blind, placebo-controlled studies of 12 weeks' duration in chronic constipation,[12,13,30] and one randomised,

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Table I. Randomised controlled trials and open-label trials with tegaserod

Population (reference)	Design	No. of patients	Women (%)	Tegaserod dosage
IBS with constipation[6] (phase III trial)	12-week, double-blind placebo-controlled RCT	881	83	2mg bid or 6mg bid
IBS with constipation[7] (phase III trial)	12-week, double-blind placebo-controlled RCT	1519	100	6mg bid
IBS with constipation[28] (phase III trial [Study 351])	12-week, double-blind placebo-controlled RCT	799	87	2mg bid or 6mg bid
IBS with constipation[28] (phase III trial [Study 307])	12-week, double-blind placebo-controlled RCT	841	84	Dose titration with 2mg bid and 6mg bid
Non-diarrhoea-predominant[8] IBS, Asia-Pacific population	12-week, double-blind placebo-controlled RCT	520	88	6mg bid
Non-diarrhoea-predominant[11] IBS, Nordic population	12-week, double-blind placebo-controlled RCT	647	86	6mg bid
IBS with constipation,[10] China population	4-week, double-blind placebo-controlled RCT	510	82	6mg bid
IBS with constipation[31] (long-term study)	12-month open-label	579	90	2mg bid or 6mg bid
Chronic constipation[12]	12-week, double-blind placebo-controlled RCT	1348	90	2mg bid
Chronic constipation[13]	12-week, double-blind placebo-controlled RCT	1264	86	2mg bid
Diarrhoea-predominant IBS[29]	8-week, double-blind placebo-controlled RCT	86	67	2mg bid or 6mg bid

bid = twice daily; **IBS** = irritable bowel syndrome; **RCT** = randomised controlled trial.

placebo-controlled study of 8 weeks' duration in IBS with diarrhoea[29] were included (table I). All investigations provided safety data for tegaserod at a dose of 6mg twice daily. Three placebo-controlled trials in IBS with constipation,[6,28] one open IBS trial,[28,31] and both chronic constipation studies also examined adverse events with tegaserod 2mg twice daily,[12,13,30] while one placebo-controlled IBS study reported on adverse effects during dose titration.[28] One of the double-blind RCTs evaluated diarrhoea-predominant IBS patients to further confirm the relatively mild nature of diarrhoeal adverse effects of the drug.[29] Adverse event data was extracted from published manuscripts, abstracts from national and international gastroenterology symposia, and unpublished data on file with Novartis Pharmaceuticals Corporation.

Demographic characteristics of study participants closely mirrored those of IBS populations in the different geographic regions involved in the tegaserod trials. All individuals studied were 12 years or older, with mean ages ranging from 36–51 years of age. Women represented the majority of study subjects in all investigations, making up 67 to 100% of patients (table I). All participants in IBS trials satisfied validated symptom-based criteria for IBS, such as the Rome criteria. In individual RCTs, patients receiving tegaserod have not demonstrated significant increases in total adverse events, serious adverse events, or severe adverse events compared with patients using placebo.[6-8,10,11,28,30] Pooled phase III data is derived from 4035 patients who participated in four phase III RCTs,[5-7,16,28] and safety data from post-US marketing RCTs encompass 1676 additional IBS patients.[8,10,11,30]

4.2 Gastrointestinal Adverse Events

Gastrointestinal adverse events are the most frequent adverse effects associated with tegaserod therapy, and are likely the consequence of the promotile activity of the drug. In many investigations, diarrhoea is reported significantly more often with

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Table II. Incidence of diarrhoea during treatment with tegaserod

Population	Design	Tegaserod (dosage)	Placebo (%)
IBS with constipation, phase III trials[28] (pooled analysis)	12-week, double-blind placebo-controlled RCT	11.4% (2mg bid) 8.8% (6mg bid) 11.6% (dose titration)	4.2
IBS with constipation, Asia-Pacific[8]	12-week, double-blind placebo-controlled RCT	10.0% (6mg bid)	3.1
IBS with constipation, Nordic[11]	12-week, double-blind placebo-controlled RCT	9.2% (6mg bid)	1.3
IBS with constipation, China[10]	4-week, double-blind placebo-controlled RCT	2.9% (6mg bid)	0.4
IBS with constipation, long-term[31]	12-month, open-label	10.1% (2 or 6mg bid)	a
Chronic constipation[12]	12-week, double-blind placebo-controlled RCT	4.5% (2mg bid) 7.3% (6mg bid)	3.8
Chronic constipation[13]	12-week, double-blind placebo-controlled RCT	3.9% (2mg bid) 5.8% (6mg bid)	2.2
Diarrhoea-predominant IBS[29]	8-week, double-blind placebo-controlled RCT	48.6% (2mg bid) 17.7% (6mg bid)	35.3

a No placebo control in this trial.

