

National PBM Monograph  
Addendum to 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.

**Chronic Idiopathic Constipation**<sup>1-13</sup>

Chronic idiopathic constipation is a condition that causes chronic or persistent constipation for an unknown reason. Prior to the diagnosis of chronic idiopathic constipation, an initial examination must be completed to rule out structural abnormalities, medical disorders, drug-induced constipation and irritable bowel syndrome (IBS). The exact definition of constipation remains rather arbitrary and is often up to patient interpretation. Some definitions of constipation employ multiple criteria based on subjective patient reporting, while other definitions are more objective (i.e., less than 3 bowel movements per week). Patients, however, often report being constipated despite having daily bowel movements, complaining of defecatory straining or a sense of incomplete defecation. As a result of these discrepancies in defining constipation, the prevalence of constipation continues to be an elusive figure ranging from 12% to 30.9%.<sup>9</sup>

An international working committee has created what is known as the Rome II Criteria for Functional Constipation to help clinicians better diagnose and study constipation in their subjects. They recommend that the diagnosis of functional constipation be based upon the presence of two or more of the following criteria for at least 12 weeks (the presence of which need not be consecutive) in the preceding 12 months:<sup>9</sup>

- Straining with  $\geq 25\%$  of bowel movements
- A feeling of incomplete evacuation after  $\geq 25\%$  of bowel movements
- Sense of anorectal obstruction/blockade in  $\geq 25\%$  of bowel movements
- Manual maneuvers to facilitate  $\geq 25\%$  of bowel movements
- Hard or lumpy stools on  $\geq 25\%$  of bowel movements
- $< 3$  defecations per week

Despite the introduction of both the Rome-I (1994) and the Rome-II (2000) criteria, the prevalence of functional constipation as defined by the Rome Criteria has varied substantially in clinical studies to date.

**Pathophysiology of Chronic Idiopathic Constipation**<sup>14-16</sup>

By its very definition, the pathophysiology of chronic idiopathic constipation is not known. There are, however, several possible factors that could contribute to the clinical manifestation of constipation and its various sub-types. Normal bowel function requires accommodation of the colon and rectum to the passage of fecal materials, which includes receptive relaxation, perception, and discrimination of rectal contents. Voluntary and reflexive relaxation of the external anal sphincters and pelvic floor structures as well as adequate rectosigmoid tone allowing the passage of contents through the anal canal are also required. In turn, the process of defecation requires the reflex relaxation of the internal anal sphincter, voluntary and reflexive relaxation of the external anal sphincters and pelvic floor structures, and adequate rectosigmoid tone to allow funneling of contents through the anal canal. The timing and coordination of the reflexive and voluntary movements is a learned response. Chronic idiopathic constipation is hypothesized to be associated with abnormalities in the aforementioned sequence of events for unknown reasons.

Chronic constipation in adults, and Irritable Bowel Syndrome (IBS) alike, are predominantly diseases of women with a female-to-male ratio ranging from 1.3 to 2.5 for chronic constipation<sup>17, 18</sup>. This predominance of females is reflected in the studies performed in the area of chronic constipation, with most studies averaging  $>85\%$  females.

A number of studies have shown that subtypes of constipation cannot be distinguished by symptoms alone and require more objective tests to differentiate them. Unfortunately, gold standard objective diagnostic tests are lacking. To further complicate the issue, there is often significant overlap in individuals between the three subtypes of chronic constipation and a clear distinction is not always possible. The 3 subtypes of chronic constipation are constipation involving normal colonic transit, slow colonic transit and pelvic floor dysfunction.

- **Normal colonic transit**<sup>14</sup> — Patients who complain of infrequent defecation and are unresponsive to laxatives and fiber supplements may indeed have normal colonic transit. Those with normal transit constipation may misperceive bowel frequency and often exhibit increased psychosocial distress. Some of these patients

demonstrate abnormalities of anorectal sensory and motor function that are indistinguishable from those in patients with slow transit constipation. The relationship of these similar findings to the patient's complaints is unclear.

