National PBM Drug Monograph

Tegaserod (Zelnorm®)

VHA Pharmacy Benefits Management Strategic Healthcare Group
and the Medical Advisory Panel

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient situation.

Executive Summary:

Irritable Bowel Syndrome (IBS)
A functional bowel disorder of unknown etiology, irritable bowel syndrome (IBS) is characterized by altered bowel habits and abdominal pain and/or discomfort.

Pathophysiology of IBS
It is thought that alterations in abdominal motility and visceral hypersensitivity play an important role in the pathophysiology of irritable bowel syndrome.

Mechanism of Action of Tegaserod (ZELNORM) in Irritable Bowel Syndrome
Tegaserod acts as a partial agonist for the 5-HT_4 receptor subtype, and has been shown to facilitate the release of mediators responsible for preserving visceral neural pathways and GI motility. The proposed advantage of tegaserod is its unique ability to improve symptom clusters rather than a single symptom, as is commonly seen with conventional agents such as bran.

Goals of Therapy
Since IBS is not curative, the goal of therapy is aimed at symptomatic and quality of life improvements.

Indication
Tegaserod is indicated for short-term treatment of IBS (no more than 12 weeks) in women with a primary bowel symptom of constipation. Tegaserod is available as 2mg and 6mg oral tablets. The recommended dose is 6mg taken twice daily orally *before meals* for 4-6 weeks. For patients who respond to therapy during this time period, an additional 4-6 weeks of treatment can be considered. Tegaserod has not been proven effective in male patients with IBS or those patients with alternating symptoms of constipation and diarrhea.

Adverse Effects
The most common adverse events include diarrhea and increasing abdominal pain with rare instances of cholecystectomy.

Introduction

A functional bowel disorder of unknown etiology, irritable bowel syndrome (IBS) is characterized by altered bowel habits and abdominal pain and/or discomfort[1]. The waxing and waning symptoms and alternation in bowel habits between diarrhea and constipation is unique to IBS. Agents currently used in the treatment of IBS target individual symptoms rather than the cluster of symptoms that patient's experience. Non-pharmacological treatment including diet modification (avoiding foods which aggravate IBS symptoms) has proven useful for many patients with IBS; the efficacy of psychological treatments continues to be of question.

Methodological inadequacies in clinical study design limit the utility of psychotherapy and treating anxiety associated with IBS.[2,3]
Initial pharmacological therapy aimed at constipation-predominant IBS largely includes bulk-forming and osmotic laxatives. Although mixed results are reported in literature, these agents have established a role in alleviation of constipation by decreasing intracolonic pressure. The major side effect of fiber, however, is increased abdominal bloating and flatulence, both symptoms commonly problematic in this patient population. Thus, in some instances, fiber may further complicate treatment.[2] Antidepressants (tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) have been used in the treatment of IBS. To date, there are no published studies evaluating the use of SSRIs in IBS. TCAs have been studied in the treatment of IBS and although possibly effective in diarrhea-predominant IBS, there have been no studies proving efficacy in patients with symptoms of constipation.[2,3]

With the advent of serotonergic (5-HT) agents, targeting symptom clusters rather than individual symptoms became possible.[2] Alosetron, an agent used in the treatment of diarrhea-predominant IBS, proved to be useful for decreasing the perception of abdominal pain and increasing colonic transit time. Initially approved by the Food and Drug Administration (FDA) in February 2000, the drug was quickly removed from the market following reports of ischemic colitis. The manufacturer has recently complied with new FDA labeling requirements and alosetron was allowed back on the market with stringent safety warnings.[4,5] Cisapride, a prokinetic agent with 5-HT_4 agonist and 5-HT_3 antagonist effects, has been studied in patients with constipation-predominant IBS. Two clinical trials lend themselves to critical evaluation and are included in this monograph. Studies with diagnostic criteria or efficacy measures not well established in current gastroenterology guidelines are not included as limited conclusions can be drawn from such data.[6,7]

Tegaserod is the first 5-HT_4 agonist available for the treatment of constipation-predominant IBS. Tegaserod increases colonic transit time and decreases abdominal pain, thus improving the cluster of symptoms often encountered in constipation-predominant IBS. The proposed advantage of tegaserod is its unique ability to improve symptom clusters rather than a single symptom, as is commonly seen with conventional agents such as bran. Of note, like all other treatments for IBS, tegaserod does not cure the illness and the goal of treatment is purely symptom relief.[8]

Pharmacology

It is thought that alterations in abdominal motility and visceral hypersensitivity play an important role in the pathophysiology of irritable bowel syndrome. Although unlikely to be the primary etiological factor in the pathogenesis of IBS, abdominal dysmotility may be responsible for symptoms such as diarrhea and constipation. Abdominal hypersensitivity, on the other hand, is thought to cause perceived abdominal distention and cramping. Approximately 95% of serotonin is located within enterochromaffin cells and gastric nerves throughout the gastrointestinal (GI) tract. GI motility and perception of abdominal distention and pain are likely mediated through various 5-HT receptor subtypes. Agents modulating these receptors may provide patients with relief from the major symptoms of IBS.[9]

Highly selective for the 5-HT_4 receptor subtype, Tegaserod acts as a partial agonist with insignificant activity for 5-HT_3 or dopamine receptors.[10] The 5-HT_4 receptor subtype has been shown to facilitate the release of mediators responsible for preserving visceral neural pathways and GI motility. 5-HT_4 receptor stimulation in the gut results in peristaltic reflex stimulation, intestinal secretion, and inhibition of visceral sensitivity.[10] This partial receptor agonist is thought to be unlike full agonists which are more likely to result in receptor down regulation and thus tolerance and tachyphylaxis. It is also thought to enhance the activity of endogenous serotonin, resulting in a return to baseline activity.[1]

Pharmacokinetics

Pharmacokinetic Parameter	Normal Renal Function	Renal Impairment	Hepatic Impairment
Absorption (oral dosing)			Mean AUC 31% higher Cmax 16% higher
Tmax	1 hr	1 hr	
Bioavailability (fasting)	10%	10%	
Distribution			
Protein Binding	98%	98%	
Vd	368 ± 223 L	368 ± 223 L	
Metabolism			
Stomach Hydrolysis	5-methoxy-indole-3-carboxylic-acid glucuronide	Cmax and AUC increased by 2-10 fold, respectively	
Direct glucuronidation	Isomeric glucuronides	Isomeric glucuronides	
Elimination	77 ± 15 L/h	77 ± 15L/h	
	Approximately 2/3 of orally administered doses are excreted in feces as unchanged drug. 1/3 is excreted as the main metabolite in the urine.		
Half-life	11 ± 5 h	11 ± 5 h	

FDA Approved Indication(s) and Off-label Uses[10,11]

Approved Indications: Tegaserod is indicated for short-term treatment of IBS (no more than 12 weeks) in women with a primary bowel symptom of constipation.

Unapproved Indications:
Gastroesophageal Reflux Disease

Current VA National Formulary Status

Non-formulary status

Dosage and Administration[10]

Tegaserod is available as 2mg and 6mg oral tablets. The recommended dose is 6mg taken twice daily orally ***before meals*** for 4-6 weeks. For patients who respond to therapy during this time period, an additional 4-6 weeks of treatment can be considered.

Renal Impairment: Dose adjustment is not required in patients with mild to moderate renal impairment. However, Tegaserod is not recommended in patients with severe renal impairment (CrCl ≤ 15mL/min/1.73m^2).

Hepatic Impairment: No dosage reduction is required in patients with mild hepatic impairment. However, since no studies have been performed in patients with moderate to severe hepatic impairment, tegaserod is not recommended in this population.

Elderly: No dosage adjustment is required in this patient population.

Adverse Effects (Safety Data)[10]

Adverse Event	Tegaserod 6mg BID (n=1,327)	Placebo (n=1,305)
Gastrointestinal Events		
Abdominal Pain	12%	11%
Diarrhea	9%*	4%
Nausea	8%	7%
Flatulence	6%	5%
Cholecystectomy	0.17%	0.06%
Abdominal Surgery**	0.3%	0.2%
Central Nervous System Events		
Headache	15%	12%
Dizziness	4%	3%
Migraine	2%	1%
Musculoskeletal Events		
Back Pain	5%	4%
Arthropathy	2%	1%
Miscellaneous		
Accidental Trauma	3%	2%
Leg Pain	1%	<1%

* The majority of patients reporting diarrhea experienced a single episode, most occurring within the first week of therapy and resolved with continued therapy. 1.6% of patients discontinued due to diarrhea. In other clinical studies
** Abdominal surgery is primarily related to cholecystectomies, but a relationship between abdominal surgeries and tegaserod has yet to be established.

Pregnancy and Lactation: Animal studies have revealed no evidence of impaired fertility or fetal harm. Since animal studies cannot predict the effect of tegaserod on humans, the drug should be administered only if clearly needed.

Precautions[10]

Diarrhea: Tegaserod should not be administered to patients currently experiencing diarrhea or are known to have frequent diarrhea.

Abdominal Pain: Administration of tegaserod should be discontinued in patients experiencing new or worsening abdominal pain.

Contraindications[10]

Severe Renal Impairment

Moderate or Severe Hepatic Impairment

History of bowel obstruction, symptomatic gall bladder disease, suspected Sphincter of Oddi dysfunction, or abdominal adhesions

Known hypersensitivity to the drug or any of its components

Drug Interactions[10]

Cytochrome P450 Interactions

Pharmacokinetic studies indicated no interactions between tegaserod and the following agents:

Dextromethorphan: There was no alteration in the pharmacokinetics of either agent. Interactions between tegaserod and drugs metabolized by CYP2D6 are not expected.

Theophylline: A pharmacokinetic interaction study indicated no interaction between tegaserod and theophylline; dose adjustment of theophylline is unnecessary. Interactions with other drugs metabolized by CYP1A2 are not expected.

Warfarin: No effect was demonstrated when conducting a pharmacokinetic and pharmacodynamic interaction study with warfarin. Therefore, no dose adjustment of warfarin is necessary.

Other Drug Interactions

Digoxin: A reduction in peak plasma concentration and exposure of digoxin by approximately 15% occurred when coadministered with tegaserod. This reduction in plasma concentration is likely clinically insignificant, however, select patients may require additional monitoring.

Oral Contraceptives: An 8% reduction in peak plasma concentration of levonorgesterol occurred following coadministration with tegaserod and no change in steady state pharmacokinetics occurred when administered with ethinyl estradiol. The risk of altering ovulation when administering tegaserod with oral contraceptives is not expected and no alteration in oral contraceptive medication is necessary.

Food: A 40-65% reduction in tegaserod bioavailability and 20-40% reduction in Cmax was observed following administration of tegaserod with food. Similar reductions of Cmax and bioavailability occur when tegaserod is administered within 30 minutes prior to or 2.5 hours following consumption of food. When taken following a meal, Tmax increases from 1 hour to 2 hours, but decreases to 0.7 hours if taken 30 minutes before a meal.