bid = twice daily; **IBS** = irritable bowel syndrome; **RCT** = randomised controlled trial.

tegaserod than with placebo (table II). In the largest study of IBS with constipation involving 1519 women, diarrhoea was experienced by 6.4% of patients during tegaserod therapy 6mg twice daily versus 2.9% on placebo,[6] and, in a study of 881 constipated IBS patients, the incidence of diarrhoea was higher on tegaserod versus placebo (7.1% on 2mg twice daily/9.6% on 6mg twice daily versus 2.5% on placebo; p-values were not reported).[5] In an analysis of weighted adverse event data from the pooled phase III database, the frequency of diarrhoea was 8.8% among patients using tegaserod 6mg twice daily versus 3.8% among patients using placebo. However, only 1.6–2.4% of tegaserod-treated patients in these studies discontinued therapy because of diarrhoea. In a long-term investigation of 579 patients followed for up to 12 months, diarrhoea considered related to tegaserod was experienced by 10.1% and was severe enough to discontinue therapy in 3.5%.[31] Post-US marketing RCTs in international populations have also noted that diarrhoea is associated with tegaserod use. In 520 non-diarrhoea-predominant IBS patients from the Asia-Pacific region, 10.0% of individuals on tegaserod reported diarrhoea versus 3.1% of placebo patients.[8,30] Of 647 Nordic patients, 9.2% noted diarrhoea with tegaserod therapy compared with 1.3% on placebo.[11,30] In these trials, discontinuation of tegaserod due to diarrhoea was 2.3–2.9%.[8,11,30]

In studies of IBS with constipation patients, diarrhoea generally was mild and produced no dehydration or electrolyte abnormalities.[28,30,32] Furthermore, in pooled data from four phase III trials in constipated IBS patients, diarrhoea occurred early and was transient in nature.[28,32] Many patients reported onset of diarrhoea within the first day of therapy; diarrhoea began after 8–29 days in only 21% of patients with diarrhoea. The median duration of diarrhoea was 2 days and many patients experienced only a single diarrhoeal episode.[28,32] A study of 114 diarrhoea-predominant IBS patients confirmed the relatively benign nature of tegaserod-induced diarrhoea.[29] Thirty-three percent of patients treated with tegaserod (6mg twice daily or 2mg twice daily) reported diarrhoea compared with 35% of those receiving placebo. Severe diarrhoea was noted by 17% of tegaserod-treated patients versus 18% of placebo-treated individuals and anti-diarrhoeal agent use was required by 23% of tegaserod-treated patients versus 24% of placebo-

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treated patients.[29] As with IBS with constipation patients, no fluid or electrolyte disturbances were associated with this diarrhoea.[29]

Other gastrointestinal symptoms have also been reported, but it is unclear if these symptoms were induced by tegaserod. In placebo-controlled RCTs in IBS with constipation or with non-diarrhoea predominant IBS, abdominal pain was reported by 4.9–16.7% of tegaserod-treated patients versus 3.1–17.1% of placebo-treated patients.[6-8,11,28,30] Only one of these studies reported significantly higher rates of development of abdominal pain with tegaserod versus placebo.[8] Similarly, abdominal pain considered related to tegaserod was reported by 7.4% of constipated IBS patients in open-label, long-term observational studies.[31] In this investigation, only one episode of severe abdominal pain was felt to be possibly related to tegaserod therapy.[31] When data from 4035 patients randomised in phase III trials up to 2000 were pooled,[28] there was a slight but statistically significant increase in the incidence of severe abdominal pain with tegaserod 6mg twice daily use compared with placebo use (4.4% vs 3.7%, respectively, $p < 0.05$). No significant difference in the incidence of abdominal pain was observed between tegaserod-treated patients and placebo-treated patients in the two RCTs performed in patients with chronic constipation.[12,13,30]

