

by Sylvia Thomley, PharmD

Column Editor: Lee Vermeulen, MS, RPh,

Director, Center for Drug Policy, University of Wisconsin Hospital and Clinics

Tegaserod (Zelnorm[®] — Novartis)

Summary

Indication: Tegaserod is approved for short-term treatment of women with irritable bowel syndrome (IBS) whose primary symptom is constipation. Safety and efficacy have not been established in men.

Dose: The recommended dose is 6 mg twice daily, taken before meals for four to six weeks. An additional four to six week course may be considered in patients with a positive response to therapy.

Monitoring Parameters: The most common adverse events are diarrhea and headache.

Pregnancy Category: B. No evidence of impaired fertility or fetal harm was found in animal studies.

Breast Feeding: Tegaserod and its metabolites are excreted in the milk of lactating rats. It is not known if they are excreted in human milk.

Pediatrics: The safety and efficacy of tegaserod in patients below the age of 18 has not been established.

Geriatrics: No differences in safety or kinetics were observed in geriatric patients. Dosage adjustment is not necessary.

Cost: Tegaserod is available in 2 mg and 6 mg tablets. The average wholesale price (AWP) of both strengths is \$161.44 per pack of 60 tablets, or \$2.69 per dose.

Introduction

Irritable bowel syndrome (IBS) is a poorly understood disease. It has been described as “a biopsychosocial disorder in which altered gastrointestinal (GI) motility, GI hypersensitivity, and psychosocial factors all interact to predispose someone to this syndrome.”¹ IBS affects 10 to 15% of the population in North America, divided equally among patients suffering from IBS with constipation, IBS with diarrhea, and IBS alternating between diarrhea and constipation.² It is the most common disorder diagnosed by gastroenterologists and its economic impact has been estimated at \$25 billion annually, with indirect costs of absenteeism from work accounting for a large portion of that cost.³ The disease is defined by the symptoms of abdominal discomfort associated with altered bowel habits and it is diagnosed in females at a rate twice that of males.² Treatment is indicated whenever IBS symptoms diminish a patient’s quality of life and should be initiated only after

screening studies have been completed in patients who show no alarm signs or symptoms such as hematochezia or weight loss.¹ Patients with IBS with constipation should receive an adequate amount of fiber, building up slowly to 20 to 30 grams each day to prevent bloating.³ Osmotic laxatives such as milk of magnesia, lactulose, or polyethylene glycol are also effective treatments for constipation.³ If abdominal pain is not relieved, antispasmodic agents may be tried.²

Recent drug developments for treating IBS have focused on serotonin (5-hydroxytryptamine, 5-HT) modifying agents. About 95% of the body’s 5-HT is in the gut, of which 90% is in enterochromaffin cells and 10% in enteric neurons.⁴ Serotonin’s actions are complex and can result in either smooth-muscle contraction or relaxation through actions at the 5-HT₃ or 5-HT₄ receptors.⁴ The development of medications to target these receptors is complex and the medications which have reached the market have had mixed results.⁵ Cisapride was effective in promoting GI motility through its effects as both a 5-HT₃ antagonist and a marked 5-HT₄ agonist, but it was withdrawn from the market in the United States in 1999 following reports of cardiac arrhythmias and associated deaths and it is now available only through a limited access program. The cardiac effects of cisapride are not related to its actions at the 5-HT receptors.⁶

Tegaserod [te-GAS-a-rod] (Zelnorm[®], Aventis) is a recently approved agent that specifically targets the 5-HT₄ receptors and is indicated for the short-term treatment of women with IBS whose primary bowel symptom is constipation.⁷ It has been extensively studied and its release on the market was initially delayed following a United States Food and Drug Administration (FDA) request for additional efficacy and safety information. The drug was approved following the development of four phase IV post marketing surveillance studies and a commitment by the manufacturer to postpone direct-to-consumer advertising.

