CHARACTERISTICS, DIAGNOSTIC AND SYMPTOM PROFILE OF PATIENTS RECEIVING TEGASEROD IN ROUTINE CLINICAL PRACTICE IN CANADA

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ABSTRACT

Objective
This study was designed to assess the diagnostic and symptom profile of patients receiving tegaserod in routine clinical practice, and to identify their demographic characteristics, as well as the association between these characteristics and diagnosis.

Methods
This prospective, observational study collected data from physicians on the symptoms and/or diagnosis, age range and gender for patients to whom they prescribed tegaserod. Details of the physician characteristics included whether they were a family physician or a specialist, and the region of Canada in which their practice was located.

Results
A total of 500 patients were enrolled at 85 sites in Canada. The majority (85%) of the patients were enrolled by family physicians, and the remainder by community-based specialists. The patients were predominantly female (87%) and the highest percentages were in the 35-44 (23%) and 45-54 (25%) age groups. Nearly all patients (96%) were prescribed tegaserod on the basis of both symptoms and diagnosis. The most frequently reported symptoms were abdominal pain and/or discomfort (87%), bloating (80%) and constipation (75%). Most patients (57%) presented with all three of these symptoms. Constipation-predominant Irritable Bowel Syndrome (IBS-C) was the most common diagnosis (55%), followed by IBS alternating between constipation and diarrhea (IBS-A) (23%). Based on this, 67% of patients were given tegaserod strictly according to the label, although it was appropriately prescribed to 87%.

Conclusions
In Canada, tegaserod is prescribed to patients with symptoms of abdominal pain and/or discomfort, bloating and constipation. Most of them will also have a diagnosis of either IBS-C or IBS. It is generally being prescribed appropriately.

Keywords: *Irritable bowel syndrome, symptoms, diagnosis*

Irritable Bowel Syndrome (IBS) is a chronic, episodic disorder generally characterized by abdominal pain/discomfort, bloating, and altered bowel habits.[1,2] IBS is one of the most common disorders encountered in general medical practice, representing a leading cause of gastroenterology and primary care consultations.[3,4] In Canada, the prevalence of IBS, as diagnosed per the Rome II criteria, is 12.1%.[5] In general, prevalence estimates are higher for women than men, with male to female ratios in Europe and North America of between 1:1.4 and 1:2.3.[6-8] Despite its

prevalence, the etiology of the disorder is not well understood and management of the affected patients is challenging. The impact of the multiple symptoms associated with IBS, abdominal pain/discomfort (with altered bowel habits), bloating, and constipation, is not restricted to individual patient discomfort. Patients with symptoms associated with IBS are more likely to have symptoms of psychological distress and have a reduced quality of life, manifested by effects on sleep, employment, sexual functioning, leisure, travel and diet.[9] Most patients can be managed at a primary-care level.[10] Nevertheless, nearly 25% of patients have more severe symptoms, with significant lifestyle impairment, requiring management by a gastroenterologist, and 5% of patients have such severe and incapacitating symptoms that they require referral to a centre with multi-specialty capability.[10]

Optimal IBS therapy would focus on management of all the multiple symptoms of the disorder. However, medications such as laxatives, smooth muscle relaxants and antispasmodics target individual symptoms associated with IBS. The fact that other symptoms remain untreated and may, at times, be exacerbated can result in the use of additional concomitant medications. The 5-HT_4 (5-hydroxytryptamine) receptor partial agonist, tegaserod maleate, activates receptors in the gastrointestinal tract, stimulating both the peristaltic reflex and intestinal secretion, as well as inhibiting visceral sensitivity. Tegaserod has been shown to be effective for global symptom relief in clinical trials designed to treat the multiple symptoms of IBS with constipation.[11,12] When the present study was initiated, tegaserod (Zelnorm®) was indicated for the treatment of women with IBS, whose primary bowel symptom was constipation (IBS-C).[13]

OBJECTIVES

The TUMMIES study (Tegaserod Utilization: Medical Management In an Exploratory Survey), was a multicentre Canadian study, whose primary objective was to assess the diagnostic and symptom profile of patients receiving tegaserod under conditions of routine clinical practice. Secondary objectives included identification of the demographic characteristics (age and gender) of patients receiving tegaserod, and the association between these characteristics and diagnosis.