Nausea was reported by similar proportions of patients using tegaserod and placebo in RCTs of IBS with constipation and non-diarrhoea predominant IBS (4.2–7.4% vs 3.4–8.7%, respectively),[6-8,11,28,30] and chronic constipation (3.8–6.1% vs 1.8–7.5%, respectively).[12,13,30] Likewise, no significant differences in the incidence of flatulence were observed in RCTs of IBS with constipation or non-diarrhoea predominant IBS patients or chronic constipation patients.[5-8,12,13,28,30] In the largest published trial, flatulence was reported by 5.7% of tegaserod-treated patients vs 4.0% of placebo-treated patients (p = NS in chi-square analysis by review authors).[7]

Serious adverse events due to severe constipation and ischaemic colitis have been reported with alosetron, a 5-HT_3 receptor antagonist, indicated for women with diarrhoea-predominant IBS. However, tegaserod is an agonist of the 5-HT_4 receptor, and is pharmacologically much different than alosetron. No episodes of severe constipation have been attributed to tegaserod use. Furthermore, data from the RCTs provide no convincing evidence of rebound constipation developing upon termination of tegaserod use. However, in postmarketing reports to the US FDA, some cases of serious consequences of diarrhoea including hypovolaemia, hypertension and syncope have been observed.[33] In some instances, hospitalisation for rehydration have been required. Furthermore, rare cases of ischaemic colitis have been reported with tegaserod therapy although a causal relationship has not been confirmed. Revised recommendations state that tegaserod should be discontinued in patients who develop new or increased abdominal pain, rectal bleeding or diarrhoea that leads to syncope or presyncope.

4.3 Rates of Abdominal and Pelvic Surgery

The FDA required the following statement in prescribing information for tegaserod: "Zelnorm (tegaserod maleate) is contraindicated in those patients with … a history of bowel obstruction, symptomatic gallbladder disease, suspected sphincter of Oddi dysfunction, or abdominal adhesions". Therefore, the incidence of abdominal and pelvic surgeries from phase III and post-US marketing RCTs is provided.

In phase III RCTs (table III),[5-7,28] 4035 patients with IBS with constipation were randomised: 2965 patients received tegaserod and 1740 patients received placebo (several trials used a 2 : 1 randomisation schedule). No differences in the incidence of abdominal and pelvic surgeries were observed between tegaserod-treated patients and placebo-treated patients (0.44% vs 0.40%, respectively, p =

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Table III. Abdominal and pelvic surgeries in phase II/III trials of tegaserod in irritable bowel syndrome patients with constipation[5-7,28]

	Tegaserod (n = 2965)	Placebo (n = 1740)	p-Value[a]
Pelvic (no. [%])	4 (0.13)	4 (0.23)	0.69
Abdominal, non-cholecystectomy (no. [%])	4 (0.13)	2 (0.11)	0.81
Cholecystectomy (no. [%])	5 (0.17)	1 (0.06)	0.22
Total (no. [%])	13 (0.44)	7 (0.40)	0.96

a Based on chi-square analysis (Mantel-Haenstzel test performed by review authors).

0.96).[5,28,30] In sub-group analysis, no significant difference was observed between tegaserod-treated patients and placebo-treated patients for incidence of pelvic surgery (0.13% vs 0.23%, respectively, p = 0.69, abdominal surgery (non-cholecystectomy) [0.13% vs 0.11%, respectively, p = 0.81], or cholecystectomy (0.17% vs 0.06%, respectively, p = 0.22). In post-US marketing RCTs (table IV),[8,10,11,30] 1676 patients with non-diarrhoea predominant IBS and/or IBS with constipation were enrolled: 840 patients received tegaserod and 836 received placebo. No differences in the incidence of abdominal and pelvic surgeries were observed between tegaserod-treated patients and placebo-treated patients (0.36% vs 0.12%, respectively, p = 0.62) in post-US marketing RCTs.[30] In sub-group analysis carried out by the review authors, no significant difference was observed between tegaserod-treated patients and placebo-treated patients for incidence of pelvic surgery (0.0% vs 0.0%), abdominal surgery (non-cholecystectomy) [0.36% vs 0.12%, respectively, p = 0.62], or cholecystectomy (0.0% vs 0.0%). The apparent 3-fold increase in non-cholecystectomy abdominal surgeries did not approach statistical significance due to the small number of such surgeries performed in each treatment group.