• **Colonic inertia (Slow Transit Constipation)**<sup>14</sup> — The majority of severe constipation patients with abnormal colonic transit are said to have colonic inertia, defined as the delayed passage of radio-opaque markers through the proximal colon. Colonic inertia patients have normal resting colonic motility but have little or no increase in motor activity after meals or with the administration of bisacodyl. These patients also often exhibit a blunted response to cholinergic agents. These findings suggest dysfunction in the enteric nerve plexus. Decreased volume of Interstitial Cells of Cajal in the myenteric plexus have been demonstrated in resected colon specimens from these patients. These cells are believed to play an important role in governing colonic motility. Due to colonic stasis occurring as a result of decreased propulsion (hypomotility) or increased distal motility with retropulsion (hypermotility) of radio-opaque markers, controversy exists regarding the accuracy of the term "colonic inertia". Therefore, it is recommended that the term colonic inertia be reserved for patients in whom transit in the proximal colon is delayed without evidence of retropulsion from the distal.<sup>14</sup>

• **Pelvic Floor Dysfunction**<sup>14</sup> — Also known as pelvic floor dyssynergia, pelvic floor dysfunction provides another plausible mechanism by which constipation can occur. Defecation normally involves the coordinated relaxation of the puborectalis and external anal sphincter muscles, together with increased intraabdominal pressure and inhibition of colonic segmenting activity. In patients with pelvic floor dysfunction, ineffective defecation is associated with failure to relax, or inappropriate contraction of, the puborectalis and external anal sphincter muscles. This narrows the anorectal angle and increases the pressure of the anal canal so that evacuation is less effective. Relaxation of these muscles involves cortical inhibition of the spinal reflex during defecation. Thus, this pattern may represent a conscious or unconscious act. The pathogenesis of pelvic floor dysfunction is not completely understood, but is probably multifactorial. It is thought to be an acquired, learned dysfunction rather than an organic or neurogenic disease. Studies indicate that rectosphincteric dysfunction often occurs in constipated patients with normal transit as well as in those with colonic inertia or outlet delay.

The relative frequency of the different abnormalities that can produce severe idiopathic chronic constipation was evaluated in 277 patients who underwent colon transit studies, measurement of anal canal pressures and reflexes, anorectal angle movements, and the efficiency of evacuation<sup>5</sup>. Balloon expulsion studies, electromyography of the pelvic floor, and defecating proctograms were also performed. The following causes of constipation were noted:<sup>14</sup>

- Slow transit constipation — 11 percent
- Pelvic floor dysfunction — 13 percent
- A combination of the two — 5 percent
- Irritable bowel syndrome — 71 percent

### **Medication Induced Constipation:**

It is important to keep the medications of the patient in mind. Over 900 drugs are listed in the *Physician's Desk Reference* (PDR) as drugs that cause constipation with over 100 of them having an occurrence of more than 3%. A study utilizing Rome II Criteria surveyed subjects who considered themselves to be constipated, 40% were using medications known to cause constipation.<sup>16</sup> Many over the counter and herbal products also are known to cause constipation.

### **Goals of Therapy for Chronic Idiopathic Constipation**<sup>17</sup>

The goal of therapy is to improve symptom control by either increasing the frequency of defecation or increasing the episodes of complete evacuation while at the same time decreasing symptoms associated with constipation-like defecatory straining.

### **Current Treatment Options for Chronic Constipation**<sup>17</sup>

Remedies for the treatment of constipation include nonprescription, prescription, dietary, lifestyle, herbal and home remedies. The chronic use of these agents in constipation has seldom been studied. Currently, all agents FDA approved for the treatment of constipation are only indicated for short-term use. No prescription agent has been approved for the long-term treatment of chronic constipation.

**Lifestyle Modifications:** Although there is few data supporting the efficacy of lifestyle interventions in the treatment of chronic constipation, patients are encouraged to incorporate modest exercise into their daily routine. Maintaining a diary recording bowel movements, stool characteristics, and associated abdominal discomfort is often helpful in assessing responses to treatment interventions.

**Bulk-Forming Laxatives:** Increasing fiber intake is often the first intervention attempted in the treatment of chronic constipation. Dietary fibers, such as psyllium, or synthetic polymers, like polycarbophil and cellulose, all increase physical volume and increase water retention in the stool. This increase in intraluminal volume stimulates motility, reduces colon transit time and eases the process of defecation by softening the stool consistency. Fiber agents are most effective in patients with normal transit times. Typically, 85% of patients with complaints of constipation and no pathological findings will improve or become symptom free with the use of fiber.<sup>19</sup> Synthetic fibers are metabolically inert and resistant to bacterial fermentation, thus resulting in less gastrointestinal complaints. Regardless of the fiber used, slow titration of the amount of fiber taken and increasing the frequency of administration time best avoids adverse events.