METHODS

Study Design and Organization

This prospective, observational, single cohort study was conducted under conditions of routine practice by 85 community-based physicians in the following regions of Canada: Western Canada (British Columbia and Manitoba), Ontario, Quebec and the Maritimes (New Brunswick, Prince Edward Island, Nova Scotia and Newfoundland and Labrador). Physicians were recruited on the basis of their frequency of prescribing tegaserod (i.e., higher prescribers were approached first), but they were excluded from participating in this study if they were already participating in another tegaserod trial. A total of 242 physicians were invited to participate, of whom 94 received ethics approval, and 85 enrolled patients. Participating physicians were asked to sequentially enroll all consenting patients who were commencing a new or repeat prescription for tegaserod. Each physician was asked to fill out a one-page CRF for patients to whom they prescribed tegaserod. The study and the consent form were approved by a central ethical review board, and all patients were required to sign the approved consent form. The principles of Good Clinical Practice and the Declaration of Helsinki were adhered to throughout the study.

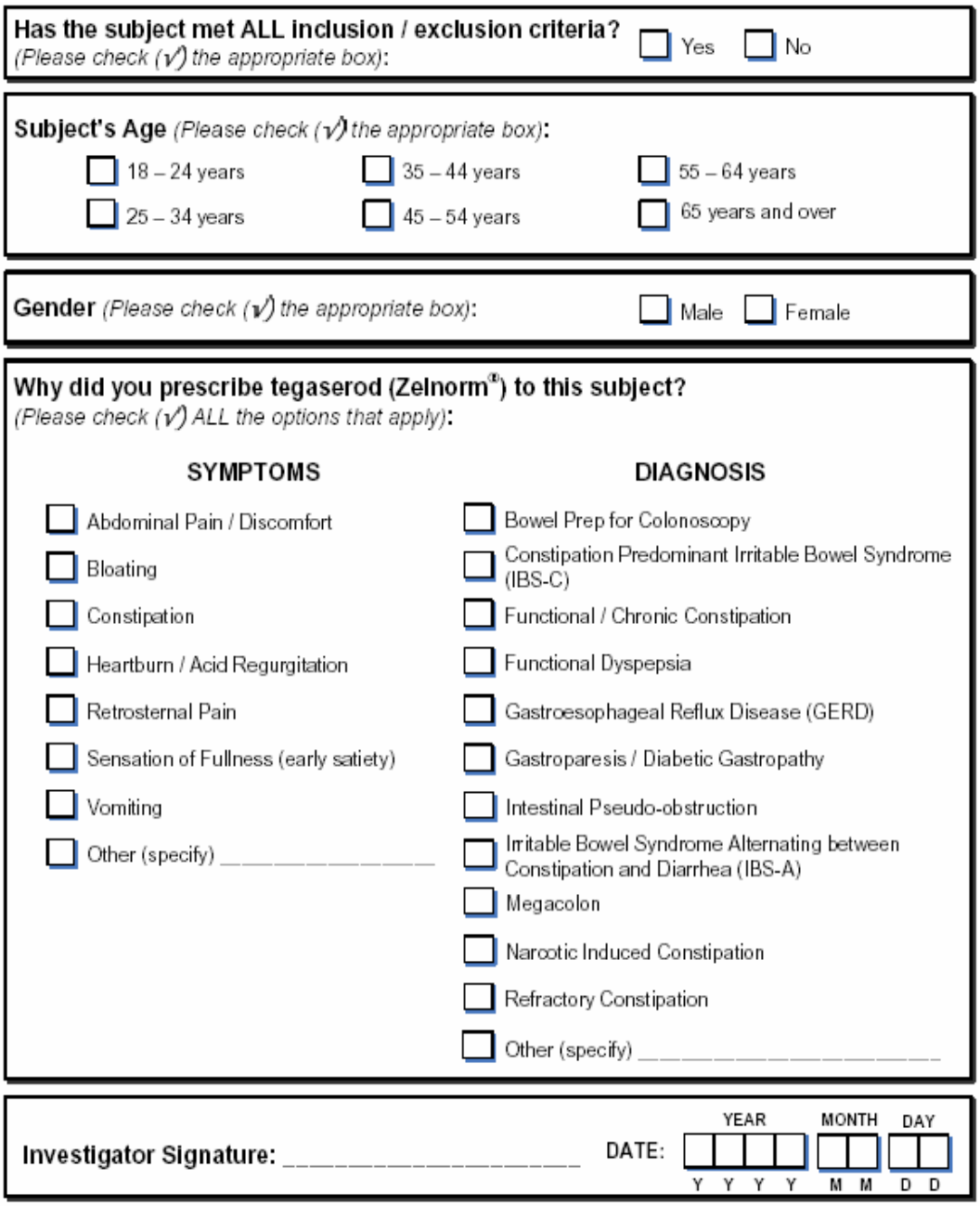
Eligibility Criteria

To be included in the study, participants were required to be at least 18 years of age, scheduled to receive a prescription for tegaserod at the time of enrollment, and were required to provide written informed consent.

Data Collection

Data were reported on a single physician-completed case-report form, which included the following information: gender, age and the diagnosis and/or symptoms which led to the prescription of tegaserod (Figure 1). Data were collected at the time of enrollment only; this study involved no follow-up visits.

FIG. 1 Case Report Form



Has the subject met ALL inclusion / exclusion criteria?
(Please check (√) the appropriate box): ☐ Yes ☐ No

Subject's Age *(Please check (√) the appropriate box)*:

☐ 18 – 24 years ☐ 35 – 44 years ☐ 55 – 64 years
☐ 25 – 34 years ☐ 45 – 54 years ☐ 65 years and over

