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Tegaserod

Lesley J. Scott and *Caroline M. Perry*

Adis International Limited, Auckland, New Zealand

Contents

Abstract

▲ Tegaserod is a serotonin (5-hydroxytryptamine; 5-HT) receptor partial agonist which has been investigated for the treatment of irritable bowel syndrome (IBS). Specifically, it binds with high affinity to human 5-HT_4 receptors, thereby stimulating the release of neurotransmitters and the peristaltic reflex *in vitro*.

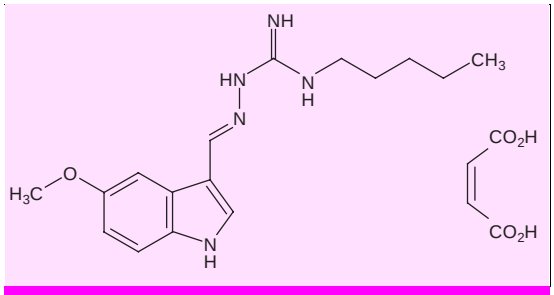
▲ Small bowel transit (increased colonic filling over 6 hours) was accelerated in patients with constipation-predominant irritable bowel syndrome (IBS) receiving oral tegaserod 2mg twice daily for 1 week compared with those receiving placebo. In addition, there was a mean 20% increase of proximal colonic emptying in these patients.

▲ Oral tegaserod 2 ($p < 0.05$) or 6mg twice daily improved symptoms of abdominal discomfort, bloating and constipation (assessed using a Subjects' Global Assessment Scale) compared with placebo in patients with constipation-predominant IBS in a double-blind, dose-ranging study.

▲ The most frequent adverse events in patients with constipation-predominant IBS receiving oral tegaserod were transient diarrhoea and flatulence.

▲ No clinically relevant changes in blood pressure, pulse rate, QRS or QT_c interval were reported with tegaserod doses of 25 to 100mg.

Features and properties of tegaserod (SDZ HTF 919, HTF 919)	
Indications	
Irritable bowel syndrome	
Mechanism of action	
Prokinetic	5-HT_4 receptor partial agonist
Dosage and administration	
Usual dosage in clinical trials	1-12mg twice daily
Route of administration	Oral
Frequency of administration	Twice daily
Pharmacokinetic profile (2-12mg twice daily)	
Peak plasma concentration at steady state	0.7-5.6 μg/L
Time to peak plasma concentration	1.0-1.3h
Area under the plasma concentration-time curve at steady state	2.4-20.4 μg/L • h
Bioavailability	11%
Apparent oral clearance	77 L/h
Terminal elimination half-life	11h
Adverse events	
Most frequent	Diarrhoea, flatulence



Tegaserod

Irritable bowel syndrome (IBS) is a common disorder in Western countries.[1] Symptoms, which occur in the absence of any detectable biochemical or structural changes, involve a complex of gastrointestinal (GI) changes including disturbed defecation, bloating and abdominal pain.[2-4] Although the pathophysiology of IBS is not fully understood, it is suggested that dysregulation of intestinal motor, sensory and CNS functions plays a key role; patients with IBS frequently have enhanced visceral sensitivity and hyperalgesia.[2,4,5]

Several neurotransmitters, including substance P, calcitonin gene-related peptide (CGRP) and serotonin (5-hydroxytryptamine; 5-HT), are reported to be involved in the regulation of motility and pain in the GI tract.[4,6] The presence of 5-HT receptors, including subtypes 5-HT_1, 5-HT_2, 5-HT_3 and 5-HT_4, throughout the GI tract and the high concentration of serotonin in gut enterochromaffin cells suggests that serotonin plays an important role in several physiological functions.[4,6] Recent investigations[4,7] have shown that 5-HT_4 receptors, which are also present in cardiovascular tissue, mediate the release of other neurotransmitters (e.g. CGRP and substance P) in the GI tract. In turn, these neurotransmitters are involved in the overall maintenance of gut motility and modulation of visceral nociceptive neural pathways.[6] Thus, agonists acting at 5-HT_4 receptors have the potential to alter GI motility, modulate visceral sensitivity and potentially improve symptoms of IBS. Tegaserod, the focus of this profile, is an indole carboxaldehyde derivative [3-(5-methoxy–1H–indole–3–ylmethylene)–N–pentylcarbazimidamide hydrogen maleate] and acts as a partial agonist at the 5-HT_4 receptor.[8,9]