**Lubricating Laxatives:** The ingestion of mineral oil has long been a treatment for constipation. Due to the inert properties of mineral oil, ingestion results in the emulsification of the stool and the coating of the rectum thus providing lubrication. Side effects associated with the use of mineral oil include anal leakage, malabsorption of lipid soluble vitamins and lipid pneumonia if aspiration occurs.

**Osmotic Laxatives:**

Saline Laxatives: Magnesium citrate, magnesium hydroxide, sodium sulfate, sodium phosphate, etc. are poorly absorbed ions that increase the osmotic potential of the intestinal contents, thus obligating water excretion into the intestinal lumen. It is important to consider co-morbid conditions when selecting the proper saline laxative for use in individual patients. Magnesium toxicity can occur in patients as well as incontinence, dehydration, and resultant cramping. Patients with renal failure and cardiac insufficiency should avoid the use of oral phosphate products as hyperphosphatemia and hypocalcemia can result.

Lactulose: Fructosidase, an intestinal enzyme lacking in humans, is responsible for the breakdown of lactulose, a galactose-fructose disaccharide. As lactulose travels to the colon, it undergoes bacterial fermentation resulting in the production of hydrogen, methane, carbon dioxide, water, acid and short chain volatile fatty acids. It is thought that these metabolic products result in an increased osmotic potential of the colonic contents and stimulation of colonic motility. Lactulose increases stool frequency in chronic constipation patients and is fairly well tolerated, bloating and flatulence being the side effects most frequently reported.

Polyethylene Glycol (PEG): PEG is a large molecule with a high molecular weight, which increases the osmotic potential of intestinal contents resulting in increased water retention in the stool. PEG is often used in bowel preparation regimens for colonoscopy procedures, however, in low-doses PEG has been used with good success in the treatment of constipation. Two randomized, double blind, placebo-controlled trials evaluated the safety and efficacy of PEG-3350 (MiraLax®) in the treatment of constipation.<sup>20, 21</sup> The results of both studies revealed a statistically significant improvement, with no adverse events (i.e., incontinence, cramps, or diarrhea). The studies also reported no change in electrolytes, calcium, glucose, blood urea nitrogen, creatinine or serum osmolality.<sup>20, 21</sup> Additional studies are needed to assess the safety and efficacy of long-term PEG use in chronic constipation.

**Stimulant Laxatives:** This group of laxatives includes several classes, each with unique mechanisms and history. Laxatives in this class not only stimulate GI motility, but they also stimulate mucosal transport. Long-term use of stimulant laxatives has been discouraged because they have been implicated in such complications as melanosis coli (cathartic colon), damage to the myenteric plexus, acid-base and electrolyte disorders, and dependency<sup>22</sup>. Neurological damage resulting from the use of this class of drugs is now thought to be unlikely.

Docosate and bile salts, anionic detergents that soften stool by mixing with aqueous and fatty components, are considered “surface-active agents”. These agents work well as adjunctive therapy to other more potent stimulant laxatives, but used alone, have little role in the management of chronic constipation.

Bisacodyl, a diphenylmethane derivative, stimulates motor activity and inhibits water absorption in the small bowel and colon by its effects on prostaglandins, kinases, and possibly adenosine triphosphatase. Ricinoleic acid (castor oil) alters intestinal water absorption and stimulates motor function, but use is limited by its side effect profile including malabsorption of nutrients and cramping.

Plant-based chemicals like anthraquinones (sennosides A and B) also stimulate motor activity and effect fluid transport. Some anthraquinones can cause a discoloration of the colon mucosa due to apoptosis and pigment deposition in macrophages, both of which are thought to be harmless. Allergic reactions and electrolyte depletion have been reported with anthraquinone use.

**Neuromuscular Agents:**

5-HT<sub>4</sub> Agonists: Cisapride, norcisapride and prucalopride have been proven effective at treating chronic constipation, however, serious cardiovascular adverse events significantly limit their use.

Colchicine: Used mostly for gout, colchicine is a mucosal poison that is known to induce diarrhea and has been used for constipation. A 4-week, double-blind, crossover trial found that colchicine increased the frequency of bowel movements and colonic transit in 16 patients with chronic idiopathic constipation.<sup>23</sup> Colchicine’s association with serious side-effects like aplastic anemia, neuromyopathy and neutropenia, and more common side-effects like nausea, vomiting, abdominal pain, alopecia, and rash limits its use.

