

Effectiveness of Tegaserod Therapy on GI-related Resource Utilization in a Managed Care Population

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Abstract

This study sought to determine the real-world effectiveness of tegaserod therapy on gastrointestinal (GI)-related resource utilization in a managed care population with a retrospective, longitudinal pre-/post-parallel cohort study of tegaserod users and a matched reference cohort of tegaserod nonusers through medical and pharmacy claims data from a large, geographically diverse, managed care organization. Continuously enrolled benefit-eligible patients newly initiated on tegaserod therapy (index prescription) were identified between August 1, 2002, and June 30, 2003, and were categorized (using *International Statistical Classification of Diseases, 9th Revision, Clinical Modification* codes) as having irritable bowel syndrome (IBS) or another GI-related disorder (eg, gastroesophageal reflux disease). GI-related resource utilization (office visits, hospitalizations, emergency department visits, endoscopic and nonendoscopic procedures, and GI drug prescriptions) was determined for the 6-month period before and after the index prescription date for tegaserod users and nonusers. The study population consisted of 3365 tegaserod users and 3364 matched nonusers. Within-cohort differences before and after therapy were tested using the Wilcoxon signed rank test. The mean age of 3365 tegaserod users and 3364 matched nonusers was 47 years (± 15 years); 92% were women, 47% had an index diagnosis of IBS, and 53% had an index diagnosis of another GI-related disorder. Within-cohort GI resource utilization comparisons before and after therapy initiation showed significant decreases ($P < .01$) in all utilization categories, except GI drug prescriptions, for tegaserod users; these decreases were not consistently observed for matched nonusers. Tegaserod use appeared to be associated with consistent decreases in GI-related resource utilization after 6 months of therapy; similarly consistent reductions were not observed in tegaserod nonusers. These early findings suggest that tegaserod may provide important clinical and economic benefits.

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Although the cause of irritable bowel syndrome (IBS) has eluded researchers for many years, recent advances in clinical research have implicated the role of serotonin (5-hydroxytryptamine [5-HT]) in gastrointestinal (GI) motility disorders. Three main physiologic manifestations of IBS lead to varied GI symptoms, including impaired GI motility, altered intestinal secretion, and increased visceral sensitivity.¹ More than one of these mechanisms may account for a patient's symptoms, but no single factor has been shown to fully explain the pathophysiology of IBS.

Although there is no cure for IBS, treatments typically aimed at the relief of individual symptoms include diet modification, changes in lifestyle, pharmacotherapeutic agents, and psychotherapy alone and in combination.^{2,3} In addition, none of the currently available pharmacologic agents used to treat the individual symptoms of IBS, including antispasmodics, antidepressants, and laxatives, have been successful in managing IBS long term.^{4,5}

One recently approved drug that targets multiple IBS symptoms is tegaserod maleate, a highly selective serotonin type 4 (5-HT₄) receptor agonist that has been approved in the United States for short-term use (≤ 12 weeks) for women with IBS with constipation (IBS-C) and, more recently, for men and women younger than 65 years old with chronic idiopathic constipation.⁶

Interestingly, the treatment gap related to IBS remains a significant issue. A survey of the American Gastroenterology Association membership indicated that IBS accounts for 12% of diagnoses made by primary care physicians and 28% of diagnoses made by gastroenterologists.⁷ In addition, among gas-

troenterologists, IBS was found to be the most common diagnosis.⁸ According to another study, in 1998 IBS was responsible for approximately 3.65 million office visits, 500 000 hospital inpatient stays, 150 000 hospital outpatient visits, and 87 000 emergency department visits.⁹

This increased utilization of healthcare resources is also associated with a significant economic burden. At a national level, the estimated annual direct medical costs associated with IBS in the United States have been estimated to be as high as \$10 billion.¹⁰⁻¹² Included in these costs are primary care and specialist physician visits, outpatient and inpatient care, and diagnostic testing, but not prescription or nonprescription medication costs.^{9,12,13} A study of Medicaid recipients found that expenditures were approximately 48% to 58% higher in patients with IBS than in matched controls.¹¹ A similar pattern of increased healthcare utilization was also observed in a study of all adult members who had undergone flexible sigmoidoscopy and who were surveyed regarding IBS symptoms in a managed care setting. This study found that IBS patients had more outpatient visits, were admitted to the hospital more often, and filled more total outpatient prescriptions than non-IBS patients and that their total costs were 51% higher.¹²