Pharmacology/Pharmacokinetics

Tegaserod is a partial agonist that binds with high affinity to human 5-HT₄ receptors.⁸ This results in stimulation of the

Sylvia Thomley, PharmD is a Pharmacy Administrative Resident at the University of Wisconsin Hospital and Clinics

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peristaltic reflex and intestinal secretion, as well as inhibition of visceral sensitivity. Tegaserod has moderate affinity for 5-HT₁ receptors and no appreciable affinity for 5-HT₃ receptors. As a partial agonist, it is less likely to induce receptor desensitization than full agonists, resulting in a normalizing effect that provides balanced modulation of the receptors.⁹

The absolute oral bioavailability of tegaserod is low (10%).¹⁰ About 20% is hydrolyzed pre-systemically in the stomach. Additional metabolism occurs through oxidation and glucuronidation in the liver. The primary metabolite is a glucuronide with negligible affinity for 5-HT₄ receptors and no known clinical effects.¹⁰ The presence of food decreases serum concentrations and total absorption by 40 to 65%.¹⁰ Tegaserod is excreted primarily unchanged in the feces (67%) and the remainder in the urine as metabolites. It displays linear pharmacokinetics in the 2 to 12 mg dose range.

Tegaserod is 98% protein bound, primarily to alpha-1-acid glycoprotein.¹⁰ Its estimated terminal half-life is 11 hours. It has been shown to inhibit cytochrome P450 1A2 and 2D6 enzymes in vitro, however no significant drug-drug interactions were shown using the substrates theophylline, dextromethorphan, digoxin, warfarin, or oral contraceptives.¹⁰

Elderly patients have statistically significantly higher exposure (AUC) than younger patients (37% vs 23%, $p < 0.001$).¹¹ However, there have been no differences shown in maximum concentration (C_{max}) or time to maximum concentration (T_{max}) and the change in AUC has not been judged to be clinically relevant. Dosage adjustment is not recommended in elderly patients.⁷

No changes in pharmacokinetic parameters were observed in patients with severe renal impairment.¹⁰ However, a 10-fold increase in the AUC of the primary metabolite was observed in patients with severe renal impairment and therefore the drug is contraindicated in these patients. While patients with mild to moderate hepatic impairment demonstrated an increased AUC and T_{max}, those changes were not statistically significant.¹⁰ No dosage adjustments are recommended in patients with mild hepatic disease, however tegaserod is contraindicated in patients with moderate to severe hepatic disease.⁷

Clinical trials

Irritable bowel syndrome (IBS)

The efficacy of tegaserod for the treatment of irritable bowel syndrome has been reported in five randomized controlled trials. Originally, three trials (B351, B301, and B307) were designed during the phase III clinical development and these will be reviewed together. A fourth trial, study B358, was submitted following a request from the FDA for additional data on safety and efficacy. The latest trial published was an open-label safety trial.

The three initial phase III trials recruited similar patients, men and women over age 18 (over age 12 for B351) who met the ROME I criteria for IBS, defined as abdominal discomfort and/or pain for at least 3 months, relieved with a bowel movement or associated with a change in frequency or consistency of stool.¹² The patients also had at least two of the three following constipation symptoms, each occurring at least 25% of the time over a three month period: less than three bowel movements per week, hard or lumpy stool, or straining with a bowel movement. All three trials were placebo-controlled, double-blind, parallel group, and multi-center studies. Patients were excluded if they had significant diarrhea, other diseases or conditions that affect bowel transit, used medications other than antidepressants that interfere with GI motility, or were young women not using approved contraception.

Originally, two primary outcome measures were developed for each of the trials, both based on the patient's subjective assessment of relief. The Subject's Global Assessment (SGA) of relief measured overall well-being, abdominal pain/discomfort, and altered bowel habit on a five-point ordinal scale (completely relieved, considerably relieved, somewhat relieved, unchanged, or worse). The SGA measure of abdominal discomfort/pain, using a 100 mm visual analogue scale (VAS) with verbal descriptors was also used.