1. Pharmacodynamic Profile

In Vitro and *In Vivo* Studies

- Tegaserod bound with high affinity to 5-HT_4 receptors in sections of human brain tissue in a radioligand binding study.[10] The mean binding affinity of tegaserod (pKd values) for human 5-HT_4 receptors was 7.74 compared with 7.23 for cisapride, 6.0 for metoclopramide and 7.16 for serotonin. The distribution of tegaserod binding in human brain sections was similar to that observed with [^{125}I]SB 207,710 (a 5-HT_4 receptor ligand). Specificity of tegaserod binding was confirmed autoradiographically by displacement of [^{125}I]SB 207,710; this displacement was similar to that observed with serotonin.

- Tegaserod 0.1 to 10 μmol/L and its glucuronide metabolite 0.1 to 100 μmol/L had no effect on the QT interval in isolated rabbit hearts; tegaserod 50 μmol/L (500- to 1000-fold higher than therapeutic concentrations) increased the QT interval by 12% compared with the baseline value ($p < 0.01$ *vs* baseline; $n = 4$).[11] In contrast, cisapride increased the QT interval by 13% at 0.1 μmol/L and >70% at 50 μmol/L. Alterations in the QT interval may cause slower repolarisation and lead to cardiac arrhythmias.

- Tegaserod increased the release of neurotransmitters *in vitro* from human jejunal segments and stimulated the peristaltic reflex.[7] Tegaserod 1 μmol/L applied to the intestinal mucosa of isolated jejunal segments increased basal release of CGRP by 348%, of substance P by 216% and of vasoactive intestinal peptide (VIP) by 191%.

- In animals, tegaserod reduced the firing rate of spinal rectal afferents following rectal distension in a dose-dependent manner.[12] The effective dose range with intravenous tegaserod was 0.3 to 1.2 mg/kg; half-maximal reduction in the firing rate was observed at a dose of 0.7 mg/kg. The reduction in firing rate was mediated via 5-HT_4 receptor stimulation; furthermore, it was not secondary to mod-

ifications of the mechanical properties (compliance) of the rectal wall.[12]

Healthy Volunteers and Patients with Constipation-Predominant Irritable Bowel Syndrome

- In a small double-blind trial, tegaserod 2mg twice daily accelerated small bowel transit (increased colonic filling at 6 hours; p = 0.015) and colonic transit time compared with placebo in patients with constipation-predominant IBS.[13] Although the mean colonic transit time (measured using radiopaque markers) was similar in both treatment groups, there was a mean 20% increase in proximal colonic emptying (measured scintigraphically) with tegaserod compared with baseline values (p = 0.05; fig. 1). In this study, 24 patients (mean baseline colonic transit time of >40 hours) were randomised after a 1-week washout period to receive tegaserod or placebo for 1 week.

- In an exploratory pharmacodynamic study in which colonic transit was prolonged by dietary means, oral tegaserod 5mg twice daily significantly ($p < 0.05$) shortened total colonic transit time in 11 healthy male volunteers given fibre supplementation.[14] Tegaserod 1 (n = 12), 5 (n = 11), 25 (n = 12) and 100mg (n = 12) twice daily reduced median total colonic transit time by 10, 22, 26 and 8 hours, respectively, compared with 16 hours in those receiving placebo (n = 12). In this randomised double-blind trial, total colonic transit time was assessed at the end of each of three 7-day intervention periods: a self-selected diet; followed by a liquid formula diet with fibre supplementation (FD); and then concurrent tegaserod with FD. It was suggested that the lack of significant effect at lower (1mg) and higher (25 and 100mg) doses of tegaserod may indicate a biphasic dose-response relationship to colonic transit time.[14]