Efficacy Measures

The Rome Criteria are currently utilized for the clinical diagnosis and research of irritable bowel syndrome. The Rome Criteria stress a positive diagnosis, rather than a diagnosis of exclusion. Developed in 1988, the Rome I Criteria recommend diagnosing IBS based on the presence of abdominal pain or discomfort plus chronic altered bowel habits and 2 or more supportive criteria. In 1998, these criteria were further developed into Rome II Criteria, confirming IBS diagnosis by the presence of abdominal pain plus 2 out of the 3 main criteria. The Rome II Criteria also allow for further classification of IBS into constipation-predominant and diarrhea-predominant disease.[2]

Veldhuyzen van Zanten et al. have developed guidelines for design, analysis and management of functional gastrointestinal disorders. Critical components of IBS subjects enrolled in clinical trials include a broad patient population using Rome Criteria and careful consideration of the patient setting, as outcome may be affected. The study design should consist of a placebo or adequate control group, parallel design (preferable), and adequate blinding (essential) with a period of baseline (recommended). Treatment duration should be at least 8-12 weeks with follow up recommended. The definition of responder should be clear and use of study results should be largely based on the primary outcome measure, with main outcome assessments performed by patients. Lastly, the use of seven point measurement scales is

recommended since they enable investigators to detect small but potentially pertinent differences in treatment regimens.[12]

Rome I Criteria for IBS [2]

1 abdominal pain or discomfort that is relieved with defecation,
and/or
associated with a change in frequency or form of stool,
and/or
associated with a change in consistency of stool, and

2 two or more of the following, on at least one quarter of occasions or days:
altered stool frequency (for research purposes, altered may be defined as > 3 bowel movements per day or >3 bowel movements per week)
altered stool form (lumpy/hard or loose/watery stool)
altered stool passage (straining, urgency or feeling of incomplete evacuation)
passage of mucus
bloating or feeling of abdominal distention

Rome II Criteria for IBS [2]

At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two of three features:

1 relieved with defecation,
and/or
2 onset associated with a change in frequency of stool,
and/or
3 onset associated with a change in form (appearance) of stool

Supportive symptoms of IBS:

1 fewer than 3 bowel movements per week
2 more than 3 bowel movements a day
3 hard or lumpy stools
4 loose (mushy) or watery stools
5 straining during a bowel movement
6 urgency (having to rush to have a bowel movement)
7 feeling of incomplete bowel movement
8 passing mucus (white material) during a bowel movement
9 abdominal fullness, bloating or swelling

Diarrhea-predominant IBS:
One or more of 2, 4, or 6 and none of 1, 3, or 5

Constipation-predominant IBS
One or more of 1, 3, or 5 and none of 2, 4, or 6

The SGA of relief is defined the same way in all tegaserod studies (except the unpublished Zelnorm Asia-Pacific). Every week patients answer the following question:

"Please consider how you felt this past week in regard to your IBS, in particular your overall well-being, and symptoms of abdominal discomfort, pain and altered bowel habit. Compared to the way you usually felt before entering the study, how would you rate your relief of symptoms the past week?"

Possible answers include:
- completely relieved
- considerably relieved
- somewhat relieved
- unchanged
- worse

The unpublished 351 Study was performed first. At the time, the SGA of relief was an endpoint that was designed with the blessings of the FDA and Rome committee, but had not been tested. The "original SGA" used in the 351 study was defined as patients who reported "completely" or "considerably" relieved for two out of the last four weeks of the study. According to the manufacturer, after the data was analyzed, it was determined that this definition was probably too strict. As a result, the SGA of relief was modified as above and patients who reported "somewhat" relieved or better, for all four weeks, were added as responders.

Because the definition of the primary endpoint was modified after the data was analyzed, the 351 Study is not considered a "pivotal" study. Mueller-Lissner et al and Novick, et.al. were conducted following this change in the primary efficacy endpoint.

Clinical Trials

Citation	**Muller-Lissner SA, Fumagalli I, Bardhan KD, Pace F, Pecher E, Nault B, et al. Tegaserod, a 5-HT_4 receptor partial agonist, relieved symptoms in irritable bowel syndrome patients with abdominal pain, bloating and constipation. *Aliment Pharmacol Ther* 2001;15:1655-66.[13]**
Study Goals	To evaluate the safety and efficacy of tegaserod in patients with symptoms of abdominal pain, bloating and constipation associated with irritable bowel syndrome.
Methods	• **Study Design** ➢ International randomized, double-blind, placebo-controlled multicenter trial ➢ Length of Study: 4 week treatment-free period followed by a 12 week double-blind period ➢ Patients randomized to receive either Tegaserod 2mg BID, Tegaserod 6mg BID or placebo to be taken in morning and evening 30 minutes before meals ➢ Patients were provided with paper diaries to rate symptoms ➢ Primary Efficacy Variable: Subject's Global Assessment (SGA) of Relief at Endpoint; also assessed weekly. ❑ Responders of SGA of Relief: at least 50% of SGA assessments as either considerably relieved or completely relieved or 100% at least somewhat relieved ❑ Nonresponders: ▪ Laxatives taken on > 5 days during double-blind period ▪ Laxative use during the last 28 days of treatment period ▪ Study period duration < 28 days ▪ No post baseline SGA of Relief was available ➢ Secondary Efficacy Variable: SGA of Abdominal Pain and Discomfort ❑ Self-administered visual analog scale (100mm length) with severity descriptors: ▪ very mild ▪ mild ▪ moderate ▪ severe ▪ very severe ➢ Daily self assessments included: ▪ number of stools ▪ stool consistency (1, watery; 2, loose; 3, somewhat loose; 4, neither loose nor hard; 5, somewhat hard; 6, hard; 7, very hard) ▪ severity of abdominal pain and discomfort (0, none; 1, very mild; 2, mild; 3, moderate; 4,

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severe; 5, very severe)
▪ severity of bloating (0, none; 1, very mild; 2, mild; 3, moderate; 4, severe; 5, very severe)
• Data Analysis
➢ Intention to treat analyses were performed on all randomized patients
➢ The study achieved adequate power to detect a 15% difference between proportion of responders at endpoint
➢ α was set at 0.05; a P value of 0.05 was considered statistically significant
➢ Cochran-Mantel-Haenszel test was used to compare each of the two doses of tegaserod with placebo
➢ Hochberg's procedure was used to ensure that the overall 2-sided type 1 error as <0.05 for the SGA of Relief at end-point.
➢ Binary data were compared using the Mantel-Haenszel test, while non-binary data were compared using an extended Mantel-Haenszel test.
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• Inclusion criteria
➢ Completion of at least 3 weekly assessments before randomization
➢ 3 month history of IBS, diagnosed by Rome I Criteria
➢ Abdominal pain or discomfort either relieved by BM or associated with change in bowel frequency
➢ 2/3 constipation symptoms at least 25% of the time during the 3 months prior to study entry (<3 BM/week, hard/lumpy stools, straining)
➢ Male and Female patients 18 years or older
➢ Normal colonic anatomy confirmed by colonoscopy, sigmoidoscopy, or barium enema within previous 5 years and after symptom onset
➢ At least mild abdominal pain and discomfort at the end of the baseline period
• Exclusion criteria
➢ History of diarrhea (loose/watery stools and/or >3 BM/day associated with urgency on 25% of days)
➢ Using or planning to use medications affecting GI motility and/or perception (prokinetics, antidiarrheals, antispasmodics, anticholinergics, antacids containing Mg or Al salts, erythromycin, octreotide, ondansetron or other 5-HT_3 antagonists. Laxative use within last 4 weeks of the study. Note: laxatives were allowed only if patients had no bowel movement for at least 4 consecutive days plus bothersome abdominal pain. Fiber, tricyclic antidepressants, and SSRIs were allowed if the patients were on a constant dose.)
➢ Pregnancy, breastfeeding, or using inadequate method of contraception
➢ Conditions affecting gastric, small bowel or colonic transit
➢ History of drug, alcohol, or laxative abuse
➢ Patients with missing data for more than 10 days during baseline period
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<tr><td>Results</td><td>
• A total of 1122 patients were enrolled in the study; 881 were randomized to one of the three groups; baseline characteristics were as follows:
<table>
<tr><th rowspan="2">Baseline Characteristic</th><th colspan="2">Tegaserod</th><th rowspan="2">Placebo n=288</th></tr>
<tr><th>2mg BID (n=299)</th><th>6mg BID (n=294)</th></tr>
<tr><td>Mean (s.d.) age (years)</td><td>45.7 (14.4)</td><td>45.6 (13.6)</td><td>46.1 (13.6)</td></tr>
<tr><td>Gender Male</td><td>52 (17.4%)</td><td>50 (17%)</td><td>48 (16.7%)</td></tr>
<tr><td>Female</td><td>247 (82.6%)</td><td>244 (83.0%)</td><td>240 (83.3%)</td></tr>
<tr><td>Mean Duration of IBS symptoms (years)</td><td>10.0</td><td>10.0</td><td>8.2</td></tr>
<tr><td>Patients (%) fulfilling Rome II Criteria</td><td>89.3%</td><td>88.8%</td><td>87.5%</td></tr>
<tr><td>Patients (%) who used bulking agents during baseline</td><td>35 (11.7%)</td><td>35 (11.9%)</td><td>30 (10.4%)</td></tr>
<tr><td>Mean (s.d.) percentage of days with at least mild abdominal pain & discomfort</td><td>60.5 (13.2)</td><td>59.8 (12.5)</td><td>60.3 (13.8)</td></tr>
<tr><td>Mean (s.d.) percentage of days with at least mild bloating</td><td>83.2 (25.4)</td><td>83.2 (24.3)</td><td>82.9 (25.3)</td></tr>
<tr><td>Mean (s.d.) percentage of days without bowel movement</td><td>43.9 (26.1)</td><td>43.6 (25.4)</td><td>43.9 (26.6)</td></tr>
<tr><td>Mean (s.d.) number of bowel movements per 28 days</td><td>21.1 (15.3)</td><td>21.9 (15.1)</td><td>22.3 (16.4)</td></tr>
<tr><td>Mean (s.d.) percentage of days with hard or very hard stools</td><td>28.9 (29.3)</td><td>29.4 (29.3)</td><td>26.0 (27.1)</td></tr>
<tr><td>Number of patients (%) with diarrhea during baseline</td><td>36 (12.0%)</td><td>42 (14.3%)</td><td>46 (16.0%)</td></tr>
</table>
➢ Patients were predominantly female (83%) and Caucasian (98%)
➢ All randomized patients fulfilled the Rome I Criteria for IBS. The Rome II Criteria were fulfilled in
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89.3%, 88.8%, and 87.5% of patients in the tegaserod 2mg BID, tegaserod 6mg BID, and placebo groups, respectively.
  - 246/299, 254/294, and 251/288 patients completed the study in the tegaserod 2mg BID, tegaserod 6mg BID, and placebo groups, respectively.
- Primary Outcome: SGA of Relief Response Rate at Endpoint

Treatment Group	Response Rate	Compared with Placebo	P value	95% CI
Tegaserod 2mg BID n=299	46.5%	12.7%	0.02	4.8 - 20.7
Tegaserod 6mg BID n=294	46.3%	11.8%	0.04	3.8 - 19.8
Placebo n=288	34.5%	N/A	N/A	N/A

- Primary Outcome: SGA of Relief **Adjusted** Response Rate at Endpoint (takes into account laxative intake, minimum treatment duration, and availability of SGA of Relief data

Treatment Group	Response Rate	95% CI
Tegaserod 2mg BID n=299	38.8%	1.6-16.5
Tegaserod 6mg BID n=294	38.4%	0.5-16.0
Placebo n=288	30.2%	

- Primary Outcome: SGA of Relief Response Rate at Endpoint **for Females**

Treatment Group	Response Rate	Compared with Placebo	P value
Tegaserod 2mg BID n=299	37.7%	10.2%	0.017
Tegaserod 6mg BID n=294	38.9%	11.4%	0.008
Placebo n=288	27.5%	N/A	N/A

- Secondary Outcome: SGA of Abdominal Pain Assessed Weekly: significant improvement in Tegaserod 6mg BID group only ($p<0.05$)
- Secondary Outcome: Severity of abdominal pain and discomfort, assessed daily was significantly reduced in patients treated with tegaserod.
- Secondary Outcome: SGA of Abdominal Pain and Discomfort at Endpoint

Treatment Group	Response Rate	P value
Tegaserod 2mg BID n=299	29.8%	0.055
Tegaserod 6mg BID n=294	29.9%	0.044
Placebo n=288	22.6%	

- Effect on Bloating: no statistically significant difference; favorable trend noted
- Effect on Bowel Movements: Both tegaserod groups had a statistically significant increase in bowel movements as compared with placebo. This occurred as early as week 1 and stabilized at 2 weeks, persisting throughout the 12-week period.
- Effect on Stool Consistency: Stool consistency was significantly decreased in both tegaserod groups.
- Laxative use: There was no statistically significant difference in laxative use between the two groups. During the baseline period, 30.3% and 28.8% of patients in the tegaserod and placebo groups, respectively used laxatives. 27.6% of tegaserod and 27.1% of placebo patients took laxatives during the 12-week study period. The mean number of days of laxative use was approximately 2.5.
- Safety Evaluation:
  - Serious Adverse Events: 13/876 (1.5%); type not stated
    - No cases of ischemic colitis reported