IBS has also been found to have a considerable impact on indirect costs, including decreased work and academic productivity and reduced quality of life (QOL).² Leong and colleagues¹⁰ found that the costs of medically related work absenteeism were significantly higher for employees with IBS than for employees without IBS. Absenteeism (days missed from work) and presenteeism (decreased productivity at work) rates were reduced 20% among bank employees with IBS and 6% among those without IBS.^{14,15} Furthermore, other studies have shown that the decrease in work productivity associated with IBS was greater than that associated with many other long-term episodic diseases, including asthma¹⁶ and migraine,¹⁷ and was comparable with that associated with the long-term persistent conditions of hypertension¹⁸ and congestive heart failure.¹⁹ Patients with IBS have been shown to

experience significant impairment in QOL, including the performance of daily activities,^{20,21} and have reported that IBS symptoms negatively affect their social lives, sexual and physical relationships,²² and school attendance.²³

Although it has been shown that tegaserod is efficacious in providing global relief of the multiple symptoms of IBS and that it significantly improves patient QOL compared with placebo,^{20,24} no effectiveness studies have been conducted regarding the benefits of tegaserod from a managed care perspective. In this study, we investigated whether tegaserod therapy was associated with a decrease in GI-related healthcare resource utilization for a cohort of tegaserod users and a matched cohort of tegaserod nonusers. We compared GI-related healthcare utilization rates for the 6-month periods before and after the actual tegaserod index date or an assigned index date based on user status and cohort matching criteria.

Subjects and Methods

This study was a retrospective, longitudinal, pre-/post-parallel cohort study of tegaserod users and a matched reference cohort of tegaserod nonusers. The study included medical and pharmacy claims data from the data warehouse of a large, geographically diverse, managed care organization (MCO). The data warehouse contains administrative claims for more than 14 million members. Four years of current and historical longitudinal member-level administrative claims data are maintained in the warehouse. In addition to medical and pharmacy claims data, the data warehouse includes such information as member demographic data, provider data, product information, and laboratory test results. The prestudy and poststudy design was chosen to minimize confounding and selection bias. A similar analysis in a matched cohort of nonusers was conducted to investigate possible regression to the mean.

Cohort Identification. Adults 18 years and older were identified as tegaserod users if they had at least 1 pharmacy claim for tegaserod between August 1, 2002, and June 30, 2003. The date of the first

tegaserod prescription became the index prescription date. Benefit eligibility and continuous enrollment criteria of 6 months before and after the index prescription date were applied. Tegaserod users were assigned an index diagnostic category of IBS or GI-related based on *International Statistical Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)* codes on the medical claim for an office, outpatient, or emergency department visit or an inpatient hospitalization closest (± 15 days) to the index prescription date. The patient was assigned the index diagnostic category of IBS if the medical claim had an *ICD-9-CM* code of IBS. If there was no IBS code but there was at least 1 *ICD-9-CM* code for another GI-related disorder (eg, esophageal disorders, gastritis/dyspepsia, gastroenteritis, gastroesophageal reflux disease, abdominal pain), the patient was assigned the diagnostic category of GI-related. The date of the medical claim was defined as the index diagnostic date.

Tegaserod nonusers were adults 18 years of age and older with 1 or more medical claims for office visits, outpatient visits, emergency department visits, and inpatient hospitalizations between July 15, 2002, and July 15, 2003. Benefit eligibility and continuous enrollment criteria during the study period were applied. Medical claims were classified as IBS or as GI-related using the methodology that was developed for the tegaserod cohort. If there was an *ICD-9-CM* code for IBS on the medical claim, it became classified as IBS; if there was no IBS code but there was at least 1 code for a GI-related disorder, the medical claim was classified as GI-related. Dates of IBS/GI-related medical claims were identified as index diagnostic dates. Nonusers without at least 1 IBS or GI-related medical claim were deleted from the analysis.