The FDA-mandated labelling for tegaserod states that "the increase (in abdominal surgeries) was primarily due to a numerical imbalance in cholecystectomies reported in patients (in phase III trials) treated with Zelnorm (5/2965 or 0.17%) vs placebo (1/1740 or 0.06%)". However, when data from 4035 patients randomised to phase III placebo-controlled RCTs were pooled,[28,30] case histories of patients who underwent cholecystectomy were reviewed and determined that two tegaserod-treated patients had symptomatic cholelithiasis diagnosed prior to study entry. A third tegaserod-treated patient with chronic right upper quadrant pain and a decreased gallbladder ejection fraction did not have cholelithiasis at cholecystectomy and experienced no postoperative symptom relief. An expert panel, blinded to each patient's treatment, reviewed all abdominal surgery cases that occurred during phase III RCTs and concluded that the performance of cholecystectomy in these three individuals was unrelated to drug therapy.[30] After exclusion of these three cases, recalculation of the cholecystectomy rates from phase

Table IV. Abdominal and pelvic surgeries in post-US marketing randomised controlled trials of tegaserod in non-diarrhoea-predominant irritable bowel syndrome (IBS) and IBS with constipation patients[30][a]

	Tegaserod (n = 840)	Placebo (n = 836)	p-Value[b]
Pelvic (no. [%])	0 (0.0)	0 (0.0)	1.00
Abdominal, non-cholecystectomy (no. [%])	3 (0.4)	1 (0.1)	0.62
Cholecystectomy (no. [%])	0 (0.0)	0 (0.0)	1.00
Total (no. [%])	3 (0.4)	1 (0.1)	0.62

a The data presented here are crude adverse event rates.

b Based on chi-square analysis (Mantel-Haenszel test performed by review authors).

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III RCTs revealed no difference in cholecystectomy rates for tegaserod-treated patients versus placebo-treated patients (0.07% vs 0.06%, respectively, p = 0.64).

A placebo-controlled, randomised crossover trial of 12 healthy volunteers and 37 IBS patients assessed the affect of tegaserod on gallbladder motility. Patients received either placebo or tegaserod (12mg daily or 24mg daily) for 2 weeks in a crossover study, followed by a 1-week washout period, and then switched to the other treatment arm. Each treatment period was followed by real-time ultrasonography. Tegaserod use did not affect gallbladder ejection fraction, emptying rate, maximal emptying, fasting and residual volume, or common bile duct diameter in healthy volunteers and IBS patients.[34] No specific data is available about the incidence of adverse events among tegaserod-using patients with suspected sphincter of Oddi dysfunction.

No evidence suggests that tegaserod increases the rates of abdominal-pelvic surgery for management of bowel obstruction due to abdominal adhesions, FDA prescribing information for tegaserod states that the drug is contraindicated for patients with a history of bowel obstruction or abdominal adhesions. For this review, data on the incidence of surgery for bowel obstruction with lysis of abdominal adhesions were extracted from individual study reports from phase III RCTs[6,7,28] and post-US marketing RCTs[8,10,11,30] of IBS patients by the authors. This pooled analysis revealed that surgery for bowel obstruction with lysis of abdominal adhesions occurred in 0.00% (0/3805) of tegaserod-treated patients versus 0.08% (2/2576) of those on placebo.

4.4 Extra-Gastrointestinal Adverse Events

Headache is the most common extra-gastrointestinal adverse event reported with tegaserod use.[28,30] In individual phase III RCTs,[6,7,28] the incidence of headache was not significantly greater among tegaserod-treated patients compared with those on placebo. However, in pooled analysis of phase III RCTs,[28] the incidence of headache was significantly greater among tegaserod-treated patients (6mg twice daily) versus placebo (15% vs 12.3%, respectively, $p < 0.05$).[28] The mechanism for this finding is uncertain; it should be noted that tegaserod does not cross the blood-brain barrier.