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<tr><th>Treatment Group</th><th>Discontinuation due to Adverse Events</th><th>% Patients with Diarrhea</th><th>Drop-outs due to Diarrhea</th></tr>
<tr><td>Tegaserod 2mg BID n=299</td><td>8.7%</td><td>7.1</td><td>2.0%</td></tr>
<tr><td>Tegaserod 6mg BID n=294</td><td>5.1%</td><td>9.6</td><td>2.4%</td></tr>
<tr><td>Placebo n=288</td><td>4.5%</td><td>2.5</td><td>0%</td></tr>
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</td></tr>
<tr><td>Conclusions</td><td>Tegaserod provides rapid and sustained relief of abdominal pain and constipation associated with irritable bowel syndrome.</td></tr>
<tr><td>Critique</td><td>• Strengths
➢ SGA of Relief was measured by overall symptom improvement, rather than single treatment variables
➢ Laxative use was considered in determination of response rate
➢ All patients were diagnosed according to the Rome I Criteria and 88% fit the diagnosis according to the Rome II Criteria
• Limitations
➢ The SGA of relief (unvalidated tool and outcome measure) was used as primary efficacy measure. Note that the definition of responder was modified post-hoc to include a larger number of patients)
➢ Patient population: mostly female and Caucasian; few male patients enrolled
➢ Other agents affecting 5-HT were allowed (SSRIs, TCAs)
➢ Randomized patients with diarrhea during the baseline period were not excluded (14% of patients had diarrhea symptoms during baseline)
➢ The nature of the 14 serious adverse events was not reported</td></tr>
<tr><td>Sponsorship</td><td>• The study was funded by Novartis</td></tr>
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<tr><td>Citation</td><td>Novick J, Miner P, Krause R, Glebas K, Bliesath H, Ligozio G, Ruegg P, Lefkowitz M. A Randomized, double-blind, placebo-controlled trial of tegaserod in female patients suffering from irritable bowel syndrome and constipation.[14]</td></tr>
<tr><td>Study Goals</td><td>To evaluate the safety and efficacy of tegaserod in female patients with irritable bowel syndrome characterized by abdominal pain/discomfort and constipation.</td></tr>
<tr><td>Methods</td><td>

Study Design

Prospective randomized (1:1 ratio), double-blind, placebo-controlled trial
Female patients were randomized from 131 treatment centers in the US to receive tegaserod 6mg BID or placebo for 12 weeks preceded by a 4-week baseline period (no drug received) and followed by a 4-week withdrawal period (no drug received)
Patients were instructed to take study medication with a glass of water within 30 minutes before morning and evening meals.
Monthly visits were scheduled for safety assessment. Evaluation of overall well-being and daily & weekly symptoms of abdominal pain/discomfort, bloating and altered bowel function were recorded via a touch-tone phone system during baseline, double-blind treatment and withdrawal periods.

Data Analysis

The planned sample size was 1528 patients; 33% placebo response rate for SGA of Relief, it was determined that the study would have 90% power to detect an 8% treatment difference
α=0.05
Intention to treat analyses were performed
“The primary efficacy variable was the response for the SGA of Relief, which was analyzed by covariable-adjusted Mantel-Haenszel analysis with baseline laxative use as a covariable, stratified by center.”
SGA of Relief, assessed monthly: Mantel Haenszel test with covariate adjustment of baseline laxative use
Number needed to treat was calculated including a 95% confidence interval
Supplemental Analysis of SGA of Relief: weekly proportions of patients at least “somewhat relieved” during the treatment period, analyzed by covariable adjusted Mantel-Haenszel statistics with baseline laxative use as covariable
Secondary Endpoints (see below) were analyzed by 2-sided Mantel-Haenszel statistics (α=0.05)
Descriptive statistics were used to analyze adverse events and laboratory changes, blood pressure, pulse, and physical examination
Number needed to harm (NNH) was calculated for adverse events (same as calculation for number needed to treat (NNT)

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<tr><td>Criteria</td><td>

Patient Population

Baseline Characteristics

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<tr><th>Demographic Variable</th><th>Placebo (n=752)</th><th>Tegaserod 6mg BID (n=767)</th></tr>
<tr><td>Age (years), mean (s.d.)</td><td>41.0 (11.7)</td><td>41.5 (10.8)</td></tr>
<tr><td>By group</td><td></td><td></td></tr>
<tr><td>< 65</td><td>725 (96.4)</td><td>744 (97)</td></tr>
<tr><td>$\geq$ 65</td><td>27 (3.6)</td><td>23 (3)</td></tr>
<tr><td colspan="3">Race</td></tr>
<tr><td>Caucasian, n (%)</td><td>586 (77.9)</td><td>589 (76.8)</td></tr>
<tr><td>Black, n (%)</td><td>121 (16.1)</td><td>127 (16.6)</td></tr>
<tr><td>Asian, n (%)</td><td>3 (0.3)</td><td>3 (0.4)</td></tr>
<tr><td>Other, n (%)</td><td>43 (5.7)</td><td>48 (6.3)</td></tr>
<tr><td>Smoker (%)</td><td>148 (19.7)</td><td>127 (16.6)</td></tr>
<tr><td>Weight (kg), mean (s.d.)</td><td>70.0 (13.9)</td><td>70.7 (15.4)</td></tr>
<tr><td>Duration of IBS symptoms (yrs), mean (s.d.)</td><td>16.3 (12.9)</td><td>16.0 (12.2)</td></tr>
</table>
</td></tr>
</table>

- Baseline Characteristics continued

Demographic Variable	Placebo (n=752)	Tegaserod 6mg BID (n=767)
Mean (s.d.) Baseline weekly Assessments		
# Responders for SGA of Relief, n (%)	0/752 (0)	0/767 (0)
SGA of Abdominal Pain/Discomfort, n (%)	3.7 (1)	3.8 (1)
SGA of Bowel Habit, n (%)	3.9 (1.1)	3.9 (1.1)
SGA of Satisfaction with Bowel Habit, n (%)	3.4 (0.6)	3.4 (0.6)
Mean (s.d.) Baseline Daily Assessments		
Bloating Score, n (%)	4.1 (1)	4.2 (1)
# BM/28 days, n (%)	16.3 (13)	15.8 (11.6)
Stool Consistency Score, n (%)	4.9 (0.8)	5.0 (0.8)
# days with straining/28 days, n (%)	17.5 (7.4)	17.9 (7.4)

  - Demographics and baseline characteristics were comparable for both treatments with the exception of laxative use (15% for tegaserod vs. 11% for placebo, P<0.05)
  - Severity of IBS symptoms at baseline were similar when comparing the 2 groups
  - >93% of patients fulfilled Rome II Criteria for IBS at baseline
  - Withdrawal from the study: 20.6% for tegaserod group and 21.4% in placebo group
- **Efficacy Measures**
  - Primary Efficacy Measure
    - SGA of Relief, assessed weekly via touch-tone telephone.
    - SGA of Relief, assessed monthly
      - Responders were defined as patients who were completely relieved or considerably relieved for at least 50% of the weeks at endpoint or somewhat relieved for 100% of the weeks at the endpoint. (Endpoint was defined as the last 4 weeks of the treatment period).
      - Nonresponders: no post-baseline SGA, <28 days of exposure, use of prohibited medication (non-bulking laxatives for ≥ 5 days during double-blind period or > 1 day during the last for weeks of double-blind period
    - SGA of Relief, assessed monthly
      - Responders: considerably or completely relieved for at least 2 of the last 4 weeks or at least somewhat relieved for each of the 4 weeks
  - Secondary Efficacy Endpoints: Symptoms were assessed daily and weekly via touch-tone telephone system
    - SGA of Abdominal Discomfort: patients were asked how "bothersome" the abdominal pain was over the last week
    - SGA of Bowel Habit: patients were asked how "bothersome" their constipation was over the past week
    - SGA of Satisfaction with Bowel Habit: patients were asked about their level of "satisfaction" with their bowel habit
      - Responder: "very satisfied" or "somewhat satisfied" at 50% of assessments
    - Intensity of Bloating: rated on a 7-point scale (0=none and 6=very severe")
    - Stool Frequency: # BM/28 days
    - Stool Consistency: rated on a 7-point scale (1=watery, 2=loose, 3=somewhat loose, 4=neither loose nor hard, 5=somewhat hard, 6=hard, 7=very hard).
    - Straining during bowel movement: Yes/No
    - Endpoint for daily diary scores: based on daily scores during last 28 days of treatment. If <28 days were available, all scores during the treatment period were used.
- **Inclusion Criteria**

  Before patients could be included in the study organic bowel disease was ruled out (by either colonoscopy or sigmoidoscopy with double-contrast barium enema) in patients > 50 years old,

performed after the appearance of symptoms and within the previous 5 years.
  - Women age ≥ 18 with at least 3 month duration of IBS (according to Rome I Criteria), characterized by lower abdominal pain/discomfort and symptoms of constipation (≥ 2 of the following: < 3BM/week, hard/lumpy stools and/or straining during a BM) at least 25% of the time which had not improved after at least 2 months of treatment with non-pharmacological treatments (high fiber diet, exercise, or bulking agents).
  - Patients were required to have at least mild abdominal pain (>1.5/7 during the baseline period).
- **Exclusion Criteria**
  - Significant diarrhea (loose or watery stools and/or > 3 BM/day associated with urgency > 25% of the days in preceding 3 months), structural abnormalities of the GI tract or diseases/conditions that affected bowel transit, or if there was evidence of a cathartic colon or a history of laxative, drug or alcohol abuse, pregnant or lactating women (women of child-bearing potential practiced a medically-approved method of contraception), concomitant use of any medication affecting GI motility and/or perception (same as Mueller-Lissner et al)
  - Patients were ***NOT*** excluded if they were on a stable dose of fiber or bulking agent for at least 3 months and if their treatment was maintained

Results

- Primary Efficacy Measure: SGA of Relief, assessed at ***endpoint***
  - Tegaserod produced a statistically significant greater response rate for SGA of Relief when compared with placebo (43.5% for tegaserod and 38.8% for placebo; P<0.003) when laxative users were considered non-responders. Without adjustment for laxative use, response rates were 48.3% and 41.7% for tegaserod and placebo, respectively (P<0.009)
- Primary Efficacy Measure: SGA of Relief, assessed ***monthly***

	Tegaserod 12 mg/d		**Placebo**	**NNT (95% CI)**
	Unadjusted Response Rate	P Value	Unadjusted Response Rate	
Month 1	40.5%	<0.001	26.2%	7.0 (5.3-10.4)
Month 2	47.2%	0.006	39.6%	13.3 (7.8-45.7)
Month 3	53%	0.026	47.1%	17.1 (8.8-387.2)

- Primary Efficacy Measure: SGA of Relief, assessed ***weekly***
  - There was a statistically significant difference in the percentage of patients either completely relieved, considerably relieved or somewhat relieved of IBS symptoms in the tegaserod group when compared with placebo.
  - Placebo response rate: At week one, 58% of tegaserod-treated patients and 40% of placebo-treated patients were at least "somewhat relieved." This 13% difference was still observed after 4 weeks of treatment. Over the 12-week treatment period, the tegaserod response rate increased to 67 and placebo increased to 61%.
- Secondary Efficacy Endpoints, ***improvements from baseline***
  - Tegaserod was associated with statistically significantly higher improvements from baseline when compared with placebo for the following: SGA of Abdominal Pain/Discomfort, SGA of Bowel Habit, and SGA of Satisfaction with Bowel Habit

Efficacy Variable	**Tegaserod 6mg BID**	**Placebo**	**P Value**
Mean change from baseline in SGA of abdominal pain or discomfort score (endpoint – baseline)	-1.01	-0.80	0.003
Mean change from baseline in SGA of bowel habit score (endpoint - baseline)	-1.30	-0.95	<0.001

- Secondary Efficacy Endpoints, assessed ***weekly***
  - The effects of tegaserod were statistically significantly greater than placebo at all weeks during the double-blind treatment period (P<0.05) except for weeks 7, 8, and 10.