Tegaserod users were matched with nonusers 1:1 for sex, age, index diagnostic category, and index diagnostic date. The matching procedure identified exact matches on sex and index diagnostic category and then selected the nearest possible nonuser match based on age and index diagnostic date. After matching, tegaserod nonusers were assigned the index prescription date of

their user match. The baseline evaluation period was defined as the 6-month period before the actual index prescription date for the tegaserod user cohort and the "assigned" index prescription date for the nonuser cohort, and the follow-up evaluation period was defined as the 6 months including and after the actual or assigned index prescription date.

Outcome Measures and Statistical Analysis. The primary outcome measure was GI-related resource utilization by category of service (ie, office visits, hospital stays, emergency department visits, endoscopic and nonendoscopic procedures, and GI medications), as determined by the number of claims during the 6-month period before and after the index date. Each person served as his or her own control in assessing change before and after the actual or assigned index prescription date.

The significance of before and after differences for tegaserod users and nonusers was determined by means of the Wilcoxon signed rank test. SAS version 8.2 (SAS Institute, Cary, NC) was used to extract and prepare the data files, and SPSS version 11.0 (SPSS, Chicago, Ill) was used to generate descriptive analytic tables and to perform statistical calculations.

Results

Demographic and Clinical Characteristics. The study initiation period was tied to the US Food and Drug Administration (FDA) approval of tegaserod in July 2002. We identified 5023 tegaserod users with at least 1 prescription for tegaserod between August 1, 2002, and June 30, 2003. After applying benefit eligibility and continuous enrollment criteria, 3365 (67%) tegaserod users remained. Matching resulted in 3364 matched pairs of tegaserod users and nonusers; 1 tegaserod user had no reference group match. Thus, the study population consisted of 3365 tegaserod users and 3364 matched tegaserod nonusers.

Demographic characteristics of the 2 cohorts are summarized in **Table 1**. The mean age of participants in each cohort was 47 years \pm 15 years. Most (54%) patients were between 41 and 64 years of age, and

Table 1. Demographic Characteristics of Tegaserod Users and Nonusers

Characteristic	Tegaserod users		Tegaserod nonusers	
	n	%	n	%
Number in cohort	3365		3364	
Sex				
Women	3108	92.4	3108	92.4
Men	257	7.6	256	7.6
Age, years*				
18-40	1166	34.7	1134	33.7
41-64	1825	54.2	1838	54.6
65 and older	374	11.1	392	11.7
Index diagnostic category				
IBS	1593	47.3	1592	47.3
GI-related	1772	52.7	1772	52.7
Intestinal disorders	723	40.8	381	21.5
GI/digestive disorders	506	28.6	697	39.3
Abdominal pain	480	27.1	490	27.7
Liver/pancreatic disorders	28	1.6	106	6.0
GI/surgical disorders	25	1.4	66	3.7
GI/cancer	10	0.6	32	1.8
Index diagnosis date				
August to December 2002	1086	32.3	1084	32.2
January to June 2003	2279	67.7	2280	67.8

SD indicates standard deviation; IBS, irritable bowel syndrome; GI, gastrointestinal.
 *Mean age 47 ± 15 years.

11% were 65 years or older. Ninety-two percent of participants in each cohort were women. In terms of the index diagnostic category, 47.3% of participants in each cohort were categorized as having a documented IBS claim, and 52.7% were categorized as having a GI-related diagnostic claim. However, within the GI-related diagnostic category, tegaserod users had more medical claims with *ICD-9-CM* codes for intestinal disorders than nonusers (40.8% vs 21.5%), whereas nonusers had more claims for GI and digestive disorders (39.3% vs 28.6%).

Although the tegaserod user and nonuser cohorts were found to be similar in terms of the prevalence of individual common coexisting conditions, including hypertension, back pain, migraine, arthritis, and asthma, tegaserod users were more likely to have 1 or more coexisting comorbid conditions than nonusers (62.4% vs 54.9%).