- In 24 healthy volunteers tegaserod 12mg reduced both the early [0.65 *vs* 0.44 (fraction of fasting volume); $p \leq 0.05$ *vs* placebo] and late (0.70 *vs* 0.84; $p \leq 0.05$ *vs* placebo) postprandial decrease in colonic tone.[15]

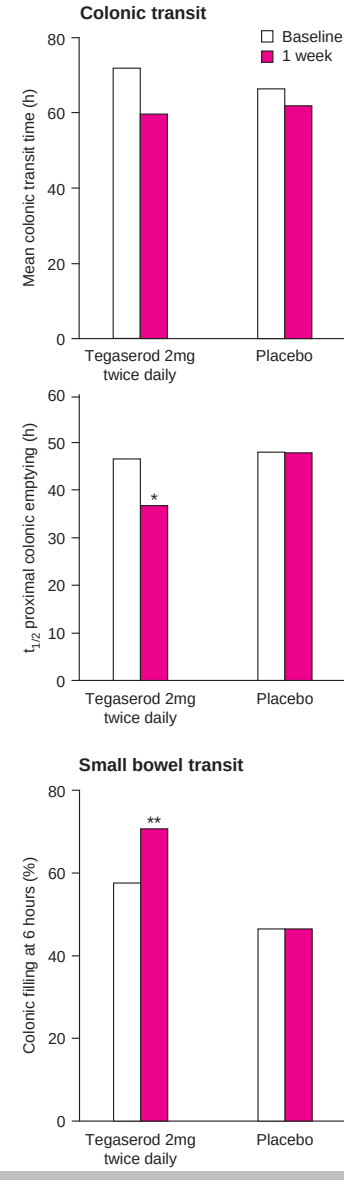


Fig. 1. Effect of oral tegaserod 2mg twice daily for 1 week on small bowel transit and colonic transit time in patients with constipation-predominant irritable bowel syndrome.[13] In this double-blind randomised study, 24 patients received tegaserod or placebo for 1 week following a 1-week washout period. At baseline and after 1 week of treatment, small bowel (colonic filling at 6 hours) and $t_{1/2}$ proximal colonic emptying rate of solids were determined scintigraphically and mean colonic transit time was measured using radiopaque markers. * p = 0.05 *vs* baseline; ** p = 0.015 *vs* placebo adjusted for baseline.

• When compared with baseline, a single oral dose of tegaserod 12mg significantly increased ($p \leq 0.05$) colonic phasic motility in both fasting and fed healthy volunteers (12.3 and 12.8, respectively; n = 18); in contrast, placebo significantly increased ($p \leq 0.05$) colonic phasic motility only in fed volunteers (11.8 and 12.6; n = 6).[15] Colonic phasic motility was measured by mannometry and expressed as a motility index [MI = ln(Σamplitude × number of contractions)].

Patients with Gastro-Oesophageal Reflux Disease

• Exposure to oesophageal acid was reduced with tegaserod 1 ($p = 0.05$ *vs* placebo) and 4 mg/day in patients with gastro-oesophageal reflux disease.[16] The percentage of time during the 3 hour postprandial period when distal oesophageal pH exceeded 4 was 5, 8, 13, 10 and 13% with tegaserod 1, 4, 12 and 24 mg/day and placebo, respectively. This reduction in acid exposure was not due to changes in lower oesophageal sphincter pressure (LESp; measured by manometry); LESp values with tegaserod 1, 4, 12 and 24 mg/day and placebo were 13, 10, 13, 13 and 14 mmHg, respectively.

2. Pharmacokinetic Profile

The pharmacokinetic properties of oral tegaserod have been investigated in healthy volunteers in single-dose[17,18] and multiple-dose[18] studies and in patients with renal insufficiency requiring haemodialysis[19] or with hepatic cirrhosis[20] in single dose, placebo-controlled studies. Volunteers received tegaserod twice daily for 5 days in the multiple-dose study.[18]

Healthy Volunteers

• Maximum steady-state concentrations of tegaserod in plasma ($C_{max,ss}$) with 2, 6 and 12mg twice daily doses were 0.7, 2.7 and 5.6 μg/L, respectively.[18] After single and multiple doses of the drug, C_{max} values were similar (data not presented).