Headaches associated with tegaserod use were usually mild, transient, and rarely required discontinuation of therapy. In pooled analysis of phase III RCTs, the incidence of severe headaches was similar in tegaserod-treated patients and placebo-treated patients (3.4% vs 2.6%, respectively).[28] The incidence of migraine headaches was also low for both tegaserod-treated patients and placebo-treated patients (0.7% vs 0.7%, respectively).[28] Headaches severe enough to force discontinuation of study participation were uncommon and occurred with similar frequency for both tegaserod- and placebo-treated patients (1.0% vs 0.8%, respectively).[28] Similarly, data from post-US marketing RCTs of IBS patients show similar incidences of severe headache, migraine headache, and discontinuation of study medication due to headache among both groups of patients.[8,30]

Other extra-gastrointestinal symptoms have also been quantified. Similar small numbers of tegaserod- and placebo-treated patients reported flu-like symptoms, upper respiratory tract infections, back pain, dizziness, sore throat, and fatigue,[28,30] although upper respiratory tract infections were less common in tegaserod-treated patients (6mg twice daily dose) compared with placebo-treated patients in pooled analysis of phase III data (4.1% vs 7.1%, respectively, $p < 0.01$).[28] In early reports, some tegaserod patients formed ovarian cysts. However, pooled analysis of phase II/III data reveals similar incidence of ovarian cysts among tegaserod-using patients and placebo-using patients (0.15% vs 0.13%, respectively, p = NS).[28]

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4.5 Lack of Effect on Cardiovascular Variables

Tegaserod has been extensively scrutinised for potential cardiac toxicity because of the cardiac toxicity associated with other gastrointestinal prokinetic drugs. Cisapride, another 5-HT_4 receptor agonist, was withdrawn from the US market because it prolonged the QT interval and was associated with potentially fatal cardiac arrhythmias, including torsades de pointes.[35] Both cisapride and the motilin receptor agonist erythromycin block the rapid component of the delayed rectifier potassium current.[36,37] Inhibition of this current, which is responsible for terminating cardiac action potentials, prolongs cardiac repolarisation. Benzamides, like cisapride, exhibit high affinity for potassium channels.[36] Furthermore, cisapride has positive chronotropic effects in the heart.[38] As an aminoguanidine indole, tegaserod has no such effects. In isolated rabbit hearts, cisapride prolongs the QT interval on electrocardiographic (ECG) testing at concentrations as low as 0.1 μmol/L with significant lengthening above 5 μmol/L.[37] Erythromycin also prolongs the QT interval, but only at concentrations above 100 μmol/L. Tegaserod has no effect on the QT interval in concentrations ranging from 0.5–10 μmol/L, while concentrations above 50 μmol/L elicit a slight lengthening.[37] However, this concentration is 500–5000 times the plasma concentration achieved during clinical use of the drug.

These *in vitro* observations correlate well with data from phase III RCTs and post-US marketing RCTs of IBS patients.[6-8,10,11,28,30] In pooled analysis of phase III RCT data, palpitations (0.6% vs 0.7%, respectively) and syncope (0.3% vs 0.1%) occurred with similar frequency among tegaserod-treated and placebo-treated patients.[28] Tegaserod elicited no significant changes in pulse or blood pressure.[28] Adverse events related to heart rate or rhythm disorders occurred with similar frequency among tegaserod-treated and placebo-treated patients (2.0% vs 2.4%, respectively, p = NS) in phase III RCTs.[39] Clinically relevant tachycardias were observed in only 0.5% of tegaserod-treated patients compared with 1.1% of placebo-treated patients. These observations have been confirmed in recent trials of patients with IBS with constipation, non-diarrhoea predominant IBS, or chronic constipation not secondary to IBS.[8,11-13,30]

In phase III RCTs of IBS patients, ECGs were performed on the first day after first dose, 4 weeks, and 12 weeks after initiation of therapy. Of 11 535 ECGs analysed, new waveform changes developed in 11% of tegaserod-treated patients versus 10% of placebo-treated patients.[39] The most common abnormalities were flattened, inverted, or biphasic T waves (5.1% vs 4.1%, respectively; p = NS with placebo). Arrhythmias were noted on ECGs of 3.7% of tegaserod-treated patients versus 3.9% of placebo-treated patients. However, serious arrhythmias (e.g. new onset atrial fibrillation, supraventricular tachycardia, bundle-branch blocks, and atrioventricular blocks) occurred in <0.3% of patients with both treatments.[28,30] Effects of tegaserod on QT_c intervals were closely scrutinised given the prior experience with cisapride (table V). QT_c prolongation of 30–60 msec was noted in 18.7% of both tegaserod- and placebo-treated patients.[39] Prolongations of >60 msec were seen in 0.9% of tegaserod-treated patients vs 1.3% of placebo-treated patients. In a correlative investigation, 36 healthy volunteers received intravenous tegaserod in doses ranging from 0.8–20mg producing plasma levels up to 100-fold greater than therapeutic concentrations.[39] ECGs obtained from these individuals 30 minutes to 6 hours after administration exhibited no prolongation of QT_c intervals. These investigators concluded that tegaserod is devoid of effects on ECG activity and is likely to have no effect on cardiac function based on this study and phase III RCT data.[39]