Gender *(Please check (√) the appropriate box)*: ☐ Male ☐ Female

Why did you prescribe tegaserod (Zelnorm®) to this subject?
(Please check (√) ALL the options that apply):

SYMPTOMS

- ☐ Abdominal Pain / Discomfort
- ☐ Bloating
- ☐ Constipation
- ☐ Heartburn / Acid Regurgitation
- ☐ Retrosternal Pain
- ☐ Sensation of Fullness (early satiety)
- ☐ Vomiting
- ☐ Other (specify) _____

DIAGNOSIS

- ☐ Bowel Prep for Colonoscopy
- ☐ Constipation Predominant Irritable Bowel Syndrome (IBS-C)
- ☐ Functional / Chronic Constipation
- ☐ Functional Dyspepsia
- ☐ Gastroesophageal Reflux Disease (GERD)
- ☐ Gastroparesis / Diabetic Gastropathy
- ☐ Intestinal Pseudo-obstruction
- ☐ Irritable Bowel Syndrome Alternating between Constipation and Diarrhea (IBS-A)
- ☐ Megacolon
- ☐ Narcotic Induced Constipation
- ☐ Refractory Constipation
- ☐ Other (specify) _____

Investigator Signature: _____ **DATE:** YEAR (Y Y Y Y) MONTH (M M) DAY (D D)

RESULTS

Patient Characteristics

A total of 500 patients were enrolled at 85 sites, between October 2004 and June 2005. The majority (85%) of patients were treated by family physicians; and the remaining 15% by community-based GI specialists. The demographic characteristics of the patients are shown in Table 1. The majority were female (87%), and the highest percentage were between 35 and 54 years of age (47.6%). Notably, a significant proportion (18%), were at least 65 years of age. Ontario was the region in which the highest percentage of patients were recruited (35%), followed by the Maritimes (29.4%), Western Canada (19.8%) and Quebec (15.8%).

TABLE 1 Patient Characteristics

Gender	**Number (Percent) (n=500)**
Male	66 (13.2%)
Female	433 (86.6%)
Missing	1 (0.2%)
Age (years)	
18-24	46 (9.2%)
25-34	48 (9.6%)
35-44	113 (22.6%)
45-54	125 (25.0%)
55-64	78 (15.6%)
≥65	90 (18.0%)
Province / Region	
Maritimes	147 (29.4%)
Ontario	175 (35.0%)
Quebec	79 (15.8%)
Western Canada	99 (19.8%)
Type of Site	
Family Physician	427 (85.4%)
Specialist	73 (14.6%)
Reason for Tegaserod Prescription	
Based on Symptoms only	16 (3.2%)
Based on Diagnosis only	3 (0.6%)
Based on both Symptoms and Diagnosis	481 (96.2%)