- Secondary Efficacy Endpoints, assessed ***monthly***
  - Response rate for Satisfaction with Bowel Habit

SGA of Satisfaction with Bowel Habit	Tegaserod 6mg BID	Placebo	P Value
Month 1	56%	41.1%	< 0.001
Month 2	58.7%	50.1%	0.002
Month 3	60.4%	52.7%	0.007

- Secondary Efficacy Variables: daily gastrointestinal symptoms
  - At endpoint, tegaserod was associated with statistically significant differences with the following variables, when compared with placebo:
    - Bloating Scores ($p<0.05$)
    - # BM/28 days ($p<0.05$)
    - Stool Consistency Score ($p<0.0001$)
    - # Days with straining ($p<0.001$)
  - There was a statistically significant improvement in stool consistency when compared with placebo during the first week of double-blind treatment period. This difference remained statistically significant at the end of the double-blind treatment period ($p<0.05$)
  - A statistically significant decrease in days with straining was seen in tegaserod group when compared with placebo at months 1, 2, and 3 ($p<0.01$).
- Withdrawal of Treatment
  - A loss of effect was noted in both groups by a decline in responder rates in both groups seen during weeks 1-3. This effect stabilized in weeks 3-4.
  - Loss of effect was more pronounced with tegaserod than placebo during the first week.
  - There was no statistically significant difference between the two groups with respect to any efficacy variable during the withdrawal period and patients did not reach back to baseline symptoms by the end of the withdrawal period (continued to be better than baseline)
- Safety and Tolerability
  - All patients (in intention-to-treat analysis (n=1519) were included in safety analysis. Adverse events occurring in $\geq$ 5% of patients were reported:

	Placebo N=752		Tegaserod 6mg BID N=767	
	n	*%*	*n*	*%*
Total patients with adverse events	419	55.7	447	58.3
Headache	43	5.7	69	9.0
Nausea	35	4.7	52	4.9
Abdominal Pain	43	5.7	49	6.4
Diarrhea	22	2.9	49	6.4
Flatulence	30	4.0	44	5.7
Upper Respiratory Infection	48	6.4	27	3.5

  - The most common adverse effects observed in the tegaserod group were HA, nausea, and diarrhea. Upper respiratory infection was more common in placebo group.
  - There were no clinically significant changes in blood pressure, heart rate, clinical laboratory or ECG parameters in either group
  - Discontinuations due to adverse effects: Tegaserod (52 patients, 6.8%) was higher than placebo (36 patients, 4.8)
    - Number needed to harm (NNH) for discontinuation: 50
    - NNH for discontinuation due to diarrhea: 62.5 in tegaserod group; no patients discontinued due to diarrhea in placebo group
  - Specific Adverse Effects:
    - Diarrhea: (6.4% in tegaserod & 2.9% in placebo groups): mild and transient; none led to hospitalization, volume depletion or electrolyte disturbances
    - 7 (0.9%) patients in tegaserod group required abdominal/pelvic surgery (4 cholecystectomies, 1 appendectomy, 1 hiatal hernia, 1 hysterectomy) and 4 (0.5%) on placebo (2 hysterectomies, 1 cholecystectomy, and one lysis of adhesions). There was no

	causal relationship established between surgery and medication group. o All cholecystectomies were uncomplicated laparoscopic surgeries in patients with pre-existing symptoms. ▪ Serious Adverse Events: o Tegaserod Group: Coronary artery disease (day 12), anxiety (day 25), vertebral disc disorder (day 1). o Placebo Group: Seizures (days 32 & 35) ➢ Adverse Events Reported During Withdrawal Period: 174 patients reported adverse events 86/661 (13%) of tegaserod patients; 88/633 (14%) of placebo patients. Those adverse events occurring >1% are as follows: ▪ Sinusitis occurred in 8/661 (1.2%) and nausea 7/661 (1.1%) occurred in tegaserod-treated patients ▪ Abdominal pain occurred in 12/633 (1.9%) of placebo-treated patients
Conclusions	• This trial has confirmed the findings of other studies in that tegaserod 6mg BID was effective and well tolerated in the rapid relief of overall IBS symptoms and in the improvement of abdominal pain/discomfort, bloating and constipation in women • 1-2 weeks following discontinuation of therapy with tegaserod, there was no longer a difference when comparing tegaserod with placebo • Tegaserod is effective in the treatment IBS for a duration of at least 12 weeks
Critique	• **Limitations** ➢ Use of an electronic telephone system to record subjects' measurements led to a high drop out rate during the screening process ➢ There was no comparison using tegaserod 2mg BID ➢ A large percentage of patients were Caucasian ➢ The efficacy of tegaserod in the male IBS patient population was not assessed and data from females cannot be extrapolated to males ➢ The SGA of relief was used as primary efficacy endpoint; this is not a validated rating scale. Also, patients who were "somewhat relieved" were classified as full responders. It is difficult to draw meaningful conclusions about the value of this drug in treating patients with IBS based on this assessment.
Sponsorship	• **Novartis Pharmaceuticals**

Citation	**Fidelholtz J, Smith W, Rawls J, Shi Y, Zack A, Ruegg, Lefkowitz M. Safety and Tolerability of Tegaserod in Patients With Irritable Bowel Syndrome and Diarrhea Symptoms. Am J Gastroenterol 2002;97(5):1176-81.[15]**
Study Goals	To assess the safety and tolerability of two separate doses of tegaserod in patients with IBS and symptoms of diarrhea.
Methods	• **Study Design** ➢ Prospective, randomized, double-blind multicenter study ➢ Length of Study: 2 week placebo-free baseline period plus 8 week double-blind treatment period ➢ Patients were randomized to receive tegaserod 4mg/d, tegaserod 12mg/d or placebo. The doses were administered as BID just before morning and evening meals. ➢ Concomitant use of loperamide was allowed (ad max 8mg/d x NMT 2d) for bothersome diarrhea (4+ loose/watery stools/day with a sense of urgency for 3 or more days) ➢ Use of medications affecting the GI tract: same as Mueller-Lissner et. al. ➢ Daily symptom severity assessments were performed by patients: ❑ Severity of abdominal discomfort/pain using a 6 point scale ▪ 0=none, 1=very mild, 2=mild, 3=moderate, 4=severe, 5=very severe ❑ Severity of bloating using a 6 point scale (same as above) ❑ Number of bowel movements ❑ Stool consistency using a 7 point scale ▪ 1=watery, 2=loose, 3=somewhat loose, 4=neither loose nor hard, 5=somewhat hard, 6=hard, 7=very hard

<table>
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- **Data Analysis**
  - Intent-to-treat analyses were performed
  - Data analysis methods were not reported

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<tr><td>Criteria</td><td>

- **Inclusion criteria**
  - Diagnosis of IBS according to the Rome I Criteria
  - Presentation with continuous or recurrent symptoms
  - Symptom duration of at least 3 months
  - Symptoms include abdominal pain or discomfort relieved by defecation or associated with change in frequency of bowel movements or consistency of stools
  - At least 2 of the 3 were present: 3 or more bowel movements per day, loose or watery stools, or urgency >25% of the time.
  - Organic bowel disease was ruled out
- **Exclusion criteria**
  - Significant changes in bowel habits during the 3 months before the screening
  - Non-IBS conditions known to significantly affect GI motility and/or sensory perception
  - Pregnant and breast-feeding women

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<tr><td>Results</td><td>

- Baseline characteristics were significantly different for the following:
  - Patients were predominantly female (67%)
  - The tegaserod 4mg/d group contained a higher proportion of male patients (49%) than the 12mg/d and placebo groups (18% and 29%, respectively) (p=0.02)
  - The patients enrolled were mostly Caucasian (88%)
  - Mean weight was lower in 12mg/d group compared to 4mg/d and placebo groups (p=0.01)
  - The number of bowel movements per week was higher in placebo than other 2 groups (p=0.02)
  - The number of days with 4 or more bowel movements per day was higher in placebo than other groups (p=0.05)

- Adverse Events
  - Adverse events were reported by 81% of patients overall

<table>
<tr><th>Adverse Event</th><th colspan="2">Tegaserod 4mg/d n=35</th><th colspan="2">Tegaserod 12mg/d n=34</th><th>Placebo n=17</th></tr>
<tr><td></td><td>Incidence</td><td>P value</td><td>Incidence</td><td>P Value</td><td>Incidence</td></tr>
<tr><td>Diarrhea</td><td>48.6%</td><td>0.39</td><td>17.7%</td><td>0.18</td><td>35.3%</td></tr>
<tr><td>Abdominal Pain</td><td>31.4%</td><td>0.75</td><td>20.6%</td><td><0.99</td><td>23.5%</td></tr>
<tr><td>Headache</td><td>28.6%</td><td><0.99</td><td>20.6%</td><td><0.99</td><td>23.5%</td></tr>
<tr><td>Flatulence</td><td>20.0%</td><td>0.70</td><td>11.8%</td><td><0.99</td><td>11.8%</td></tr>
<tr><td>Fatigue</td><td>11.4%</td><td><0.99</td><td>2.9%</td><td><0.99</td><td>5.9%</td></tr>
</table>

- Concomitant Antidiarrheal Medication Use:

<table>
<tr><th>Loperamide Use</th><th colspan="2">Tegaserod 4mg/d n=35</th><th colspan="2">Tegaserod 12mg/d n=34</th><th>Placebo n=17</th></tr>
<tr><td></td><td>Incidence</td><td>P value</td><td>Incidence</td><td>P Value</td><td>Incidence</td></tr>
<tr><td>% Patients using antidiarrheal medication during double-blind period</td><td>31%</td><td>0.75</td><td>15%</td><td>0.46</td><td>24%</td></tr>
<tr><td>Mean number of days of antidiarrheal use</td><td>1.7</td><td>0.45</td><td>0.2</td><td>0.85</td><td>1.1</td></tr>
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Discontinuation

19 patients (22%) discontinued prematurely- all from the tegaserod groups

<table>
<tr><th>Treatment Group</th><th># patients discontinued</th><th># patients discontinued due to abdominal pain &/or diarrhea</th></tr>
<tr><td>Tegaserod 4mg/d (n=35)</td><td>6</td><td>3</td></tr>
<tr><td>Tegaserod 12mg/d (n=34)</td><td>5</td><td>2</td></tr>
</table>

ECG Evaluation: no consistent changes in ECG; 4 patients in the 12mg/d tegaserod group had nonspecific ST changes; they were not considered to be clinically relevant
Bowel Function:

Mean number of bowel movements and number of days patients experienced loose/watery stools increased from baseline in both tegaserod groups and not placebo. This occurred during the first few weeks of double-blind period and tended to decrease over time.
Mean stool consistency decreased in both tegaserod groups, but not the placebo group transiently during the first few weeks of treatment
Mean abdominal pain decreased in all 3 groups during the second half of the double-blind period

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<tr><td>Conclusions</td><td>

No significant safety problems were observed with the use of tegaserod in patients with diarrhea symptoms at doses shown to be effective in patients with constipation symptoms.
The results suggest that tegaserod may be used in patients with IBS and predominant symptoms of constipation who occasionally experience episodes of diarrhea as part of their course of disease.

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<tr><td>Critique</td><td>

Strengths

Safety of tegaserod in patients with diarrhea is a concern and may be of clinical utility in prescribing

Limitations

Tegaserod was tested in patients with diarrhea-predominant symptoms. This data may not extrapolate to patients with constipation-predominant symptoms who sometimes experience diarrhea.
Tegaserod administration occurred prior to meals. If taken less than 30 minutes prior to meals, the absorption, peak and toxicity may be decreased.
Small patient population with predominance of females and Caucasians
Dissimilar baseline characteristics
No statistical analyses were reported
A 6-point scale (rather than a 7-point scale) was used to assess severity of bloating and severity of abdominal pain/discomfort.