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Table V. Effects of tegaserod on corrected QT (QTc) intervals on electrocardiographic testing (reproduced from Morganroth et al.,[39] with permission)

QTc interval parameter	Tegaserod (n = 1679)[a]	Placebo (n = 837)	Difference (95% CI)
Baseline (mean ± SD, msec)	383 ± 29	380 ± 28	
Change from baseline at end of therapy (msec)	2.1 ± 22.2	3.1 ± 22.7	−1 (−1.9, 1.4)
Increase by 30–60 msec (% patients)	18.7	18.7	0 (−3.3, 3.2)
Increase by >60 msec (% patients)	0.9	1.3	−0.4 (−1.3, 0.5)
Normal at baseline to prolonged during study (% patients)	0.4	0.6	−0.2 (−0.8, 0.4)
Normal at baseline to borderline prolonged during study (% patients)	3.5	4.0	−0.5 (−2, 1.2)
Borderline prolonged at baseline to prolonged during study (% patients)	0.3	0.4	−0.1 (−0.5, 0.4)

a 4 or 12 mg/day.

4.6 Additional Safety and Tolerability Data

No abnormalities in liver chemistries, renal function, electrolytes, plasma glucose, lipid profiles, or urinalyses were attributable to tegaserod based on data from phase III RCTs and post-US marketing RCTs in IBS patients.[28,30] Complete blood counts showed no changes in haemoglobin or most white cell populations. Elevated eosinophil counts were noted more commonly among tegaserod-treated patients compared with placebo-treated patients, although fewer than 5% of tegaserod-treated patients demonstrated this increase. Six patients (0.14%) receiving tegaserod had eosinophil counts in excess of 1×10^9/L, whereas no person on placebo (0%) showed such levels.[28] Although these findings are suggestive of possible infrequent allergic responses to the drug, no patient exhibited symptoms of hypersensitivity. Thus, the relevance of these observations is uncertain. Investigations in Asia-Pacific and Nordic populations with non-diarrhoea-predominant IBS and from patients with chronic constipation not secondary to IBS have shown no reproducible laboratory abnormalities associated with tegaserod use.[8,12,13,30]

Twenty-two pregnancies were reported in phase III RCTs of tegaserod in IBS with constipation;[28] another nine occurred during the long-term, open-label trial.[28,31] The miscarriage rate per pregnancy was 17% (4/23) on tegaserod compared with 12% (1/8) on placebo. This difference is not significant given the small number of pregnancies observed. No other adverse outcomes from pregnancy were reported.

5. Conclusions

The selective 5-HT_4 receptor agonist tegaserod was recently approved for treatment of IBS with constipation in women based on its clinical effects to reduce global IBS symptoms, to relieve abdominal discomfort and bloating, and to improve stool frequency and stool consistency. Tegaserod exhibits no significant drug interactions. Diarrhoea is the most common gastrointestinal adverse event associated with tegaserod use. Diarrhoea occurs in up to 10% of patients, although fewer than 3% of patients discontinue treatment due to diarrhoea. In rare instances, diarrhoea has produced severe consequences including hypovolaemia. Infrequent cases of ischaemic colitis also have been reported although a causal relationship to tegaserod use is unproven. No significant increase in any type of abdominal or pelvic surgery has been observed with tegaserod-treated patients compared with placebo-treated patients. Headache is the most common extra-gastrointestinal adverse event associated with tegaserod use, and occurs more frequently with tegaserod use compared with placebo use in some studies. No deleterious actions on most laboratory

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parameters have been observed, although individuals exhibit increased eosinophil counts on the rare occasion. In contrast to the effects of the 5-HT_4 receptor agonist cisapride, tegaserod produces no cardiac toxicity and does not prolong electrocardiographic intervals. Thus, the drug appears to exhibit minimal toxicity in patients with IBS, and this favourable safety profile has been confirmed in patients with chronic constipation. Post-US marketing surveillance will further define the safety profile of tegaserod.