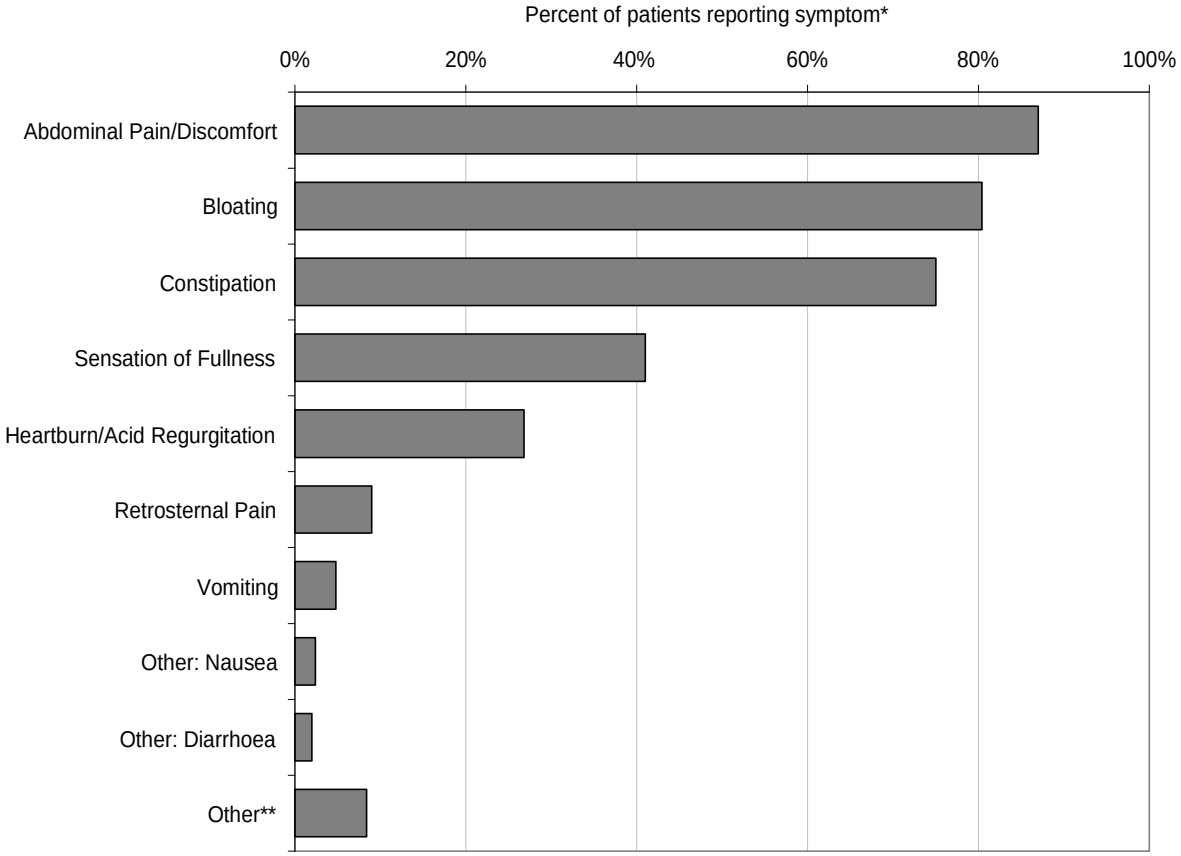
TABLE 2 Number of Symptoms and Diagnoses by Patient

	Number (Percent) (n=500)
No symptoms selected	3 (0.6%)
One symptom selected	38 (7.6%)
More than one symptom selected	459 (91.8%)
No diagnosis selected	16 (3.2%)
One diagnosis selected	385 (77.0%)
More than one diagnosis selected	99 (19.8%)