GI-related Resource Utilization. Tegaserod users had a higher frequency of GI-

related office visits, emergency department visits, inpatient hospital stays, endoscopic procedures, and nonendoscopic procedures than nonusers during the 6 months before the initiation of tegaserod therapy. Comparing usage rates before and after therapy initiation, all GI-related resource categories showed a significant and absolute decrease ($P < .01$) for tegaserod users that was not consistently observed for nonusers (**Table 2**). **Figure 1** presents the relative change in resource utilization rates for tegaserod users and nonusers. Tegaserod users had at least a 20% decrease in rates for all medical GI-related resource utilization categories. Relative changes in rates for nonusers were not as consistent and included a 25% decrease in emergency department use and a 24% increase in endoscopic procedure use.

GI-related Drug Usage. **Table 3** presents absolute changes in GI drug prescriptions for tegaserod users and nonusers, and relative change data are presented in **Figure 2**.

Table 2. Absolute GI-related Resource Utilization Rate Comparisons (6 Months Before and 6 Months After Index Prescription Date)

GI-related resource category	Tegaserod users (n = 3365)					Tegaserod nonusers (n = 3364)				
	Before use mean	After use mean	Mean difference	SD difference	P*	Before use mean	After use mean	Mean difference	SD difference	P*
GI-related office visits	1.90	1.48	-0.42	2.19	<.001	1.01	0.93	-0.08	1.73	<.001
GI-related hospitalizations	0.06	0.04	-0.02	0.34	.012	0.02	0.02	0.00	0.19	.272
GI-related ED visits	0.10	0.06	-0.04	0.51	<.001	0.04	0.03	-0.01	0.29	.005
Endoscopic procedures	0.39	0.31	-0.08	1.08	<.001	0.17	0.21	0.04	0.77	.001
Nonendoscopic procedures	0.52	0.36	-0.16	1.29	<.001	0.22	0.20	-0.02	0.87	.229

All values are per patient.

*Wilcoxon signed rank test.

GI indicates gastrointestinal; SD, standard deviation; ED, emergency department.

Tegaserod users demonstrated significant decreases in the mean number of prescriptions for antispasmodic and promotility drugs compared with nonusers. Mean number of proton pump inhibitor (PPI) prescriptions increased significantly for tegaserod users and nonusers alike. The relative increase in total mean numbers of prescriptions before and after therapy was only 2% (mean absolute change, 0.04) for tegaserod users, which was not statistically significant; however, the relative increase of 15% (mean absolute change, 0.14) for nonusers was statistically significant ($P < .001$).

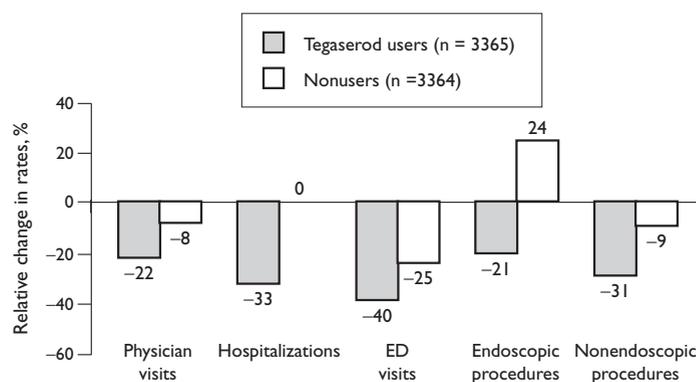
Clinical Appropriateness of Tegaserod Prescribing. A subsidiary analysis related to the clinical appropriateness of tegaserod prescribing in this managed care population found that 82% of tegaserod users had at least 1 diagnostic claim consistent with IBS or the cardinal symptoms of IBS (ie, abdominal pain, bloating, or constipation) during the 12-month study period and that 92% were women.²⁵ Tegaserod was prescribed for 80% of users for 12 or fewer weeks and for 20% of users for more than 12 weeks.

Tegaserod Usage. The 3365 tegaserod users filled 7646 prescriptions between August 1, 2002 and December 31, 2003. The mean number of prescriptions per user was 2.3 ± 1.6 prescriptions, and the median number of prescriptions was 2. Forty-eight per-

cent of users filled only 1 prescription each. There was no difference between the mean number of prescriptions for patients with the index diagnostic category IBS and the mean number of prescriptions for patients with the index diagnostic category GI-related (2.30 vs 2.24). However, the mean number of tegaserod prescriptions for women ($N = 3108$) was significantly greater than it was for men ($N = 257$) (2.28 vs 2.07; $P = .04$).