• Areas under the plasma concentration-time curve over a 12-hour dosage period at steady state (AUC_τ) for tegaserod 2, 6 and 12mg twice daily were 2.4, 8.9 and 20.4 μg/L · h.[18]

• Dose-normalised AUC_τ and $C_{max,ss}$ values indicate that 2, 6, and 12mg doses of tegaserod demonstrate dose-proportionality and that there is no accumulation of the drug.[18]

• Mean times to reach maximum plasma concentration of tegaserod over a 12-hour dosage period at steady state ($t_{max,ss}$) for 2, 6 and 12mg twice daily oral doses were 1.1, 1.0 and 1.3 hours, respectively.[18]

• Oral tegaserod 12mg had a mean absolute bioavailability of 11%, a terminal elimination half-life of 11 hours, an apparent oral clearance (clearance/bioavailability) of 77 L/h, and an apparent volume of distribution at steady state of 368L.[17]

Patients with Liver and Renal Dysfunction

• There were no significant changes in the pharmacokinetic parameters (C_{max}, t_{max} and AUC) of tegaserod 12mg in patients with severe renal insufficiency requiring haemodialysis[19] or in patients with hepatic cirrhosis[20] compared with healthy volunteers.

3. Therapeutic Trials

The clinical efficacy of oral tegaserod was assessed in patients with constipation-predominant IBS in double blind, dose-escalating[21] (1 to 24 mg/day; discontinued prematurely for administrative reasons) and a dose-ranging trial.[22-24] In the dose-ranging trial, patients received tegaserod 0.5, 2, 6 or 12 mg twice daily or placebo for 12 weeks. The primary end-points measured were considerable or complete relief from baseline in overall symptoms, abdominal discomfort (pain and bloating) and constipation.[21,22,24] These were assessed using a 5-point ordinal Subject's Global Assessment (SGA) scale. The appropriateness of the SGA as a measure of efficacy was recently tested and validated versus other subjective measures (diary score of symptoms and SF-36 subscales).[24]

• Tegaserod 2 ($p < 0.05$) or 6mg twice daily improved symptoms of abdominal discomfort, consti-

pation and bloating in patients compared with placebo.[22,23] In addition, tegaserod 2mg twice daily reduced the number of days per month that patients had significant pain from 14.6 to 10 days ($p < 0.05$ *vs* placebo). The clinical efficacy of tegaserod after 12 weeks of treatment is shown in figure 2.

- Tegaserod 0.5 and 2mg twice daily reduced the number of days per month with significant pain by 4.4 and 4.6 days, respectively, compared with placebo (reduced by 2.3 days), decreased the number of days per month with significant bloating by 3.3, 4.9 and 2.4 days, and decreased the number of days per month without bowel movement (median % change) by 29.8, 26.5 and 16.1%.[24]

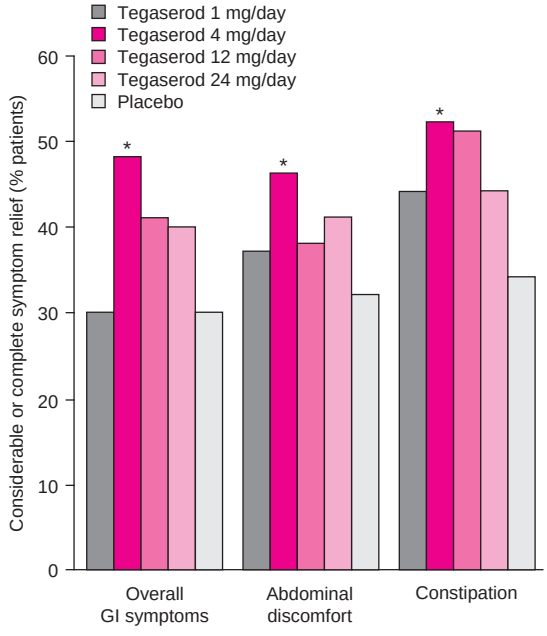


Fig. 2. Effects of oral tegaserod versus placebo on gastrointestinal symptoms after 12 weeks in patients with constipation-predominant irritable bowel syndrome.[22] Patients received oral tegaserod 0.5 (n = 89), 2 (n = 87), 6 (n = 91) or 12mg (n = 90) twice daily or placebo (n = 93) in a double-blind, dose-ranging trial. Efficacy was assessed at monthly intervals using a 5-point ordinal Subject's Global Assessment scale for overall gastrointestinal symptoms, abdominal discomfort and constipation. The definition of considerable or complete symptom relief was not stated. * $p < 0.05$ *vs* placebo.