Symptoms and Diagnosis

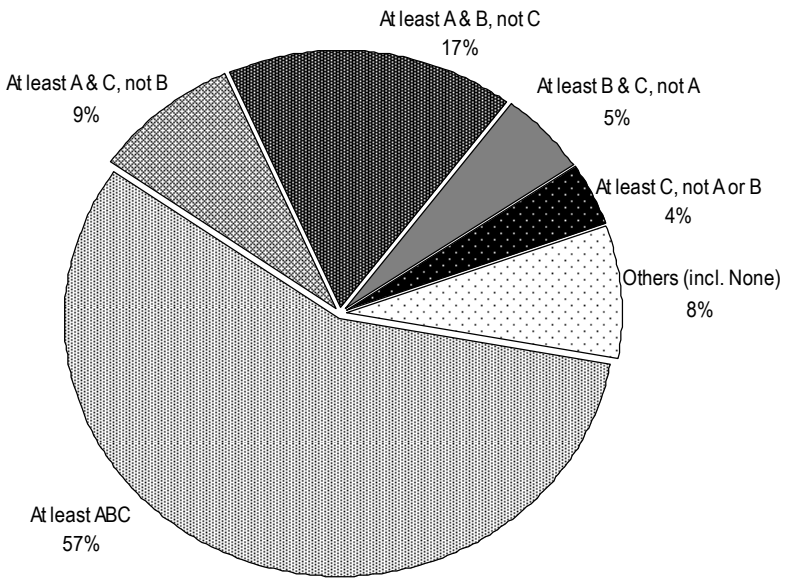
For nearly all the patients prescribed tegaserod (96%), the physicians recorded at least one symptom and at least one diagnosis. Multiple symptoms were reported for the majority of patients (92%), while multiple diagnoses were reported in only 20% of patients (Table 2). The most frequently reported symptoms (Figure 2) were abdominal pain and/or discomfort (87%), bloating (80%) and constipation (75%). As illustrated in Figure 3, the majority of patients (57%) presented with all three ABC symptoms (abdominal pain/discomfort, bloating and constipation). Most of the remainder had at least two symptoms; with abdominal pain and bloating (17%), abdominal pain and constipation (9%) or bloating and constipation (5%) being the more common. Overall, 92% of patients reported one or more of the abdominal pain and/or discomfort, bloating and constipation symptoms.

FIG. 2 Frequency Distribution of Symptoms Reported



*****More than one symptom could be selected for each patient
******Other includes: bowel movement irregularity, bowel sounds abnormal, decreased appetite, defaecation urgency, dysmenorrhoea, eructation, faecal incontinence, flatulence, impaired gastric emptying, menorrhagia, micturition urgency, muscle spasms, premenstrual syndrome, rectal cramps & stress

FIG. 3 Distribution of Selected Combinations of ABC Symptoms



LEGEND

At least ABC
Abdominal pain and/or discomfort and Constipation and Bloating

At least A & C, not B
Abdominal pain and/or discomfort and Constipation, but not Bloating

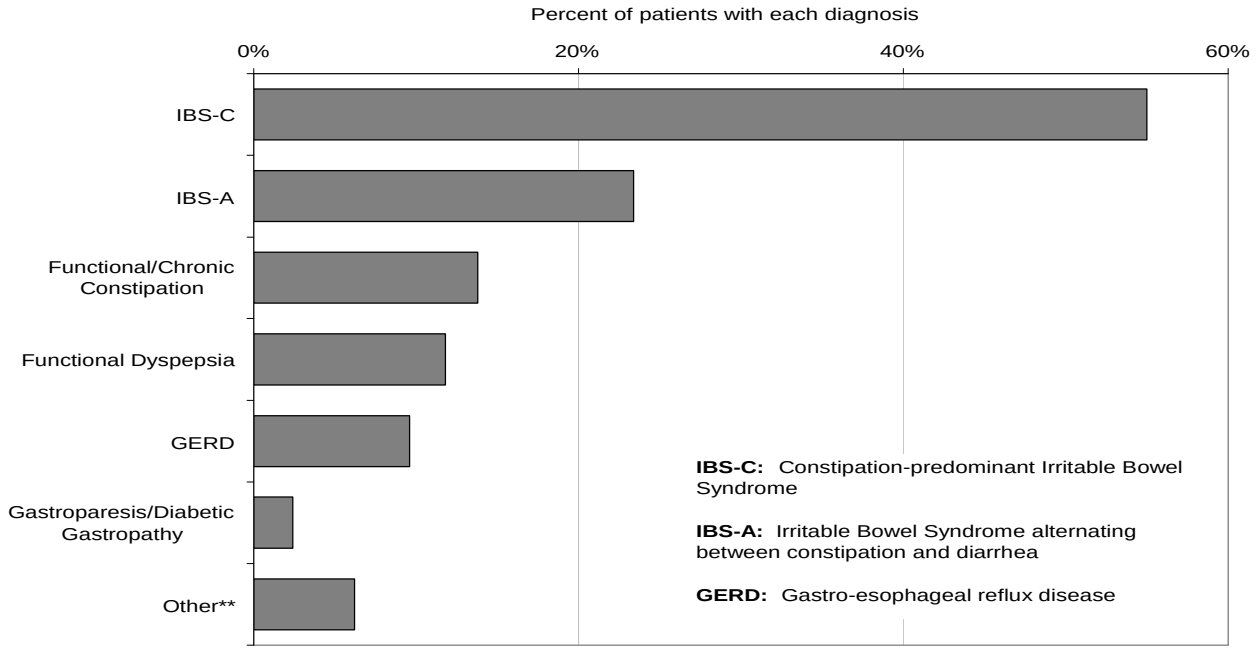
At least A & B, not C
Abdominal pain and/or discomfort and Bloating, but not Constipation