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References

1. Zimmermann AE. Tegaserod: a 5-HT_4 agonist for women with constipation-predominant irritable bowel syndrome. Formulary 2002; 37: 449-61
2. Degen L, Matzinger D, Merz M, et al. Tegaserod, a 5-HT_4 receptor partial agonist, accelerates gastric emptying and gastrointestinal transit in healthy male subjects. Aliment Pharmacol Ther 2001; 15: 1745-51
3. Prather CM, Camilleri M, Zinsmeister AR, et al. Tegaserod accelerates orocecal transit in patients with constipation-predominant irritable bowel syndrome. Gastroenterology 2000; 118: 463-8
4. Coffin B, Farmachidi JP, Ruegg P, et al. Tegaserod, a 5-HT_4 receptor partial agonist, decreases sensitivity to rectal distension in healthy subjects. Aliment Pharmacol Ther 2003; 17: 577-86
5. Schoenfeld P, Chey WD, Drossman D, et al. Effectiveness and safety of tegaserod in treatment of irritable bowel syndrome: a meta-analysis of randomized controlled trials [abstract]. Gastroenterology 2002; 122: A1486
6. Muller-Lissner SA, Fumagalli I, Bardhan KD, et al. Tegaserod, a 5-HT_4 partial agonist, relieves symptoms in irritable bowel syndrome patients with abdominal pain, bloating and constipation. Aliment Pharmacol Ther 2001; 15: 1655-66
7. Novick J, Miner P, Krause R, et al. A randomized, double-blind, placebo-controlled trial of tegaserod in female patients suffering from irritable bowel syndrome with constipation. Aliment Pharmacol Ther 2002; 16: 1877-88
8. Kellow J, Lee OY, Chang FY, et al. An Asia-Pacific, double-blind, placebo-controlled, randomised study to evaluate the efficacy, safety and tolerability of tegaserod in patients with irritable bowel syndrome. Gut 2003; 52: 671-6
9. Cohen Munoz V. Relapse of symptoms following withdrawal of tegaserod treatment in irritable bowel syndrome with constipation (IBS-C) [abstract]. Gastroenterology 2003; 124: T1804
10. Lin S, Zhou L, Xinguang L, et al. Tegaserod provides rapid, effective relief of abdominal pain/discomfort, bloating and constipation in Chinese patients with irritable bowel syndrome with constipation [abstract]. Gastroenterology 2003; 124: S1017
11. Nyhlin H, Bang C, Elsborg L, et al. Tegaserod is an effective and safe therapy for irritable bowel syndrome in a Nordic population [abstract]. Gastroenterology 2003; 124: M1645
12. Wald A, Johanson J, Tougas G, et al. Safety and tolerability of tegaserod in patients treated for chronic constipation (CC): a 12-week, double-blind, placebo-controlled multicenter study performed in the Americas [abstract]. Gastroenterology 2003; 124: T1818
13. Hugot S, Fordham F. Study E2301: a randomized, double-blind, placebo-controlled multicenter study to assess the efficacy, safety and tolerability of tegaserod 2mg bid and 6mg bid given orally vs placebo in patients with chronic constipation. Novartis Pharmaceuticals Corp., 2002. (Data on file)
14. Appel-Dingemanse S. Clinical pharmacokinetics of tegaserod, a serotonin 5-HT_4 partial agonist with promotile activity. Clin Pharmacokinet 2002; 41 (15): 1021-42
15. Vickers AE, Zollinger M, Dannecker R, et al. In vitro metabolism of tegaserod in human liver and intestine: assessment of drug interactions. Drug Metab Dispos 2001; 29: 1269-76
16. Camilleri M. Review article: tegaserod. Aliment Pharmacol Ther 2001; 15: 277-89
17. Appel S, Kumle A, Hubert M, et al. First pharmacokinetic-pharmacodynamic study in humans with a selective 5-hydroxy-tryptamine$_4$ receptor agonist. J Clin Pharmacol 1997; 37: 229-37
18. Appel-Dingemanse S, Hirschberg Y, Osborne S, et al. Multiple-dose pharmacokinetics confirm no accumulation and dose proportionality of the novel promotile drug tegaserod (HTF 919). Eur J Clin Pharmacol 2001; 56: 889-91
19. Appel-Dingemanse S, Lemarechal MO, Kumle A, et al. Integrated modeling of the clinical pharmacokinetics of SDZ HTF 919, a novel selective 5-HT_4 receptor agonist, following oral and intravenous administration. Br J Clin Pharmacol 1999; 47: 483-91