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<tr><td>Sponsorship</td><td>

Novartis pharmaceuticals funded this study

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</table>

Citation	**Tougas G, Snape Jr WJ, Otten MH, Earnest DL, Langaker KE, Pruitt RE, Pecher E, Nault B, Rojavin MA. Long-term safety of tegaserod in patients with constipation-predominant irritable bowel syndrome. Aliment Pharmacol Ther 2002; 16:1701-1708.[16]**
Study Goals	To determine long-term safety and tolerability of tegaserod in patients suffering from irritable bowel syndrome with constipation as the predominant symptom of altered bowel habits
Methods	• **Study Design** ➢ In this open label, unblinded trial, tegaserod was administered at either 2mg BID or 6mg BID doses during the 12 month treatment period ➢ Doses were administered within 30-60 minutes before morning and evening meals ➢ During the first 4 weeks, patients received 4mg daily and then either 4mg or 2 mg daily during the following months depending upon the therapeutic effect assessed during the visits at months 1, 2, 4, 6, 8,and 10. If the drug was poorly tolerated, a dose reduction from 12 mg to 4mg/d was allowed. However, once reduced, a subsequent dose increase back to 12mg/d was disallowed. ➢ The following rescue medications were allowed for relief of constipation: magnesium sulphate, lactulose, sodium sulphate, sodium picosulfate, polyethylene glycol or bisacodyl suppository. If there was inadequate relief overnight using one of the above medications, other laxatives, including enemas, could be used. ➢ Patients using chronic bulk-forming agents could continue to do so at the same dose throughout the duration of the study. ➢ Antidiarrheal medications (such as loperamide) were allowed ➢ Following completion of a 1 week screening period, patients were randomized into the study ➢ At months 1, 2, 4, 6, 8, 10, and 12, patients were scheduled for office visits, where the following took place: physical examination, monitoring of vital signs, and assessment of GI symptoms. ➢ ECG monitoring took place during the screening period and at months 2, 6, and 12 of the study ➢ Telephone monitoring (collection of information about GI-related symptoms and recording patients' comments) took place between office visits at months 3, 5, 7, 9, and 11. • **Data Analysis** ➢ During the 1 year treatment period, data was collected from 300 subjects ➢ Additional patients were enrolled to compensate for dropouts ➢ Methods of statistical analysis were not reported
Criteria	• **Safety Measures** ➢ All adverse events were recorded, including their severity and relationship to tegaserod and the influence on the course of the study ➢ The following parameters were monitored: hematology, blood chemistry, urinalysis, repeated pregnancy testing (all performed by central agency), vital sign recordings, and ECG monitoring (interpreted centrally by an independent reader) ➢ Definition of Adverse Event: any adverse change from the baseline condition occurring during the course of treatment, whether thought to be related to tegaserod or not ▪ Mild Adverse Event: barely noticeable to a patient; does not influence performance or functioning ▪ Moderate Adverse Event: Severe enough to cause discomfort; daily activity performance is affected ▪ Severe Adverse Event: severe discomfort, possibly resulting in cessation of therapy and requiring treatment for the symptom ▪ Serious Adverse Event: fatal or considered to be life-threatening; requiring prolonged hospitalization, caused permanent disability, led to cancer or congenital anomaly or resulted from study drug overdose. Serious adverse events were reported as such even if not strictly fitting the above criteria. • **Efficacy Measures** ➢ Assessed by SGA of GI symptoms; results not reported • **Inclusion criteria** ➢ Male and non-pregnant female outpatients between 18-70 years of age ➢ Patients suffering from irritable bowel syndrome defined by Rome I Criteria ➢ Females of child-bearing potential practiced an approved method of contraception and agreed continue it throughout the study

Exclusion criteria

- All patients underwent radiologic or endoscopic examination to rule out other causes of GI dysfunction
- Clinically relevant diarrhea as a component of the illness, diagnosed with other conditions that could affect GI motility, clinical evidence of significant cardiovascular, respiratory, renal, hepatic, or other disease which may interfere with the study
- Ingestion of concomitant medications prohibited by the study protocol (certain anti-arrhythmics, narcotics, and prokinetic agents)

Results

Patient Population

- 601 patients were enrolled at 35 treatment centers (Canada, Germany, France, Finland, Italy, Netherlands, UK, Norway, and USA)
- 579 patients entered the treatment phase of the study
- 12/579 patients were not included in safety and efficacy analysis due to lack of post baseline assessment; 567/579 patients were included in the analysis
- 138 (24%) patients received tegaserod in previous studies
- Of the 601 patients screened, 22 were not treated (10 withdrew consent, 9 did not fulfill entry criteria, 3 failed to return to clinic). Of the 579 patients treated, 138 were previously treated with tegaserod and 441 were de novo patients; 275 patients withdrew (48%, 72 with intervention ineffective, 65 adverse events, 61 withdrew consent, 49 lost to follow-up, 18 protocol violation, 10 other).

Baseline Characteristics: The study population consisted mainly of Middle-aged, Caucasian females with a history of chronic IBS.

Parameter	***All Treated Patients (n=579)***
Sex, n (%)	
Male	56 (9.7)
Female	523 (90.3)
Age (years) (mean ± s.d.)	44.2 ± 12.4
Race, n (%)	
Caucasian	538 (92.9)
Black	33 (5.7)
Asian	4 (0.7)
Other	4 (0.7)
Weight (kg) (mean ± s.d.)	68.6 ± 14.5
Median Duration of Symptoms (years)	6.4
Previously Treated, n (%)	138 (23.8)

Withdrawal from the Study

- Withdrawals due to adverse events were similar between those patients who previously received tegaserod than those who did not
- Discontinuations due to lack of efficacy were higher in those patients not receiving the drug before [62 patients (14.1%)] vs. 10 patients (7.2%) discontinuing who previously received the drug
- 52.5% of patients receiving treatment completed the planned 12 month treatment period

Reason For Discontinuation	**All Patients Entering the Treatment Phase, n (%)**	**Previous Tegaserod Exposure, n (%)**	**No Previous Tegaserod Exposure, n (%)**
Total Patients Discontinued	275 (100.0)	51 (100.0)	224 (100.0)
Lack of Efficacy	72 (26.2)	10 (19.6)	62 (27.7)
Adverse Event	65 (23.6)	11 (21.6)	54 (24.1)
Withdrawal of Consent	61 (22.2)	17 (33.3)	44 (19.6)
Failed to Return	49 (17.8)	9 (17.6)	40 (17.9)
Protocol Violation	18 (6.5)	0 (0.0)	18 (8.0)
Other	10 (3.6)	4 (7.8)	6 (2.7)

- **Dosage Adjustments**
  - The majority of patients had the dose increased to 12mg/d within the first 3 months of therapy
  - Downward titrations of tegaserod were infrequent; 82% of patients were receiving tegaserod 12mg/d at the end of the 12 month period
  - Exposure to tegaserod was a mean duration of 209.7 $\pm$ 122.01 days
- **Safety Assessments**
  - **Most Common Adverse Events:**

	N (%) all tegaserod treated patients			**N (%) possibly related to tegaserod**		
Adverse Event	**All N=567**	**Previous tegaserod exposure N=137**	**No previous tegaserod exposure (n=430)**	**All (N=567)**	**Previous tegaserod exposure (n=137)**	**No previous tegaserod exposure (n=430)**
Abdominal Pain	97 (17.1)	19 (13.9)	78 (18.1)	42 (7.4)	7 (5.1)	35 (8.1)
Back Pain	49 (8.6)	15 (11.0)	34 (7.9)	3 (0.5)	1 (0.7)	2 (0.5)
Diarrhea	83 (14.6)	21 (15.3)	62 (14.4)	57 (10.1)	17 (12.4)	40 (9.3)
Dyspepsia	41 (7.2)	9 (6.6)	32 (7.4)	12 (2.1)	4 (2.9)	8 (1.9)
Flatulence	43 (7.6)	9 (6.6)	34 (7.9)	31 (5.5)	7 (5.1)	24 (5.6)
Headache	167 (29.5)	35 (25.6)	132 (30.7)	47 (8.3)	8 (5.8)	39 (9.1)
Flu-like symptoms	34 (6.0)	6 (4.4)	28 (6.5)	1 (0.2)	0 (0)	1 (0.2)
Insomnia	29 (5.1)	5 (3.7)	24 (5.6)	8 (1.4)	0 (0)	8 (1.9)
Nausea	46 (8.1)	10 (7.3)	36 (8.4)	19 (3.4)	5 (3.7)	14 (3.3)
Pharyngitis	30 (5.3)	7 (5.1)	23 (5.4)	1 (0.2)	0 (0)	1 (0.2)
Rhinitis	39 (6.9)	14 (10.2)	25 (5.8)	0 (0.0)	0 (0)	0 (0)
Sinusitis	47 (8.3)	13 (9.5)	34 (7.9)	0 (0.0)	0 (0)	0 (0)
Upper Respiratory Infection	92 (16.2)	18 (13.1)	74 (17.2)	3 (0.5)	0 (0)	3 (0.7)

    - The majority of adverse events were gastrointestinal disturbances, affecting 46% of patients. The most common adverse events were: transient diarrhea (10.1%), HA (8.3%), abdominal pain (7.4%), and flatulence (5.5%)
    - When comparing previously exposed patients and de novo patients, the above adverse events were distributed equally between the 2 groups, with abdominal pain more frequent in de novo group.
    - Nausea, dyspepsia, and insomnia were equally reported by 1-3% of patients
  - Severe Adverse Events: 81 patients (14.3%) of patients had severe adverse events: abdominal pain, HA, diarrhea, constipation and flatulence. No deaths occurred during the study
  - Serious Adverse Events: 25 patients (4.4%) experienced serious adverse events. One report of severe abdominal pain occurred 199 days following initiation of therapy with 12mg/d of tegaserod (considered to be possibly drug related). This patient completed the full duration of treatment
    - 10 patients experienced > 1 serious adverse event during the study. All other serious adverse events were considered to be either unlikely to be related or unrelated to the tegaserod. These events included: abdominal pain in 4 patients (0.7%), chest pain and cholelithiasis in 2 patients (0.4%) each, and back pain, constipation, cystadenofibroma, depression, ovarian cyst and pelvic adhesion in one patient (0.2%) each.
  - Discontinuation due to adverse events
    - 65 patients discontinued (11.2% of all patients or 23.6% of discontinued patients) withdrew from the study due to adverse events- 6 for serious adverse events
    - Discontinuation due to diarrhea (3.5%) was the most common reason; discontinuation was not accompanied by dehydration, electrolyte imbalance, or need for hospitalization
    - Diarrhea was somewhat more frequent in the previously-treated group than the de novo group (5.1% vs. 3.0%).

Adverse Event	N (%) all tegaserod-treated patients		
	All Patients (n=567)	**Previous Tegaserod Exposure (n=137)**	**No Previous Tegaserod Exposure (n=430)**
Diarrhea	20 (3.5)	7 (5.1)	13 (3.0)
Abdominal Pain	16 (2.8)	3 (2.2)	13 (3.0)
Flatulence	15 (2.6)	3 (2.2)	12 (2.8)
Headache	6 (1.1)	0 (0)	6 (1.4)
Nausea	5 (0.9)	1 (0.7)	4 (0.9)
Constipation	3 (0.5)	0 (0)	3 (0.7)
Alopecia	2 (0.4)	0 (0)	2 (0.5)
Back Pain	2 (0.4)	1 (0.7)	1 (0.2)
Dizziness	2 (0.4)	0 (0)	2 (0.5)
Dyspepsia	2 (0.4)	1 (0.7)	1 (0.2)

- Laboratory Assessments
  - One patient was prematurely withdrawn on day 40 of tegaserod 12mg/d due to worsening of a pre-existing eosinophilia
  - The results of other laboratory evaluations were generally unremarkable and failed to reveal any specific pattern of abnormality associated with prolonged tegaserod administration
  - Laboratory abnormalities revealing presence of other diseases (such as diabetes) remained stable throughout the duration of the study.
- Vital Sign Assessments
  - A small number of patients had blood pressure decreases within clinically noticeable ranges (Systolic blood pressure (SBP) $\leq$ 90 + decrease $\geq$ 20 or < 75 mmHg; for diastolic blood pressure (DBP), either $\leq$ 50 + decrease $\geq$ 15 or < 40mmHg).
  - Treatment-emergent, lowered, sitting SBP and DBP was registered in 10 (1.8%) and 7 (1.2%) patients, respectively
  - One patient with known hypertension had a reported serious adverse event of severe hypertension (considered to be unrelated to therapy with tegaserod).
  - ECG evaluations failed to show any clinically relevant new or worsening abnormalities and no clinically relevant prolongation of QTc interval.