At least B & C, not A
Bloating and Constipation, but not Abdominal pain and/or discomfort

At least C, not A or B
Constipation but not Bloating or Abdominal pain and/or discomfort

Others (incl. None)
Combinations of symptoms not described above (including no reported symptoms).

FIG. 4 Frequency Distribution of Diagnoses* Reported



***** More than 1 diagnosis could have been indicated by the physician

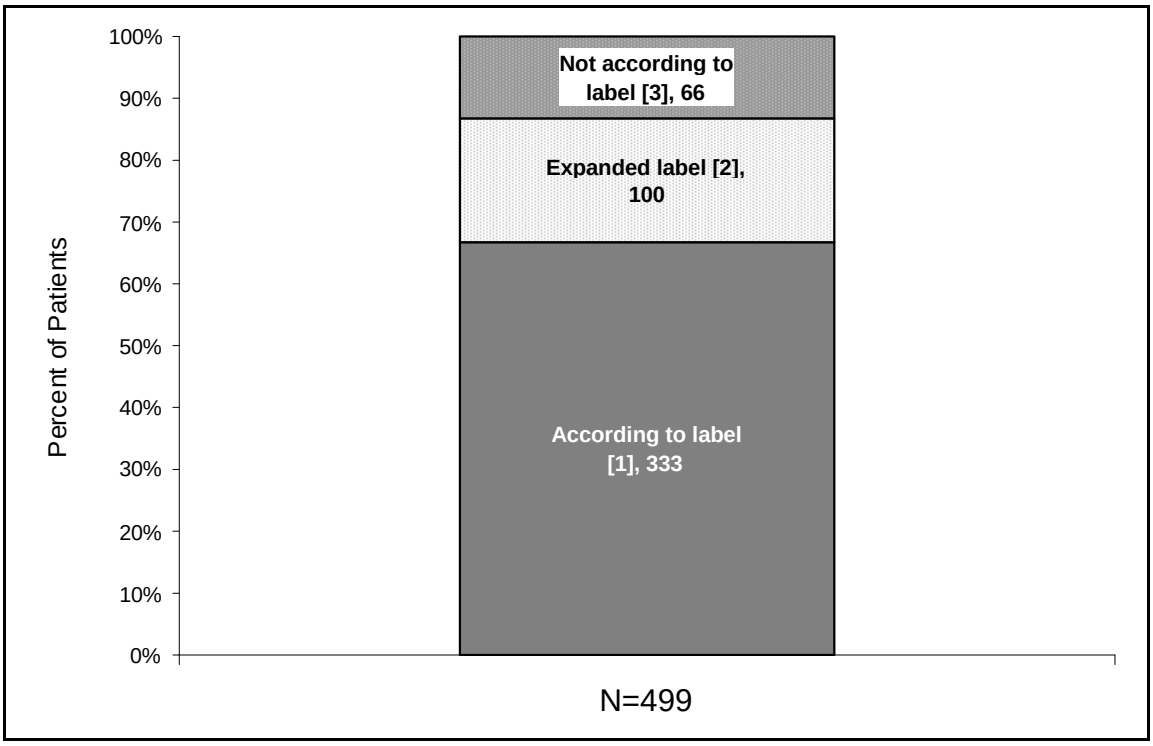
******Other diagnoses, each reported in <2% of patients were: narcotic induced constipation, refractory constipation, intestinal pseudo-obstruction, bowel prep for colonoscopy, megacolon, cholelithiasis, gastrointestinal infection, helicobacter infection, suspected irritable bowel syndrome (abdominal pain/discomfort and bloating), multiple sclerosis, malignant neoplasm, psychosomatic disease, pyloroplasty, rectal prolapse