These outcomes were from weekly descriptions in patient diaries. Patients were also asked to complete a weekly SGA of bowel habits and daily self-assessments of their intensity of abdominal pain/discomfort, intensity of bloating, frequency of bowel movements, and average stool consistency. Patients

Table 1. Proportion of Patients Responding, based on SGA of relief*

Study	Placebo	Tegaserod 4 mg/d	p-value(vs. placebo)	Tegaserod 12 mg/d	p-value(vs. placebo)
B301	30.2%	38.8%	0.018 [†]	38.4%	0.033 [†]
B307	37.0%	38.3%	0.837	42.2% [‡]	0.142
B351	33.3%	38.9%	0.157	45.7%	0.004 [†]

* Adjusted for missing SGAs, treatment duration, and laxative use. Response defined as $\geq 50\%$ complete/considerable relief or 100% at least somewhat relief at endpoint.

[†] Statistically significant ($p < 0.05$), adjusting for two tegaserod doses.

[‡] Results from patients in the dose-titration group (4-12 mg/day) were included in the 12 mg/day.

Table 2. Summary of differences in efficacy variables in phase III studies at endpoint (adapted from reference 12)

Study	B351		B301		B307	
Doses	4 mg/day	12 mg/day	4 mg/day	12 mg/day	4 mg/day	12 mg/day
SGA efficacy variables (measured weekly)						
SGA of relief	+	p<0.01	p<0.05	P<0.05	+	+
≥ 50% complete or considerable relief (original SGA of relief)	p<0.05	+	p<0.05	+	-	-
100% at least somewhat relief	+	p<0.01	p<0.05	P<0.05	+	+
SGA of abdominal discomfort/pain	+	+	+	P<0.05	-	-
SGA of bowel habits	+	+	+	+	+	-
Daily diary variables						
Mean % change from baseline in days significant abdominal pain	+	p<0.05	+	+	+	+
Mean % change from baseline in days significant abdominal bloating	+	p<0.01	+	+	-	-
Mean % change from baseline in number of bowel movements	p<0.01	p<0.001	p<0.001	P<0.01	p<0.05	p<0.001
Mean % change from baseline in number of days without BMs	+	p<0.01	P<0.05	P<0.05	+	p<0.05
Mean % of days with hard or very hard stools	+	p<0.01	+	+	+	+

Key:

(+) Endpoints demonstrated a positive trend in favor of tegaserod (vs. placebo), but that trend was NOT statistically significant

(-) Endpoints demonstrated a positive trend in favor of placebo (vs. tegaserod), but that trend was NOT statistically significant

Indicated p-values represent the statistical findings for that endpoint, in favor of tegaserod (vs placebo)

were included if they had at least mild abdominal discomfort/pain (average VAS \geq 35) following a 4-week baseline assessment period. During the trial, patients were allowed to use laxatives only after meeting rescue requirements (no bowel movement for 4 consecutive days and bothersome abdominal discomfort/pain or bloating) and to continue taking antidepressants if they were taken in constant doses for at least one month prior to study entry and throughout the study.

In Study B351, the first phase III trial to be completed, 799 patients were randomly assigned to receive either tegaserod 4 mg or 12 mg daily in divided doses or placebo for 12 weeks following a 4-week baseline assessment period.¹³ Responders were defined as patients who had complete or considerable relief at least 50 percent of the time on their SGA of relief assessments,

and a reduction of at least 40% and an absolute reduction of at least 20 mm their average VAS for the SGA of abdominal discomfort/pain at endpoint compared with baseline. Responders also had to have five or fewer days of laxative use. The study results showed greater efficacy in patients receiving tegaserod, with responder rates for the SGA of relief of 29.4% and 26.2% for 4 mg and 12 mg doses respectively, vs 22.1% for placebo, and for the SGA of abdominal discomfort/pain of 23.4% and 25.1% for 4 mg and 12 mg doses respectively, vs 18.7% for placebo. These differences were not statistically significant.

The response rates for all treatment groups, including placebo, were low compared to previous response rates in phase II tegaserod studies and other IBS trials in the literature.

Table 3. Statistical significance by treatment group, pooled analysis

		<i>p-values</i>
Endpoint Analysis	4 mg / day vs placebo	0.0141
	12 mg / day vs placebo	0.0028
Longitudinal Analysis	4 mg / day vs placebo	0.0085
	12 mg / day vs placebo	<0.001

The investigators, with approval of the FDA, determined that the efficacy definition for SGA of relief lacked the sensitivity to detect a treatment difference. The responder definition was then changed to capture patients who also had a persistent positive response (100% of their SGA of relief assessments showed at least “some relief”).