Conclusions

- Tegaserod within the range of 4-12mg/day was well-tolerated by constipation-predominant IBS patients during a 12-month period
- Previous exposure to tegaserod does not result in an imbalanced frequency of adverse events compared to tegaserod-naïve patients

Critique

- **Strengths**
  - Length of study
  - Fairly large patient population
  - Measurements were assessed fairly frequently
- **Limitations**
  - Patients previously enrolled in tegaserod studies made up a fairly large percentage of this population, thus decreasing the number of patients likely to experience significant/intolerable adverse events
  - The patient population is largely female and Caucasian
  - There was no comparison group, such as a gold standard or placebo group
  - Statistically analyses were not performed, making it unclear if statistically significant adverse events occurred
  - Efficacy parameters were not assessed so long-term efficacy not established

Sponsorship

- **Novartis Pharmaceuticals**

Citation Unpublished manufacturer data	**Protocol B351. A Randomized, double-blind, placebo-controlled, multicenter study to assess the safety and efficacy of ZELNORM at two dose levels and placebo in subjects with IBS with constipation.**[17]
Study Goals	To assess the safety and efficacy of Tegaserod at two separate doses in patients with IBS and constipation.
Methods	• **Study Design** ➢ Randomized, double-blind, placebo-controlled, double-dummy, parallel group, multicenter trial ➢ Length of study: 4 week pretreatment period followed by a 12 week double-blind period ➢ Patients were randomized to receive tegaserod 4mg/d, 12mg/d or placebo ➢ Primary Efficacy Endpoint: SGA of Relief, collected weekly ❑ Responders were defined as: ▪ Fulfilled criteria regarding laxative intake, treatment duration, and minimum number of efficacy measurements ▪ Completely relieved or considerably relieved assessments for at least 50% of the last 4 SGA of Relief available or somewhat relieved for the last 4 SGA of Relief available ➢ Secondary Efficacy Endpoints ❑ SGA of Abdominal Pain or Discomfort ❑ SGA of Bowel Habit ❑ SGA of satisfaction with bowel habit ❑ Daily diary efficacy ➢ Concomitant laxatives were allowed for rescue medication (bulk-forming laxatives, SSRIs, and TCAs) • **Data Analysis** ➢ Not available
Criteria	• **Patient Population** ➢ 1,093 patients enrolled, 799 of whom were randomized to 1 of the 3 treatment groups • **Inclusion Criteria** ➢ Men and women >12 years of age who satisfied Rome I Criteria for IBS with constipation for at least 3 months before study entry, other causes for GI symptoms were ruled out by endoscopic or radiologic procedures ➢ At least mild abdominal pain/discomfort after 4 week baseline period • **Exclusion Criteria** ➢ Patients with diarrhea as predominant symptom (defined by Rome I Criteria), structural abnormality of GI tract, planning to use medications which affect GI motility, history of drug/alcohol abuse, pregnancy or breastfeeding ➢ Use of medications affecting the GI tract: Same as Mueller-Lissner et al.
Results	• Baseline Measurements ➢ Mean visual analog scale (VAS) assessment was 63mm/100mm ➢ Patients were predominantly female (87%), mean age 43 years, mean 14-year history of IBS ➢ Mean number of days with significant abdominal pain/bloating was 24-25/28 in 3 treatment groups ➢ Percentage of patients using laxatives/cathartics was slightly higher in the placebo group compared to tegaserod 12mg/d group • Primary Efficacy Endpoint: SGA of Relief, assessed weekly ➢ Statistically significant difference in weekly percentage of patients “completely” or “considerably relieved” for SGA of Relief were observed between tegaserod 12mg/d group and placebo at weeks 1, 5, 6, 9, and 10.

- Primary Efficacy Endpoint: SGA of Relief at **Endpoint**

	Tegaserod 12mg/day n=267	**Placebo n=267**
Responder Rate	45.7%	33.3%
Treatment difference in responder rate*	12.4%	
P value	0.004	
Unadjusted responder rate	53.2%	38.9%
Treatment difference in unadjusted responder rate	14.7%	
P value	0.001	

** adjusted for missing SGAs, treatment duration, laxative use*

  - Monthly unadjusted responder rate for the SGA of Relief for tegaserod was higher than placebo consistently over the 3 month period ($p<0.05$ at months 1 and 2)

- Secondary Efficacy Endpoints

  - Responder rate for SGA of abdominal pain or discomfort at endpoint

	Tegaserod 12mg/day n=267	**Placebo n=267**
Adjusted Responder Rate*	25.1%	18.7%
Difference in Response Rate	6.4%	
P Value	0.075	

*Adjusted for missing SGAs, treatment duration, laxative use

  - Monthly Unadjusted Responder rate for SGA of abdominal pain or discomfort (Reported as % Response unadjusted, whereby significant is defined as 'at least mild.'

	Tegaserod 12mg/day N=267	**Placebo n=267**	**Statistically Significant?**
Month 1	20	14	No
Month 2	27	24	No
Month 3	32	24	Yes
Endpoint	29	21	Yes

  - Summary of Secondary Efficacy Variables at Endpoint

	Tegaserod 12mg/day n=267		**Placebo n=267**
Secondary Efficacy Endpoint	%	P Value	%
Mean % change from baseline in # days with significant abdominal pain/discomfort (≥2 points/6)	-16.9	0.017	3.9
Mean % change from baseline in # days with significant bloating	-15.1	0.006	-5.6
Responder rate for SGA of bowel habit	24.7	0.218	20.2
Mean % change from baseline in # of days without bowel movements	-31.2	0.002	-21.4
Mean % change from baseline in # bowel movements	69.3	<0.001	44.8
Mean % of days with hard/very hard stool	11.3	0.003	18.9

  - Weekly number of bowel movements: An increase in weekly number of bowel movements was observed in the first week of double-blind treatment. This decreased thereafter, but remained higher than placebo throughout the rest of the study.

Conclusions

- Statistical significance was achieved in IBS symptom improvement of abdominal pain or discomfort, abdominal bloating and bowel habits (stool frequency and consistency) in the 12mg tegaserod group compared to placebo

	• The primary and secondary endpoints showed trends for a treatment effect compared with placebo.
Critique	• **Strengths** ➢ Large patient population • **Limitations** ➢ Data unpublished and incomplete information ➢ SGA of Relief used as primary endpoint ➢ 4mg/day group data was not reported ➢ Predominantly female patient population ➢ Time of administration with regard to meals is not reported. Absorption may be affected, which may result in changes in Cmax and thus efficacy.
Sponsorship	• Not reported

Citation Unpublished manufacturer data	**ZAP (Zelmac in Asia Pacific) Study. A Randomized, multicenter, double-blind, placebo-controlled, parallel-group, fixed-dose study to evaluate the efficacy, safety and tolerability of ZELNORM in IBS patients with non-diarrhea.[18]**
Study Goals	• To determine the efficacy of ZELNORM in a non-diarrhea IBS population. • To assess safety and tolerability of tegaserod. • To assess the use of rescue medication in patients on tegaserod.
Methods	• **Study Design** ➢ Double-blind, placebo-controlled, double-dummy, parallel group trial ➢ Patients were randomized to receive tegaserod 6mg BID or placebo ➢ 2-week placebo-free baseline period followed by 12 weeks of treatment and a 4-week withdrawal period (no medication) ➢ Concomitant medications were allowed for rescue only (bulk-forming laxatives) ➢ Tegaserod was administered within 30 minutes of a meal • **Data Analysis** ➢ Primary Efficacy Endpoint, assessed weekly ❑ "*Over the past week do you consider that you have had satisfactory relief from your IBS symptoms? Yes/No* ➢ Secondary Efficacy Endpoints ❑ Primary Analysis: short-term relief; overall satisfactory relief from IBS over first 4 weeks of treatment ❑ Secondary Analysis: long-term relief; overall satisfactory relief from IBS over 12 weeks of treatment ➢ All testing was 2-sided and α=0.05

Criteria

- **Patient Population**
  - 670 patients were enrolled in the study- 520 were randomized to receive tegaserod 12mg/d or placebo.
  - Males and females 18-65 years of age
  - Patients were ruled out for gastric disease in last 5 years
  - IBS with non-diarrhea (according to Rome II criteria) was confirmed during baseline
  - Ethnicity: 33% Chinese, 27% Korean, 16% Caucasian, 24% other
  - Laxatives were only allowed for rescue purposes

- **Inclusion Criteria**
  - Men and women ages 18-65 who satisfied Rome II Criteria for IBS (excluding those with diarrhea as predominant symptom), during baseline period, patients had to have < 3 bowel movements/week and one defecation of hard/very hard stools and/or one defecation/attempted defecation connected with straining, patients considered themselves as having unsatisfactory relief of IBS at baseline, other causes for GI symptoms were ruled out by endoscopic or radiologic procedures.

- **Exclusion Criteria**
  - Patients with diarrhea as predominant symptom (defined by Rome II Criteria) during baseline period, laxative-dependence, untreated lactose malabsorption, structural abnormality of GI tract, planning on using medications which affect GI absorption, pregnancy or breastfeeding
  - Patients meeting Rome II criteria for diarrhea-predominant IBS
  - Patients meeting the following criteria:
    2 or more of the following: >3 BM/day, loose (mush) or watery stools, urgency AND one of the following: <3 BM/week hard/lumpy stools, straining during a BM.
  - Medications affecting the GI tract: Same as Mueller-Lissner et al.

Results

- Baseline characteristics
  - The mean number of days with significant abdominal pain or discomfort and with significant bloating was 15/28 for each of the variables at endpoint.
  - Patient population by ethnicity and gender:

Ethnicity	***Percentage of Patient Population***
Chinese	34%
Korean	27%
Thai	12%
Caucasian	16%
Other Asian	10%
Other	0.8%
Gender	***Percentage of Patient Population***
Male	12%
Female	88%

  - Mean patient age was 35.9 yrs and mean duration of IBS symptoms was 91.4 months

- Primary Efficacy Measure
  - The proportion of patients with satisfactory relief increased above pretreatment values in both treatment groups starting week 1 (50.8% in tegaserod 12mg/d group and 28.3% of patients in placebo group).
    - This increase was observed from weeks 1-12.
    - During the withdrawal period, the percentage of patients with satisfactory relief was smaller in both groups compared to treatment period, but remained greater in the tegaserod 12mg/d group than placebo.

- Statistical analyses of the overall assessment of satisfactory relief from IBS symptoms were statistically significant for Weeks 1-4 and Weeks 1-12.