Figure 4 illustrates the frequency of diagnoses. It should be kept in mind that some patients had multiple diagnoses. Constipation-predominant Irritable Bowel Syndrome (IBS-C) was the most common diagnosis (55 %), followed by Irritable Bowel Syndrome alternating between constipation and diarrhea (IBS-A) (23 %). Of the 117 patients with a diagnosis of IBS-A, constipation was reported as one of the symptoms in 52 (44 %) cases, and diarrhea was reported in 7 (6 %) cases. Abdominal pain/discomfort (96 %) and bloating (84 %) were the most frequently reported symptoms in this group. The third most frequently reported diagnosis was Functional or Chronic Constipation (14 %). Other frequent diagnoses were associated with upper GI disorders. There were no clear differences in the frequency of the different diagnoses between family physicians and specialists (Table 3).

Appropriate Use of Tegaserod

At the time of the study, tegaserod was approved for female patients presenting with IBS-C with symptoms of Abdominal Pain/Discomfort and Constipation. A total of 333 patients (67%) fulfilled these criteria (Figure 5). When male patients with IBS and those with a diagnosis of IBS-A were included, the proportion rose to 87%. Therefore, only a small percentage of patients received tegaserod for disorders other than IBS.

FIG. 5 Number of Patients Receiving Tegaserod According to Label



[1] At least constipation-predominant Irritable Bowel Syndrome (IBS-C) or the symptoms abdominal pain and/or discomfort and constipation and Female;

[2] At least constipation-predominant Irritable Bowel Syndrome (IBS-C) or Irritable Bowel Syndrome alternating between constipation and diarrhea (IBS-A) or at least the symptoms abdominal pain and/or discomfort and constipation;

[3] One patient excluded because of missing gender.

TABLE 3 Association Between Diagnosis and Specialty of Treating Physician

Diagnosis*	Family Physician (n=427)	Specialist (n=73)	Overall (n=500)
Functional Dyspepsia	3.7%	9.6%	4.6%
Functional Dyspepsia & IBS-A†	2.3%	0.0%	2.0%
Functional/Chronic Constipation	7.5%	8.2%	7.6%
GERD‡ & IBS-C**	4.2%	2.7%	4.0%
IBS-A	17.8%	12.3%	17.0%
IBS-C	43.8%	43.8%	43.8%
None	3.0%	4.1%	3.2%
Other	17.6%	19.2%	17.8%

* Where more than one of the listed diagnoses was indicated by the physician, these have been included under 'Other'
† Irritable Bowel Syndrome alternating between constipation and diarrhea
‡ Gastro-esophageal reflux disease
** Constipation-predominant Irritable Bowel Syndrome

DISCUSSION

The relative incidence of the subtypes IBS-C, IBS-A and diarrhea-predominant IBS (IBS-D) in the general population in North America is broadly similar.[14,15] The higher proportion of patients with a diagnosis of IBS-C in this study reflects the fact that this was the indication for which tegaserod has been developed and for which it was approved at the time of the study. Tegaserod is not indicated for the treatment of diarrhea-predominant IBS, and these patients, who constitute around a third of IBS patients in the general population, are underrepresented in the current study. About 20% of the patients in the study were diagnosed with IBS-A, and of these, 44% reported constipation as one of their symptoms. This finding is supported by previous studies of patients meeting the Rome II criteria for IBS-A, in which the majority of patients considered their primary symptom to be constipation.[16] Moreover, it suggests that many IBS-A patients were in the constipation phase of their disorder at the time of the prescription. It has been shown that patients with IBS can move between constipation-predominant and diarrhea-predominant over a period of time.[17,18] Finally, the observation that only 50% of IBS-A patients presented with the symptoms of either constipation or diarrhea, the majority having abdominal pain/discomfort and/or bloating, suggests that many patients may have been in transition between constipation and diarrhea at the single time-point that the data were collected; and therefore, ancillary symptoms were identified because of the normal bowel function at the time.