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20. Zhou H, Khalilieh S, Lau H, et al. Effect of meal timing not critical for the pharmacokinetics of tegaserod (HTF 919). J Clin Pharmacol 1999; 39: 911-9
21. Appel-Dingemanse S, Horowitz A, Campestrini J, et al. The pharmacokinetics of the novel promotile drug, tegaserod, are similar in healthy subjects: male and female, elderly and young. Aliment Pharmacol Ther 2001; 15: 937-44
22. Sarkar MA, Hunt C, Guzelian PS, et al. Characterization of human liver cyctochromes P-450 involved in theophylline metabolism. Drug Metab Dispos 1992; 20: 31-7
23. Zhou H, Khalilieh S, Svendsen K, et al. Tegaserod coadministration does not alter the pharmacokinetics of theophylline in healthy subjects. J Clin Pharmacol 2001; 41: 987-93
24. Grieff JM, Rowbotham D. Pharmacokinetic drug interactions with gastrointestinal motility modifying agents. Clin Pharmacokinet 1994; 27: 447-61
25. Manninen V, Apajalahti A, Melin J, et al. Altered absorption of digoxin in patients given propantheline and metoclopramide. Lancet 1973; I: 398-400
26. Kirch W, Janisch HD, Santos SR, et al. Effect of cisapride and metoclopramide on digoxin bioavailability. Eur J Drug Metab Pharmacokinet 1986; 11: 249-50
27. Zhou H, Horowitz A, Ledford PC, et al. The effects of tegaserod (HTF 919) on the pharmacokinetics and pharmacodynamics of digoxin in healthy subjects. J Clin Pharmacol 2001; 41: 1131-9
28. Ruegg P, Dunger-Baldauf C. Clinical development: tegaserod. Integrated summary of safety: update. Novartis Pharmaceuticals Corp., 2000. (Data on file)
29. Fidelholtz J, Smith W, Rawls J, et al. Safety and tolerability of tegaserod in patients with irritable bowel syndrome and diarrhea symptoms. Am J Gastroenterol 2002; 97: 1176-81
30. Ruegg P, Heggland J, Dunger-Baldauf C. Clinical development: tegaserod. Integrated summary of safety: update. Novartis Pharmaceuticals Corp., 2002. (Data on file)
31. Tougas G, Snape WJ, Otten MH, et al. Long-term safety of tegaserod in patients with constipation-predominant irritable bowel syndrome. Aliment Pharmacol Ther 2002; 16: 1701-8
32. Earnest D, Ruegg ED, Dunger-Baldauf C, et al. Diarrhea in patients treated with tegaserod for irritable bowel syndrome with constipation (IBS-C) is infrequent and usually self-limited [abstract]. Am J Gastroenterol 2002; 97: A843
33. Dear Healthcare Professional [letter; online]. Available from URL: http://www.fda.gov/medwatch/SAFETY/2004/safety04. html#zelnorm [Accessed 2004 Apr 29]
34. Fisher R, Thistle J, Lembo A, et al. Tegaserod does not alter meal-induced gallbladder emptying or concomitant bile duct diameter [abstract]. Novartis Pharmaceuticals Corporation, 2002. (Data on file)
35. Bran S, Murray WA, Hirsch IB, et al. Long QT syndrome during high-dose cisapride. Arch Intern Med 1995; 155: 765-8
36. Mohammad S, Zhou Z, Gong Q, et al. Blockade of the HERG human cardiac K^+ channel by the gastrointestinal prokinetic agent cisapride. Am J Physiol 1997; 273: H2534-8
37. Drici MD, Ebert SN, Wang WX, et al. Comparison of tegaserod (HTF 919) and its main human metabolite with cisapride and erythromycin on cardiac repolarization in the isolated rabbit heart. J Cardiovasc Pharmacol 1999; 34: 82-8
38. Olsson S, Edwards IR. Tachycardia during cisapride treatment. BMJ 1992; 305: 748-9
39. Morganroth J, Ruegg PC, Dunger-Baldauf C, et al. Tegaserod, a 5-hydroxytryptamine type 4 receptor partial agonist, is devoid of electrocardiographic effects. Am J Gastroenterol 2002; 97: 2321-7

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