Period	% Gain in weekly therapeutic effect (range)	Odds Ratio (95% CI)	P Value
Weeks 1-4	19-24	2.57 (1.86; 3.56)	<0.0001
Weeks 1-12	13-24	2.35 (1.77; 3.13)	<0.0001

- Secondary Efficacy Variables
  - Percent reductions from baseline in significant abdominal pain or discomfort and significant bloating were statistically significantly greater in Tegaserod 12mg/d group compared with placebo at the last 28 days of treatment, but not during weeks 1-4
  - Percent reductions from baseline in the occurrence of no bowel movements and hard/lumpy stools were statistically significantly greater in the Tegaserod 12mg/d group compared with placebo during weeks 1-4, but not during the last 28 days of treatment.
  - Summary of Secondary Endpoints derived from daily diary data

Weeks 1-4			
	Tegaserod 12mg/d	Placebo	P value
Mean Percent Change:			
Significant abdominal pain & discomfort	-30.6	-29.3	0.1822
Significant bloating	-30.8	-20.6	0.0680
No bowel movements	-37.5	-17.5	**<0.0001**
> 3 bowel movements	-48.0	-78.6	0.7081
Hard or lumpy stools	-69.4	-40.0	**<0.0001**
Normal Stools	10.3	6.3	0.9929
Urgency	-6.0	-1.2	0.6018
Straining	18.2	7.1	0.3504
Sensation of incomplete evacuation	11.1	0.0	0.6116
Mean absolute change:			
Significant abdominal pain & discomfort	-4.2	-2.8	0.1029
Significant bloating	-3.9	-2.4	0.0825
No bowel movements	-4.5	-2.8	**0.0002**
> 3 bowel movements	0.3	0.1	0.1933
Hard or lumpy stools	-6.6	-2.6	0.6257
Normal Stools	3.2	2.6	0.6257
Urgency	-2.0	-0.7	0.2828
Straining	4.6	2.8	**0.0234**
Sensation of incomplete evacuation	2.9	1.5	0.0754

Last 28 days of Treatment			
	Tegaserod 12mg/d	Placebo	P value
Mean Percent Change:			
Significant abdominal pain & discomfort	-75.0	-58.1	**0.0005**
Significant bloating	-61.5	-43.9	**0.0079**
No bowel movements	-34.5	-19.6	0.1531
> 3 bowel movements	-60.7	---	0.3434
Hard or lumpy stools	-75.0	-67.4	0.2346
Normal Stools	14.3	16.7	0.4047
Urgency	0.0	0.0	0.5093
Straining	23.4	16.1	0.8074
Sensation of incomplete evacuation	8.3	3.4	0.7403
Mean absolute change:			
Significant abdominal pain & discomfort	-7.4	-5.7	**0.0134**
Significant bloating	-6.1	-4.7	0.2624
No bowel movements	-4.2	-3.8	0.4018
> 3 bowel movements	0.1	-0.1	0.4778
Hard or lumpy stools	-6.8	-4.2	**0.0200**
Normal Stools	5.5	4.4	0.8902
Urgency	-0.7	0.0	0.9790
Straining	5.9	5.0	0.2172
Sensation of incomplete evacuation	3.9	2.6	0.2877

Conclusions	• Tegaserod is an effective therapy, safe and well tolerated, for the treatment of IBS with non-diarrhea, with a sustained effect over 12 weeks
Critique	• **Strengths** ➢ Patient population consists of more broad ethnicity than other studies • **Limitations** ➢ Statistical analyses not reported and incomplete unpublished data ➢ Non-validated single question used for primary efficacy endpoint ➢ Use of a binary endpoint (yes/no) for primary efficacy variable may explain why this data is more robust than in other studies ➢ Chinese patient population predominant
Sponsorship	• Not reported

Citation	**Farup PG, Hovenak N, Wetterhus S, Lange OJ, Hovde O, Trondstad R. The Symptomatic Effect of Cisapride in Patients with Irritable Bowel Syndrome and Constipation. Scan J Gastroenterol 1998;3:128-31.[19]**
Study Goals	• To evaluate the symptomatic effect of cisapride compared with placebo in patients with IBS and constipation ➢ Primary Goal ▪ To compare the effect of cisapride with placebo based in the patients global rating scale for bowel disease ➢ Secondary Goals ▪ To compare the effect of cisapride with placebo on the following o Patients' score for each IBS symptom and general well-being o The investigators' global evaluation of effect o Safety
Methods	• **Study Design** ➢ Randomized, double-blind, placebo-controlled, parallel-group study ➢ Normal findings of colonoscopy or double-contrast radiologic examination obtained during a symptomatic period within 6 months prior to the study in patients > 40 years old. ➢ Patients were randomized to receive cisapride 5mg or placebo TID for 12 weeks with follow-up after 4, 8, and 12 weeks. ➢ In patients with improvement after 4 weeks, the dose could be doubled (cisapride 10mg TID) ➢ In patients without improvement, the dose remained the same for the duration of the trial. • **Data Analysis** ➢ IBS symptoms were rated on a 100mm visual analog scale (VAS), with 0=best, 100=worse for abdominal pain, stool frequency, stool consistency, difficulty in stool passage, urge to defecate, but unable to do so, feeling of incomplete evacuation, bloating (distention/windiness), global rating of bowel disease, general well-being (quality of life). ➢ Investigators rated the overall therapeutic effect as: excellent, good, moderate, or bad. Investigators also noted side effects. ➢ Intention-to-treat analysis was performed. ➢ Unless otherwise indicated, all values are expressed as median values with range ➢ To evaluate comparisons between groups: Fisher's Exact, Chi-Square and Mann-Whitney U-tests were performed. ➢ All tests were two-tailed ➢ Significance was defined as $p<0.05$
Criteria	• **Inclusion criteria** ➢ Continuous or recurrent symptoms for more than 6 months, with symptoms at least 3 times a week, and without favorable or long-lasting effect of previous therapies ➢ Constipation Variation of IBS in accordance with Rome Criteria ▪ Abdominal pain or defecation associated with a change in frequency or consistency of stool, constipation (at least 2 of the following: defecation <3 days/week, hard stools, abdominal bloating or feeling of abdominal distention) • **Exclusion criteria** ➢ Diarrhea or alternating stool pattern without constipation ➢ Doubtful compliance ➢ Proven or clinically suspected disorders that might interfere with symptom evaluation ➢ Significant abnormalities in blood chemistry or hematology ➢ Previous gastrointestinal surgery (except for cholecystectomy and appendectomy) ➢ Pregnancy or lactation ➢ Patients receiving drugs that affect GI motility ➢ Patients placed on a fiber-rich diet during the past 2 months ➢ Patients receiving other drug therapy for IBS or constipation (except laxatives, which were allowed if patient did not pass stools for $\geq$ 3 consecutive days
Results	• Baseline characteristics were similar except for the difference in age of diagnosis between the 2 groups: ➢ Cisapride 26 (4-48) versus placebo 35 (17-50) ($p<0.05$) • 62/70 patients were available for analysis after 12 weeks of treatment

	•

Reason for Dropout	Cisapride	Placebo
Adverse Events	3	0
Insufficient Response	1	1
Lost to Follow-up	1	1
Pregnancy Plans	0	1

- The dose was doubled after 4 weeks in 17 and 23 patients in the cisapride and placebo groups, respectively.
- Patients' Assessments of Symptoms were recorded at start and after 12 weeks of treatment. Measurements were based on VAS 90=best, 100=worst). Values are expressed as standard error of the mean (SEM). There were no statistically significant differences between treatment groups for any of the efficacy groups for any of the efficacy variables.

	Start			
	Cisapride n=33	Placebo n=37	Cisapride n=28	Placebo n=34
Primary Efficacy Variable				
Global Rating of Bowel Symptoms	73 (2.8)	7.1 (2.7)	47 (5.0)	41 (3.8)
			Difference 6 mm 95% CI 6,18 (not significant)	
Secondary Efficacy Variable				
Abdominal Pain	55 (3.4)	55 (4.2)	32 (4.9)	27 (3.8)
Frequency of stool passage	83 (3.1)	80 (2.1)	59 (4.5)	58 (2.7)
Consistency of Stool	87 (2.0)	82 (2.3)	62 (3.9)	61 (2.3)
Difficulty of stool passage	86 (2.3)	82 (2.1)	55.5 (5.4)	56 (3.7)
Need to defecate	42 (4.3)	48 (3.6)	51 (3.4)	53 (2.0)
Feeling of incomplete evacuation	69 (4.4)	64 (4.0)	52 (5.2)	58 (4.3)
Bloating	71 (3.1)	66 (3.7)	48 (5.2)	39 (4.4)
General well-being	49 (4.4)	44 (3.9)	31 (3.9)	29 (3.8)

  - Investigators' assessment of overall therapeutic effect is good or excellent in 11 patients (39.2%) in the cisapride group and in 20 patients (58.8%) in placebo group. The difference in favor of placebo was 19.5% (95% CI 5,44)
  - There were no reports of serious adverse events or clinically significant minor adverse events, vital signs or laboratory variables.

Conclusions	• This trial seems to exclude the possibility that 15-30mg of cisapride/day has a clinically significant effect in patients with IBS and constipation during a 12 week period.
Critique	• **Strengths** ➢ Diagnosis was based on Rome Criteria ➢ Baseline characteristics were generally similar • **Limitations** ➢ Small treatment groups may result in type II error ➢ Patients in cisapride group had a lower age of IBS diagnosis, implying longer disease duration and severity
Sponsorship	➢ Financial and administrative support was provided by Janssen-Cilag

Citation	**Schutze K, Brandstatter G, Dragosics B, Judmaier G, Hentschel E. Double-blind study of the effect of cisapride on constipation and abdominal discomfort as components of the irritable bowel syndrome. Aliment Pharmacol Ther 1997;11:387-94.[20]**
Study Goals	To assess the effects of a prokinetic drug on the symptoms of constipation-predominant irritable syndrome.
Methods	• **Study Design** ➢ Double-blind, placebo-controlled, ➢ Patients were randomized to receive either cisapride 5mg TID or matching placebo for 12 weeks ➢ Patients showing improvement in visual analog scale (VAS) for bowel disease after 4 weeks, treatment was continued at the 5mg TID dose. If improvement did not occur after 4 weeks, the dose could be doubled to 10mg TID. If the dose was increased after 4 weeks, the dose remained the same for the duration of the trial. ➢ The following medications were disallowed during the study: anticholinergics, major neuroleptics, cholinergics, antispasmodics, antidiarrheals, or any drug affecting GI motility. ➢ Laxatives were allowed if stool passage did not occur for ≥ 3 consecutive days ▪ Laxative use was recorded by patients in the patients' daily diaries for the duration of the study ➢ Patient visits occurred at the time of selection and after 4, 8, and 12 weeks ➢ Patients were instructed to maintain a consistent diet throughout the study period ➢ The Kruis questionnaire was administered on occasion at the investigators' selection visit; this was performed to determine the compatibility between the 2 groups • **Data Analysis** ➢ 42 patients/group were required assuming a response rate of 35% in placebo group and 65% in cisapride group to detect a difference at α=0.05 (two-tailed) and 80% power. ➢ Intention to treat analysis was performed on primary efficacy measures ➢ Comparisons between groups for the visual analog scale (VAS) data (see below) were done using Wilcoxon-Mann-Whitney U-test ➢ Chi-Square tests were used for categorical variables ➢ VAS comparisons within the groups were performed using Friedman test and multiple comparisons were made using Wilcoxon and Wilcox tests ➢ P<0.05 indicated statistical significance ➢ Hypothesis testing was performed only for primary efficacy measures between groups ➢ Other p values and comparisons were regarded as descriptive and not statistical hypotheses ***Investigators' Assessments*** ➢ Primary Efficacy Measure: Target and associated symptom assessments at each visit. ▪ Target Symptoms: abdominal pain, constipation (including frequency, consistency, stool and mucus passage), and abdominal bloating or distention ▪ Associated Symptoms: o Upper GI symptoms: eructation/belching, heartburn, postprandial nausea or vomiting, postprandial epigastric bloating, epigastric pain/bloating o Other Symptoms: nervousness, anxiety, tenseness, feeling depressed ▪ Severity rated as 3=severe, 2=moderate, 1=mild, or 0=absent ▪ Frequency rated as 3=almost continuously, 2=every day, 1=occasionally, 0=never ▪ Localization and form of pain (nagging, constant, dull, diffuse) were recorded in case report format at entry visit ➢ Secondary Efficacy Measure ▪ Overall therapeutic effect (# patients with good/excellent response) of the drug, abdominal pain, constipation and bloating; assessed by investigator at each visit. o Effect was rated as: excellent (complete remission of symptoms), good (significant remission of symptoms), moderate (partial remission of symptoms, or bad (no change or worsening symptoms) o At the end of treatment, comparisons between treatment groups were made as: much better, better, equivalent, or worse. ***Patients' Assessments*** ➢ Primary Efficacy Measure: Visual analog scale (VAS) for global rating of bowel disease; assessed at each visit

<table>
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Patients were to mark a horizontal line 10 cm long between 0 (as good as possible) and 10 (as bad as possible)

➢ Secondary Efficacy Measures

VAS for the following: general well-being, stool passage frequency, abdominal pain, stool consistency, difficulty in stool passage, need to defecate (strength the call to stool), feeling of incomplete evacuation & bloating
Daily diary of bowel habits (frequency & consistency), abdominal pain & bloating throughout entire treatment period
Documentation of laxative use and intake of study drug