Responders for trials B301 and B307 were then re-defined, prior to their database lock and unblinding, as patients who stated they had complete or considerable relief in at least fifty percent of their SGA of relief reports, or complete, considerable, or some relief 100% of the time.¹² The SGA of abdominal discomfort/pain was moved to a secondary endpoint in these two studies.

In trial B301, 881 patients were randomized to receive either 4 mg or 12 mg daily of tegaserod, in divided doses, or placebo for 12 weeks following the 4-week baseline assessment period. In trial B307, 841 patients received tegaserod 4 mg daily in divided doses or placebo for 4 weeks following the baseline assessments. At this time, patients underwent a dose-titration if they had an SGA of relief response of complete or considerable relief less than 50% of the time. For patients randomized to receive placebo or to receive 4 mg daily throughout the study, the titration was done through the use of placebo. In patients randomized to the 4 to 12 mg dose-titration group, the tegaserod dose was increased to 12 mg daily in divided doses. The results for the updated SGA of relief primary endpoint analysis for all three studies are summarized in table 1.

All three studies also showed significant improvement for a number of secondary endpoints (Table 2). The average percent change from baseline in number of bowel movements was significantly different from placebo for each of the doses in each of the studies (range $p < 0.001$ to $p < 0.05$). In study B351, all secondary variables showed a positive trend for tegaserod treated patients, with significantly positive differences in percent change from baseline for all of the daily variables

related to abdominal pain, bloating, bowel movements, and bowel consistency (range $p < 0.001$ to $p < 0.05$). In study B301, each endpoint also showed a positive trend, however the only significant endpoints were SGA of abdominal discomfort/pain ($p < 0.05$) and the percent changes in bowel movements ($p < 0.01$) and in number of days without bowel movements ($p < 0.05$). In study B307, the only significantly positive changes were in the percent change from baseline of number of bowel movements (BMs) ($p < 0.001$) and days without BMs ($p < 0.05$), and a positive trend was shown for days with significant abdominal pain or hard or very hard stools. The SGA of bowel habits had a positive trend in the 4 mg daily group but a negative trend in the 12 mg daily group. Negative trends were also seen in both treatment groups for the SGA of abdominal discomfort/pain and days with significant abdominal bloating.

The investigators pooled the results of the three phase III studies by dose group and analyzed them based on their respective primary efficacy variables (using the original responder definition for trial B351).¹² Patients in the 4 to 12 mg dose-titration group of trial B307 were pooled with the 12mg/day groups of the other studies. The pooled data were analyzed at endpoint and longitudinally. The longitudinal analysis applied responder criteria to month 1, month 2, and month 3. Intent-to-treat methods were used. Each of the efficacy variables showed significant differences (Table 3).

A pooled subgroup analysis was also performed to analyze the treatment effects stratifying by gender, race, baseline severity of disease, baseline stool frequency and consistency, dietary fiber intake, and use of antidepressants and acid-suppressant medications. Overall, about 85% of the population was female, at least 88% were Caucasian, and more than 90% were under the age of 65. Tegaserod was shown to be more effective in females and those patients with documented constipation during the baseline run-in period, with about a 15% advantage for each. Data were insufficient to make firm conclusions regarding the efficacy in men, the elderly, or minority patients. Baseline differences, such as the degree of constipation symptoms, may account for some of the decreased effect seen in males. There were no differences in efficacy observed based on severity of abdominal discomfort/pain or consumption of fiber, antidepressants, or acid suppressants. Patients with normal or hard stools did better than those with looser stools at baseline.