- In a dose-escalating study, tegaserod (mean dose 15.5 mg/day) significantly reduced discomfort compared with placebo at 20 weeks in 65 evaluable patients (50 *vs* 24%; $p = 0.05$); it also improved the SGA of overall symptoms (52 *vs* 29%; $p < 0.1$) and constipation (57 and 33%; $p < 0.1$).[21] Increasing the dose of tegaserod from 12 to 24 mg/kg did not enhance efficacy (data not provided).

4. Tolerability

- The incidence of transient diarrhoea in patients with constipation-predominant IBS receiving tegaserod 2, 6 and 12mg twice daily was 26.2, 30.7 and 26.5%, respectively, compared with 12.8% for those receiving placebo (no data given for 0.5mg dose).[22,23] The diarrhoea was transient and resolved spontaneously after a few days. Flatulence was also a common, but less frequent, adverse event. The incidence of nausea, abdominal pain and headache was reported to be similar to that with placebo.

- Tegaserod administered at dosages of 25, 50 and 100mg twice daily for 14 days caused no clinically relevant changes in blood pressure, pulse rate, QRS or QT_c interval in 24 healthy volunteers.[25]

5. Tegaserod: Current Status

Tegaserod is a 5-HT_4 receptor partial agonist that stimulates the peristaltic reflex *in vitro* and shortens small bowel and colonic transit time in patients with constipation-predominant IBS. Tegaserod, which is in clinical development, effectively improves GI symptoms (including abdominal discomfort, bloating and constipation) in patients with constipation-predominant IBS.

References

1. American Gastroenterological Association Patient Care Committee. American Gastroenterological Association Medical Position Statement: irritable bowel syndrome. Gastroenterology 1997 Jun; 112: 2118-9
2. Harris MS. Irritable bowel syndrome: a cost-effective approach for primary care physicians. Postgrad Med 1997 Mar; 101 (219-220 & 223-226): 215-6
3. Forbes A. IBS: guide to diagnosis and recommended treatment. Prescriber 1997: 67-70
4. American Gastroenterological Association Patient Care Committee. Irritable bowel syndrome: a technical review for prac-