Discussion

Tegaserod is a drug that was approved in the United States for short-term use in women with IBS-C. In clinical trials, tegaserod has

Figure 1. Relative Changes in GI-related Resource Utilization Rates (6 Months Before and 6 Months After Index Prescription Date)

GI indicates gastrointestinal; ED, emergency department.

Table 3. Absolute Changes in GI Drug Prescriptions (6 Months Before and 6 Months After Index Prescription Date)

GI-related resource category	Tegaserod users (n = 3365)					Tegaserod nonusers (n = 3364)				
	Before use mean	After use mean	Mean difference	SD difference	P [†]	Before use mean	After use mean	Mean difference	SD difference	P [†]
Antidiarrheal	0.01	0.01	0.00	0.19	.462	0.03	0.03	0.00	0.22	.643
Antispasmodic	0.42	0.33	-0.10	1.08	<.001	0.23	0.27	0.03	0.74	.012
IBD drugs*	0.04	0.03	-0.01	0.33	.093	0.02	0.03	0.01	0.28	.058
Laxatives	0.34	0.40	0.06	1.18	.003	0.05	0.06	0.00	0.35	.764
Promotility	0.16	0.13	-0.03	0.61	.002	0.03	0.03	0.00	0.27	.847
PPI	1.11	1.24	0.13	1.48	<.001	0.48	0.57	0.09	0.99	<.001
H ₂ blockers	0.15	0.13	-0.01	0.54	.131	0.08	0.09	0.01	0.48	.104
Total drugs	2.24	2.29	0.04	2.55	.914	0.94	1.08	0.14	1.55	<.001

All values are per patient.

*Excludes tegaserod; [†]Wilcoxon signed rank test.

GI indicates gastrointestinal; SD, standard deviation; IBD, inflammatory bowel disease; PPI, proton pump inhibitor.

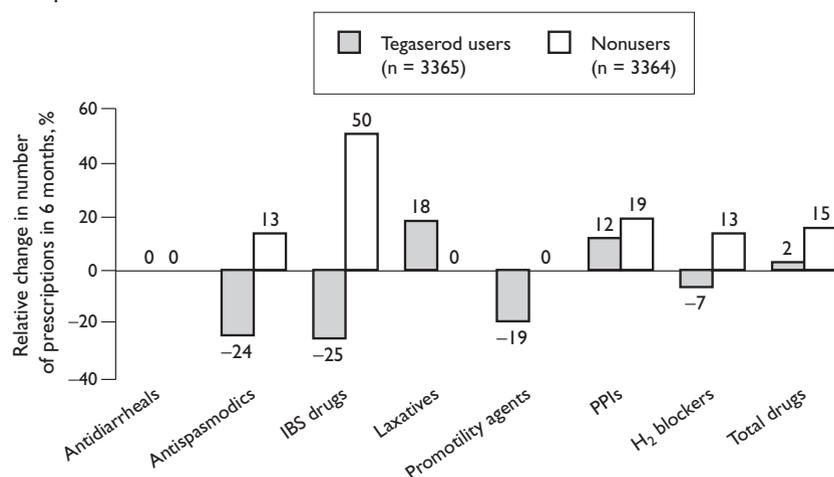
provided global symptom relief and improved the QOL of patients with IBS compared with placebo.^{20,23} The purpose of this study was to evaluate whether the efficacy observed in clinical trials translated into real-world effectiveness in a large geographically diverse managed care population.

This study is the first assessment of GI-related healthcare resource utilization associated with tegaserod in a usual care setting. Principal outcomes demonstrated statistical-

ly significant decreases in all medical GI-related resource categories for tegaserod users that were not consistently observed for tegaserod nonusers. In particular, a meaningful decrease of almost half (0.42) a physician visit in a 6-month period for tegaserod users was observed.