Study B358 was a randomized, double-blind, placebo-

Table 4. Response rates and number needed to treat to receive benefit

	Tegaserod 12 mg/day	Placebo	<i>p-value</i>	NNT (95% CIs)
Month 1	40.5%	26.2%	$p < 0.001$	7.0 (5.3-10.4)
Month 2	47.2%	39.6%	$p = 0.006$	13.3 (7.8-54.7)
Month 3	53.0%	47.1%	$p = 0.026$	17.1 (8.8-387.2)

controlled multi-center trial of tegaserod use in 1,519 female patients.¹⁴ The women were randomized to receive either tegaserod 12 mg in divided doses or placebo for twelve weeks following a 4-week baseline assessment period, followed by a 4-week open withdrawal period. The study inclusion criteria were similar to the phase III trials, with the addition that patients had to fail at least 2 months of treatment with high-fiber, exercise, or bulking forming agent therapies. Concomitant use of any medication affecting GI motility and/or perception was not allowed, except patients who were on stable treatment with fiber or bulking treatments consistently for three months. Efficacy assessments were done weekly using a touch-tone telephone system to record patient's SGA of relief. Responders were defined the same as in studies B301 and B307. The results show a significantly greater response rate for the SGA of relief than placebo with (48.3% vs. 41.7%, $p < 0.009$) and without (43.5% vs. 38.8%, $p < 0.033$) adjustments for laxative use. A high placebo response was seen in the study, however a statistically significantly greater number of patients on tegaserod vs. placebo were at least "somewhat relieved" each week of the study, except week 8. The response rates by months are shown in table 4. The investigators also estimated the benefit of tegaserod by calculating the monthly number needed to treat (NNT) to successfully treat one patient (using the "somewhat relieved" criteria).

The following secondary efficacy variables showed statistically significant positive differences in patients on tegaserod vs. placebo: SGA of abdominal pain/discomfort, SGA of

bowel habit, satisfaction with bowel habit, bloating scores, number of bowel movements per 28 days, and number of days with straining (at least $p < 0.05$ for all). During the 4-week withdrawal period, the responder rates in both treatment and placebo groups declined. The loss of effect was more marked in the treatment group, however no statistically significant difference was observed for any of the efficacy variables. Tegaserod was well tolerated, with only headache, nausea, and diarrhea more common in the tegaserod group vs. placebo.

In a multicenter, open-label safety trial, 579 patients received a flexible dose titration of tegaserod 4 mg divided twice daily for four weeks, followed by 4 or 12 mg divided twice daily for an additional 11 months.¹⁵ Adverse events were defined as any adverse change from baseline that occurred during the treatment, whether considered related to tegaserod or not. The most common adverse events were: mild and transient diarrhea (10.1%), headache (8.3%), abdominal pain (7.4%), and flatulence (5.5%). Eighty-one patients had severe adverse effects, the most common being abdominal pain, headache, diarrhea, constipation, and flatulence. Of these, forty were considered serious adverse events, occurring in 25 patients and resulting in six patients discontinuing the drug. Only one serious event, acute abdominal pain, was classified as possibly related to tegaserod although this patient completed the 12 months of treatment. An additional fifty-six patients discontinued therapy as a result of adverse events classified as mild or moderate.

Table 5. Adverse Events Occuring in $\geq 1\%$ of IBS Patients

System/Adverse Experience	Tegaserod 12 mg / day (n=1,327)	Placebo (n=1,305)
Gastrointestinal System Disorders		
Abdominal Pain	12%	11%
Diarrhea	9%	4%
Nausea	8%	7%
Flatulence	6%	5%
Central and Peripheral Nervous System		
Headache	15%	12%
Dizziness	4%	3%
Migraine	2%	1%
Body as a Whole – General Disorders		
Accidental Trauma	3%	2%
Leg Pain	1%	<1%
Musculoskeletal System Disorders		
Back Pain	5%	4%
Arthropathy	2%	1%

Gastroesophageal Reflux Disease (GERD)

In a prospective, randomized, double-blind, placebo-controlled multicenter crossover study, twenty-three patients received an initial 24 mg dose of tegaserod and followed by either tegaserod 1 mg, 4 mg, 12 mg, or 24 mg daily in divided doses or placebo for 14 days.¹⁶ Patients then crossed over to other treatment doses, with no washout period, until each treatment dose had been received. On the transition day, manometry and esophageal pH recordings were obtained. Fasting and postprandial lower esophageal sphincter pressure, postprandial esophageal acid exposure, and GERD activity index scores were used to evaluate the effects. There were no significant differences in postprandial lower esophageal sphincter pressures between the treatment groups and placebo. Treatment was associated with a more than 50% decrease in postprandial esophageal acid exposure for patients receiving 1 mg daily and 4 mg daily of tegaserod. However, only the 1 mg dose response demonstrated significant differences from placebo in the percentage of time patients had a postprandial esophageal pH less than 4 (5% vs. 13%, $p=0.05$). All treatment groups showed a reduction in GERD activity index scores from baseline, but there were no significant differences observed among the four treatment groups or compared to placebo.