tice guideline development. Gastroenterology 1997 Jun; 112: 2120-37
5. Dalton CB, Drossman DA. Diagnosis and treatment of irritable bowel syndrome. Drugs Today 1998 Jul; 34: 585-92
6. Farthing MJG. New drugs in the management of the irritable bowel syndrome. Drugs 1998 Jul; 56: 11-21
7. Grider JR, Foxx-Orenstein AE, Jin JG. 5-Hydroxytryptamine$_4$ receptor agonists initiate the peristaltic reflex in human, rat, and guinea pig intestine. Gastroenterology 1998 Aug; 115: 370-80
8. Bucheit K, Gamse R, Giger R, et al. The serotonin 5-HT$_4$ receptor: Design of a new class of agonists and receptor map of the agonist recognition site. J Med Chem 1995; 38: 2326-30
9. Buchheit K, Gamse R, Giger R, et al. The serotonin 5-HT$_4$ receptor. 2. Structure-activity studies of the indole carbazimidamide class of agonists. J Med Chem 1995; 38: 2321-38
10. Hoyer D, Fehlmann D, Langenegger D, et al. High affinity of SDZ HTF-919 and related molecules for calf and human caudate 5-HT$_4$ receptors [abstract no. 104]. Naunyn Schmiedebergs Arch Pharmacol 1998; 357 (4) Suppl.: 29
11. Drici M-D, Ebert S, Wang W-X, et al. Comparative effects on cardiac repolarization of cisapride, erythromycin, tegaserod and its metabolite in isolated rabbit hearts [abstract no. PII-37]. Clin Pharmacol Ther 1999 Feb; 65: 156
12. Schikowski A, Mathis C, Thevsen M, et al. Dose-dependent modulation of rectal afferent sensitivity with a 5-HT$_4$ receptor partial agonist [abstract no. G2805]. Gastroenterology 1999; 116 (4) Part 2: A643
13. Prather CM, Camilleri M, McKinzie S, et al. HTF919, a partial 5HT$_4$ agonist, accelerates small bowel transit in patients with constipation-predominant irritable bowel syndrome [abstract no.G4629]. Gastroenterology 1999; 116 (4) Pt. 2: A1066
14. Appel S, Kumle A, Meier R. Clinical pharmacodynamics of SDZ HTF 919, a new 5-HT$_4$ receptor agonist, in a model of slow colonic transit. Clin Pharmacol Ther 1997 Nov; 62: 546-55
15. von der Ohe MR, Klingenburg S, Goebell H, et al. In vivo modulation of left colonic motor function in healthy humans: Role of the 5HT$_4$ receptor [abstract no. GaPP0069]. Digestion 1998; 59 Suppl. 3: A856
16. Kahrilas PJ, Quigley EMM, Castell DO, et al. The selective 5-HT$_4$ receptor partial agonist HTF 919 reduces acid exposure in patients with gastroesophageal reflux disease (GERD) [abstract no. G0881]. Gastroenterology 1999; 116 (4) Pt. 2: A202
17. Appel-Dingemanse S, Lemarechal M, Kumle A, et al. Integrated modelling of the clinical pharmacokinetics of SDZ HTF919, a novel selective 5-HT$_4$ receptor agonist, following oral and intravenous administration. Br J Clin Pharmacol 1999; 47: 483-91
18. Appel-Dingemanse S, Guerret M, Hirschberg Y, et al. Single- and multiple-dose pharmacokinetics of SDZ HTF 919 in healthy subjects [abstract no. PI-44]. Clin Pharmacol Ther 1999 Feb; 65: 128
19. Zhou H, McLeod J, Alladina L, et al. Pharmacokinetics of SDZ HTF 919 not altered in subjects with severe renal insufficiency requiring hemodialysis [abstract no. PIII-108]. Clin Pharmacol Ther 1999 Feb; 65: 203
20. Appel-Dingemanse S, Hubert M, Alladina L, et al. Pharmacokinetics and safety of SDZ HTF 919, a new promotile drug in healthy subjects and patients with hepatic cirrhosis [abstract no. EXhB5331]. Digestion 1998; 59 Suppl. 3: 736
21. Hamling J, Bang CJ, Tarpila S, et al. Titration regimen indicates partial 5-HT$_4$ agonist HTF 919 improves symptoms of constipation predominant irritable bowel syndrome (C-IBS) [abstract no. ExhB5324]. Digestion 1998; 59 Suppl. 3: 735
22. Langaker KJ, Morris D, Pruitt R, et al. The partial 5-HT$_4$ (HTF919) improves symptoms in constipation-predominant irritable bowel syndrome (C-IBS). [Abstract no. GaPP0064]. Digestion 1998; 59 Suppl. 3
23. Phase II data support value of Novartis' IBS drug. Marketletter 1998 Sep 21; 23
24. Lefkowitz MP, Ruegg P, Shi Y, et al. Relief of overall symptoms and abdominal pain and discomfort as outcome measures in a clinical trial of irritable bowel syndrome with HTF919 [abstract and poster no. G4462]. Gastroenterology 1999; 116 (4) Pt 2: A1027
25. Appel S, Kumle A, Hubert M, et al. First pharmacokinetic-pharmacodynamic study in humans with a selective 5-hydroxytryptamine-4 receptor agonist. J Clin Pharmacol 1997 Mar; 37: 229-37

Correspondence: *Lesley J. Scott,* Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand.
E-mail: demail@adis.co.nz