In this study, as in other studies,^{7-9,13} GI-related healthcare resource utilization primarily involved physician office visits; there were relatively few inpatient hospital stays or emergency department visits. Significant

Figure 2. Relative Changes in GI Drug Prescriptions (6 Months Before and 6 Months After Index Prescription Date)



GI indicates gastrointestinal; IBS, irritable bowel syndrome; PPI, proton pump inhibitor.

differences in resource utilization were observed between the tegaserod user and nonuser cohorts during the 6-month period before the actual/assigned date associated with drug initiation. GI-related utilization rates of tegaserod nonusers were approximately 30% to 50% lower than rates of tegaserod users for all GI-related utilization categories, suggesting that tegaserod users and nonusers may have been at different stages of disease in terms of symptom severity and length of time since diagnosis. A decrease in healthcare utilization among patients with more severe symptoms (ie, tegaserod users) could potentially offset the costs of greater utilization observed in previous studies.^{9,10,12,13}

We found that prescription drug use was consistent with the types of drugs used to treat the symptoms of IBS. Drug classes with the greatest use were antispasmodic drugs, laxatives, and PPIs. However, as with the consumption of healthcare resources, there were significant differences in drug use between the tegaserod user and nonuser cohorts during the 6-month period before therapy, with nonusers requiring significantly fewer drugs than tegaserod users. Significantly greater decreases in the mean number of prescriptions for antispasmodic and promotility agents were observed for tegaserod users than for nonusers. Interestingly, PPI prescriptions increased for both tegaserod users and nonusers. This would suggest that, regardless of tegaserod therapy, patients with IBS might also have multiple GI-related healthcare needs.

Given the complexity of treating patients with IBS and the specific action of tegaserod, it is important that physicians prescribe the medication as indicated and directed. A preliminary analysis of tegaserod users indicated that their treatment appeared clinically appropriate. Despite the lack of specificity associated with administrative claims data, 82% of patients prescribed tegaserod had at least 1 diagnostic claim consistent with IBS or the cardinal symptoms of IBS (ie, abdominal pain, bloating, or constipation) during the 12-month study period, and 92% were women.

In conducting this study, our challenge was to identify an appropriate comparison group for our cohort of tegaserod users.

Although our constructed reference group provided a frame of reference, it might not have been a true control group related to the propensity to have potential requirements for tegaserod use. Patients whose physicians prescribed tegaserod might have differed clinically from those whose physicians did not in ways that could have independently affected healthcare utilization and therefore biased the observed results. In addition, the severity and chronicity of the disease and the existence of other comorbidities were not tightly controlled within this study approach.

Another limitation relates to the timing of this study and to the commercial launch of tegaserod. This product was approved by the FDA in July 2002 for use in women with IBS-C and became commercially available in August 2002. Initiating the study so quickly after product launch might have resulted in some physicians prescribing tegaserod to patients with severe symptoms. Moreover, the follow-up period was not long enough to allow for long-term evaluation of healthcare utilization over the natural progression of the disease and its management. For example, office visits might have been prompted by many conditions other than IBS alone. In this study, 48% of tegaserod users filled only 1 prescription each, which minimized the duration of exposure during follow-up. Consequently, the effect on overall utilization may be overstated.

Most important, evaluating this agent at the time of launch would have been associated with high product sampling, affecting use and our ability to study causal relationships related to therapy. In addition, we could not control for the use of other therapeutic remedies, including lifestyle modifications, over-the-counter remedies, and alternative therapies. Although no other studies have measured healthcare resource utilization in tegaserod users, these findings build on earlier research around QOL issues to extend the impact of this medication on patients with IBS and GI-related disorders.

Conclusion

In this study population, tegaserod therapy was associated with consistent decreases

in all GI-related resource utilization categories (office visits, hospital stays, emergency department visits, endoscopic procedures, and nonendoscopic procedures) after 6 months of therapy. These early findings suggest that tegaserod may provide important clinical and economic benefits for the population of patients for whom it is indicated. Additional research is necessary to compare findings in other MCO settings and to substantiate the longer-term implications of these findings, including an economic analysis to understand the impact of cost offsets to payers and patients.

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