Adverse effects

Diarrhea is the only adverse event reported more frequently in the groups of patients taking tegaserod than in the placebo groups in the phase III clinical trials (11.7% vs 9%), with no apparent dose relationship.¹² Almost half of these cases were reported within the first week of treatment and the frequency of first occurrence was only slightly greater in the tegaserod treated group than placebo for the following weeks. The majority of patients reported only a single episode. These rates were similar in the other clinical trials. Patients discontinued the medication due to diarrhea at a rate of 2.1%. Table 5 shows the frequency of adverse events reported in greater than 1% of patients.

Other side effects leading to discontinuation were related to GI symptoms of IBS and nonspecific events that occurred at nearly the same frequency in both the tegaserod and placebo treated patients. The Food and Drug Administration noted increased rates of patients requiring treatment for ovarian cysts and requiring pelvic and abdominal surgery.¹⁷ Further review of each of these adverse events demonstrated that some cases were misreported or existed prior to beginning treatment and the concerns have diminished. In their approval letter, the FDA is requiring phase IV prospective epidemiological monitoring of abdominal and pelvic surgeries and a mechanistic gallbladder study to further evaluate these events. Tegaserod is contraindicated in patients with a history of bowel obstruction, symptomatic gallbladder disease, suspected sphincter of Oddi

dysfunction, or abdominal adhesions.⁷ Patients suffering from diarrhea should not receive tegaserod and the medication should be discontinued immediately if new or sudden worsening of abdominal pain develops.⁷

No laboratory or electrocardiographic (ECG) abnormalities have been associated with tegaserod. Cardiac effects were analyzed by reviewing the cardiac profiles of the 2516 patients included in the phase III clinical trials and from a phase II trial of 36 healthy men who received one IV dose of tegaserod.⁶ Investigators compared electrocardiograms obtained at baseline and during treatment and found that the tegaserod ($n=1,715$) and placebo ($n=837$) groups had similar percentages of patients with prolonged QT intervals or other ECG abnormalities. No patient developed supraventricular or ventricular tachycardia. ECG results were not affected in healthy volunteers achieving plasma concentrations of tegaserod as high as 100 times those measured after a single 6 mg dose.

Cost, dose, how supplied

Tegaserod is available in 2 mg and 6 mg tablets in blister packs of 60 tablets each. The labeled dose is 6 mg twice daily, before meals, for four to six weeks.⁷ An additional four to six weeks can be considered for patients who respond to the therapy. The average wholesale price (AWP) is \$161.44 per pack of 60 tablets or \$2.69 per dose.

Conclusion

Tegaserod is the first medication in a new class of medications to treat patients who have IBS with constipation. It is indicated only for use in women. As seen in trials for other agents treating IBS, there is a high placebo effect and while efficacy appears to decrease after first month, this may be a result of more beneficial effects in some groups of patients than in other groups. These patients will be hard to identify prior to initiating therapy, however the medication should not be used in patients currently experiencing diarrhea or who develop severe or worsening abdominal pain. Tegaserod appears to be generally safe and well tolerated. Specific safety concerns are being monitored in phase IV trials and the use of tegaserod is contraindicated in patients with gallbladder disease or specific other abdominal conditions. The potential exists for off-label use in patients with functional dyspepsia or gastroparesis. Studies are ongoing for these disease states and currently no data has been published, although results for functional dyspepsia are expected soon. The off-label use is expected to be quite low and only in patients who have failed other prokinetic agents. ■

References available at <http://pswi.org/communications/PDFs/index.htm>