The complex pathophysiology of this disorder is reflected in the fairly high proportion of patients (20%) who had multiple diagnoses, and the broad and overlapping symptom profile. Of particular note was the prevalence of upper gastrointestinal symptoms, including functional dyspepsia and gastro-esophageal reflux disease (GERD), in the study population. The co-existence of upper and lower intestinal symptoms has been well documented in the literature.[19,20] Notwithstanding the high incidence of multiple diagnosis, abdominal pain and/or discomfort was present in almost 90% of patients, bloating and/or constipation were each present in over 70%, and the combination of all three ABC symptoms was present in over half the patients. The infrequently reported diagnoses (present is less than 2% of patients) deserve mention. A common feature of many of these is that constipation is a consequence, irrespective of the etiology. Examples include narcotic-induced constipation, intestinal pseudo-obstruction, multiple sclerosis and refractory constipation. In these cases, tegaserod may have been prescribed, in the absence of alternative therapies, or as an alternative to unsuccessful

treatment with other agents. A total of 333 patients (67%) fulfilled the criteria for the use of tegaserod strictly according to the label (female and presenting with IBS-C or the symptoms abdominal pain/discomfort and constipation). This is consistent with the primary mechanism of action of tegaserod, which is to normalize impairment in both gut motility and sensory function, through the activation of 5-HT_4 receptors in the gastrointestinal tract. Based on this mechanism of action, a further 20% of patients were prescribed tegaserod in a manner which could be considered clinically appropriate (defined as use in patients with at least IBS-C or IBS-A, or at least the presence of abdominal pain/bloating and constipation symptoms, irrespective of gender). Thus, male patients were included in the category of 'clinically appropriate' where their symptom profile or diagnosis was indicated for tegaserod.

While three randomized, placebo-controlled studies have shown no significant benefit of tegaserod over placebo among men.[13] The combined number of subjects in these three trials comprised between 83-87 percent women, and therefore it was unable to yield sufficient power to examine any potential differences between placebo and tegaserod among male subjects. This is compounded by the fact that many subsequent, published trials have enrolled only women[12,21] or also included less than 20% men in their samples.[22,23] Approximately half the patients who were in the category of appropriate use (but not according to the Product Monograph) were women, all of whom presented with a diagnosis of IBS-A, along with one or more of the abdominal pain/discomfort, bloating and/or constipation symptoms. The coexistence of these symptoms with the diagnosis of IBS-A indicates that the patients were likely in the constipation phase of their alternating IBS, and therefore, the tegaserod treatment could have been seen as beneficial. The most common uses not according to the Product Monograph, were functional dyspepsia and GERD (along with the associated symptoms of heartburn, sensation of fullness and/or retrosternal pain), or functional/chronic constipation. Chronic Idiopathic Constipation was added as a new indication for tegaserod after the completion of this study. However, it is interesting to note that tegaserod was already being prescribed for chronic constipation among almost 8% of participating physicians.

Among the limitations of this study, the potential bias associated with the selection of participating physicians deserves mention. To facilitate a good rate of recruitment, high tegaserod prescribers were approached first. Therefore, it is possible that the study failed to capture information on the important subset of physicians who use the drug infrequently. However, as many potential participants (high prescribers) were also excluded because of involvement in other tegaserod trials, the eighty-five physicians are thought to offer a fair representation of community-based tegaserod prescribers in Canada. Moreover, the distribution of patients by region is broadly representative of Canadians treated for IBS.

CONCLUSION

Almost all (92%) patients being prescribed tegaserod in Canada present with at least one of the main symptoms of IBS-C (abdominal pain and/or discomfort, bloating and constipation). In the majority of cases, tegaserod is being prescribed appropriately. While this study provides useful insight about the profile of patients receiving tegaserod, and confirms that IBS therapy seems to focus more and more on the multiple symptoms of the disorders, some of the differences and inconsistencies between the diagnostic and symptom profiles merit further investigation.

Disclaimer

IMPORTANT NOTE: At Health Canada's request, as of March 30, 2007, Novartis Pharmaceuticals Canada Inc. has suspended the marketing and sales of Zelnorm*(tegaserod hydrogen maleate) in Canada.

**Zelnorm is a registered trademark.*

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