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<tr><td>Criteria</td><td>
• Inclusion Criteria
➢ Male and female outpatients ages 18-75
➢ Normal rectosigmoidoscopy and double-contrast radiographic exam of colon
➢ Normal biochemical and hematological parameters
➢ Normal thyroid function
➢ Negative stool exam for occult blood
➢ Constipation-predominant IBS according to Rome Criteria and symptoms were to occur ≥ 3 times/week
▪ Abdominal pain, relieved with defecation, or associated with a change in frequency or consistency of stool
▪ Constipation (fulfilling at least 2 of the following criteria):
o Decreased stool frequency (<3 days/week)
o Altered stool passage (straining or urgency, feeling of incomplete evacuation)
o Passage of mucus
▪ Abdominal bloating or feeling of abdominal distention
➢ All previous therapies failed to show a favorable or sustained response
• Exclusion Criteria
➢ Diarrhea or alternating stool pattern (diarrhea/constipation)
➢ Low abdominal pain without constipation
➢ Intake of drugs causing constipation or drugs affecting colonic motility prior to study
➢ Pregnancy or lactation
➢ Alcoholism
➢ Heavy smoking, defined as >40 cigarettes/day
➢ Terminal disease
➢ Severe cardiovascular, pulmonary, hepatic, nephrologic, neurologic, or psychiatric disorders, or AIDS
➢ History of GI surgery, except cholecystectomy or appendectomy
➢ Cholelithiasis, pancreatitis, liver disease, thyroid gland disease, diverticulitis, Crohn's disease, ulcerative colitis, amyloidosis, prophyria, malignancy, severe dehydration, gynecologic disorders, significant weight loss (>5 kg within past 6 months), bleeding or occult blood loss, significant blood chemistry or hematology abnormalities, doubtful compliance
</td></tr>
<tr><td>Results</td><td>
• Baseline characteristics were similar
• 96 patients were enrolled in the study (48 in each treatment group)
• Dropouts
<table>
<tr><th>Reason</th><th>Cisapride n=48</th><th>Placebo n=48</th></tr>
<tr><td>Adverse Events</td><td>1</td><td>2</td></tr>
<tr><td>Insufficient Response</td><td>2</td><td>0</td></tr>
<tr><td>Withdrawal of consent</td><td>1</td><td>0</td></tr>
<tr><td>Lost to follow-up</td><td>1</td><td>1</td></tr>
<tr><td>Patient moved</td><td>0</td><td>1</td></tr>
</table>
• 13 patients in cisapride group and 14 patients in placebo group required dose adjustments.
• Investigators' Assessments
</td></tr>
</table>

- Primary Efficacy Measure: There was no statistically significant difference in any of the improvement parameters
- Secondary Efficacy Measure: There was no statistically significant difference in results between the two groups

Primary Efficacy Measure	**Start**		**Week 12***		**End-point[$]**	
	Cisapride n=48	Placebo n=48	Cisapride n=48	Placebo n=48	Cisapride n=48	Placebo n=48
Target Symptoms						
# (%) patients without:						
Abdominal pain	0 (0)	0 (0)	15 (36)	14 (32)	15 (31)	15 (31)
Constipation	0 (0)	0 (0)	27 (64)	26 (59)	27 (56)	28 (58)
Bloating	0 (0)	0 (0)	13 (31)	9 (21)	13 (27)	9 (19)
Associated Symptoms						
# (%) patients without						
Eructation/ belching	36 (75)	35 (73)	39 (93)	40 (91)	44 (92)	43 (90)
Heartburn	42 (88)	39 (93)	41 (98)	43 (98)	47 (98)	46 (96)
Postprandial nausea/vomiting	42 (88)	43 (90)	39 (93)	42 (96)	44 (92)	45 (94)
Postprandial epigastric bloating	30 (36)	38 (79)	40 (95)	39 (89)	46 (96)	43 (90)
Epigastric pain	36 (75)	44 (92)	38 (91)	43 (98)	43 (90)	46 (96)
Other symptoms:						
# (%) patients without:						
Nervousness	24 (50)	23 (48)	26 (62)	29 (60)	29 (60)	31 (65)
Anxiety	38 (79)	36 (75)	32 (76)	36 (75)	36 (75)	42 (88)
Tenseness	33 (69)	36 (75)	36 (86)	41 (86)	41 (85)	42 (88)
Feeling Depressed	32 (67)	41 (85)	28 (67)	33 (69)	33 (69)	41 (85)

** indicates efficacy analysis parameter*
[$] indicates intention-to-treat analysis parameter

- Patients' Assessments
  - Primary Efficacy Measure: There was no statistically significant difference in VAS scores between the cisapride and placebo groups for global rating of bowel disease
  - Secondary Measures: There was no statistically significant difference in score improvements between treatment groups using intention-to-treat analysis. Using efficacy analysis, there was no statistically significant difference in score improvements between treatment groups except for difficulty in stool passage. There was a statistically significant improvement in stool passage in cisapride compared to placebo groups ($p<0.05$).

	Start		Week 12*		End-point$	
VAS of…	Cisapride n=48	Placebo n=48	Cisapride n=48	Placebo n=48	Cisapride n=48	Placebo n=48
Global rating of bowel disease	66.3	68.8	36.9	42.5	41.1	43.2
General well-being	36.2	34.2	64.4	58.4	60.6	57.1
Frequency of stool passage	29.2	26.4	49.6	50.2	49.0	49.1
Abdominal Pain	56.8	58.5	30.7	37.5	35.0	38.4
Consistency of Stools	71.4	75.4	52.0	55.1	52.8	56.3
Difficulty of stool passage	64.9	69.7	38.6	47.2	41.9	47.6
Need to defecate	49.6	47.4	45.2	45.2	47.4	45.6
Feeling of incomplete evacuation	64.8	62.8	39.7	46.4	43.6	47.6
Bloating	68.4	69.8	41.4	48.9	46.1	49.3

** indicates efficacy analysis parameter*
$ indicates intention-to-treat analysis parameter

- Diary Cards: No statistically significant differences were noted for the following parameters when comparing cisapride and placebo groups.

	Start		Week 12*		End-point$	
	Cisapride n=48	Placebo n=48	Cisapride n=48	Placebo n=48	Cisapride n=48	Placebo n=48
# days with no defection	4.0	4.2	1.8	1.8	1.7	2.0
# days with hard stools	2.3	2.3	1.3	1.8	1.6	1.8
# days with normal stools	0.7	0.6	3.6	3.0	3.3	2.9
# days with diarrhea	0.0	0.0	0.2	0.4	0.3	0.3
# days with alternating diarrhea & constipation	0.0	0.0	0.0	0.0	0.0	0.0
# days with normal stools in % of days with stools	19.3	13.1	67.5	53.1	61.0	52.8
# days of laxative use	0.3	0.4	0.3	0.3	0.2	0.0
Perception of normal bowel habit, n (%)	0 (0)	0 (0)	27 (64.3)	27 (61.4)	27 (56.3)	28 (58.3)
# patients with dose adjustment (%), not only at week 4	---	---	13 (27.1)	14 (29.2)	---	---

** indicates efficacy analysis parameter*
$ indicates intention-to-treat analysis parameter

- Adverse Events
  - Cisapride Group: 4 patients complained of nausea & vomiting- 1 discontinued due to the adverse event
  - Placebo Group: diarrhea occurred in 1 patient; 2 patients withdrew due to vomiting

Conclusions

- Results of the study suggest a lack of effect on abdominal pain and discomfort when comparing cisapride and placebo on constipation and abdominal discomfort associated with IBS.
- Cisapride may be of use in improving difficulty in stool passage associated in IBS patients.

Critique	• **Strengths** ➢ Rome Criteria were used for diagnosis ➢ Baseline characteristics were similar between the 2 groups • **Limitations** ➢ 4- point scales (rather than 7 point scales) were used to measure efficacy. ➢ High proportion (80%) of female patients were included in the study
Sponsorship	• Not reported

Acquisition Costs

Drug	Dose	Cost/Day/patient ($)	Cost/month/patient ($)*
Tegaserod	6mg BID	$3	$90
Tegaserod	2mg BID	$3	$90
Tegaserod	6mg ½ tab BID	$1.50	$45

** Only indicated for duration of 12 weeks*

Conclusions

The goals of therapy in the treatment of irritable bowel syndrome target alleviation of symptoms and quality of life improvement, rather than eradication of disease. Conventional irritable bowel syndrome treatment targets management of individual symptoms, such as abdominal pain, constipation, and diarrhea, but lacks the ability to treat the cluster of symptoms experienced by the patient.[9] Fiber provides relief of constipation by decreasing intracolonic pressure and thus decreasing abdominal pain, but increases abdominal bloating and flatulence. Osmotic laxatives have also been used to treat IBS-related constipation, but provide little relief of other symptoms. TCAs have not been proven useful in patients with constipation and IBS and there is a lack of data on the use of SSRIs in this patient population.[3] Clinical studies involving cisapride fail to demonstrate efficacy in the treatment of constipation-predominant IBS despite its prokinetic effect. Efficacy trials favorably support the use of tegaserod in women with constipation-predominant IBS. However, results in females cannot necessarily be extrapolated to male patients with IBS. As a whole, the data show improvement in global symptom assessment scores (SGA of Relief). Correlation of SGA of Relief with other clinical outcomes (such as decreased utilization of health care resources) was not reported in such studies.

Fidelholtz et al concluded that no significant safety problems were observed with tegaserod in patients with IBS and diarrhea symptoms. These results suggest that tegaserod may be used in patients with constipation-predominant IBS who occasionally experience episodes of diarrhea as part of their course of disease. Conversely, the dose was administered just before meals, likely leading to decreased absorption, Cmax, and toxicity. Tougas et al concluded that tegaserod is safe to administer over a 12 month period, however, statistical analyses were not performed and there was no comparison of the study medication with either another medication or placebo. Consistency in common adverse effects in tegaserod clinical trials indicate diarrhea as the most common side effect. Other safety concerns lie in the incidence of abdominal surgery and cholecystectomy. Serotonergic agents, such as cisapride and alosetron have been removed from the market due to safety concerns and even death. Neither Tougas et al nor Fidelholtz et al have shown significant ECG changes (as seen with Cisapride) or reports of ischemic colitis (as seen with Alosetron). Cholecystectomy and increased abdominal surgery has been reported, although follow-up studies have shown no significant difference between tegaserod and placebo.

Recommendations

Diet modification and the use of bran, laxatives, and antispasmodics (if indicated) should be considered as first line therapy in all patients with IBS and constipation.

In women with intractable or resistant disease who fail first line therapy, have no contraindications to the drug, and require short-term control of IBS symptoms, Tegaserod 6mg BID may be administered for 4-6 weeks. If symptom improvement is noted, the drug may be administered for an additional 4-6 weeks. In those patients without symptom improvement after the first 4-6 weeks of treatment, the drug should be discontinued. Patients should initially receive only a 4-6 week supply of medication to ensure efficacy before continuing therapy for an additional 4-6 weeks.

As tegaserod has not been proven effective for male patients with constipation-predominant IBS, the drug should not be administered to this patient population unless potential benefit clearly outweighs risk.

Studies have not been conducted to assess efficacy of tegaserod beyond twelve weeks and has not been evaluated by the Federal Food and Drug Administration. Until future studies provide long-term efficacy data, providers must demonstrate that benefits of using tegaserod beyond 12 weeks clearly outweigh potential risks.

Further data is necessary to support the use of tegaserod in patients with alternating constipation and diarrhea. Administration of tegaserod in this patient population should be limited to those patients with rare instances of diarrhea and intractable, resistant disease in patients not responding to first line therapy. The use of tegaserod in this patient population should be carefully evaluated by risk vs. benefit analysis and patients fitting such criteria should be closely evaluated by providers for exacerbation of diarrhea and other IBS symptoms.

Recommended National Formulary Status

Tegaserod should remain non-formulary. Individual VISNs should not add this drug to their formularies. Should data on long-term efficacy and efficacy in the male population become available, this medication should be re-reviewed and new data considered.

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Date: January 29, 2003