### **Mechanism of Action: Tegaserod (Zelnorm™) in Chronic Idiopathic Constipation**<sup>24, 25</sup>

Tegaserod acts as an agonist of the serotonin type 4 (5-HT<sub>4</sub>) receptor in the gastrointestinal (GI) tract. The mechanism by which 5-HT<sub>4</sub> agonists mediate gastrointestinal motility remains unclear, although modulation of intramural cholinergic nerve pathways, with subsequent release of acetylcholine has been suggested. The manufacturer of tegaserod (Zelnorm™) suggests that the activation of the 5-HT<sub>4</sub> receptors results in normalization of impaired motility in the GI tract, inhibition of visceral sensitivity and stimulation of intestinal secretion<sup>D</sup>.

### **Indication**<sup>25</sup>

Tegaserod (Zelnorm™) received FDA approval in July 2002 for treatment of constipation predominant-irritable bowel syndrome (IBS) in women only. Clinical trials did not show efficacy in men and no study has investigated efficacy beyond 12-weeks in the treatment of constipation predominant-IBS. In 2004, tegaserod received FDA approval for the treatment of chronic idiopathic constipation in both men and women below the age of 65. Clinical trials did not show efficacy in patients older than 65 years of age and no study has investigated efficacy beyond 12-weeks.

### **Precautions and Adverse Drug Reactions**<sup>25</sup>

Ischemic colitis and other forms of intestinal ischemia have been reported in patients receiving tegaserod during post-marketed use of the drug, although a casual relationship has not been established. Placebo-controlled trials of 7,000 patients using tegaserod for a 3-month period of time demonstrated no cases of these events. Tegaserod should be discontinued in patients who develop symptoms of ischemic colitis, such as rectal bleeding, bloody diarrhea, or new or worsening abdominal pain. Diarrhea is the most common reported adverse event and appears to be dose related. In one large trial of patients receiving 2 mg twice daily diarrhea occurred in 26% of the subjects.<sup>26</sup> In a study of 70 IBS patients on either 4 or 12 mg daily, diarrhea was reported in 49% and 18%, respectively, with a pooled rate of 33%, this however was identical to the placebo rate.<sup>27</sup> Novartis reported diarrhea to occur in 8.8% of patients receiving tegaserod in phase 3 clinical trials compared to placebo 3.3%. In clinical studies 0.04% of patients experienced clinically significant diarrhea, including hospitalization, hypovolemia, hypotension and needed IV fluids.<sup>28</sup> Patients who experience severe diarrhea during therapy with tegaserod should consult their physician. Headache and dizziness in the absence of blood pressure changes have also been reported.

## Evidence Review

<b>Citation</b>	<b>Kamm M, Muller-Lissner S, Talley N, Tack J, Boeckxstaens G, Minushkin O, et al. Tegaserod for the treatment of chronic constipation (CC): a randomized, double blind, placebo-controlled multinational study<sup>29</sup></b>
<b>Study Goals</b>	To assess the effect of tegaserod in patients with chronic constipation in comparison with placebo.
<b>Methods</b>	<ul style="list-style-type: none"> <li>• <b>Study Design</b> <ul style="list-style-type: none"> <li>➤ Prospective randomized, double-blind, placebo-controlled trial</li> <li>➤ 12 week, 3 arm study (preceded by 2-week baseline washout period)               <ul style="list-style-type: none"> <li>○ Tegaserod 2mg po bid (n=417)</li> <li>○ Tegaserod 4mg po bid (n=431)</li> <li>○ Placebo po bid (n=416)</li> </ul> </li> <li>➤ Patients not experiencing a bowel movement (BM) for more than 96 hours were instructed to use bisacodyl as a rescue medication (max 15mg/d)</li> <li>➤ Subjects were seen by study investigator on day 1, and following 4, 8, and 12 week of treatment, when efficacy data and information on adverse events were collected.</li> <li>➤ Patients recorded their constipation symptoms in a paper diary, during baseline and throughout the 12-week treatment period.               <ul style="list-style-type: none"> <li>○ The time of any BM, and whether this was associated with any straining or a feeling of incomplete evacuation (yes/no).</li> <li>○ They also recorded the form of each stool using the 7-point Bristol Stool Form Scale (1= separate hard lumps, to 7= watery no solid pieces).</li> <li>○ Time of intake of any bisacodyl taken as rescue medication.</li> <li>○ Time of intake of study medication.</li> </ul> </li> </ul> </li> <li>• <b>Data Analysis</b> <ul style="list-style-type: none"> <li>➤ Sample size calculations were based on the responder rate for complete spontaneous bowel movement (CSBM) during weeks 1-4.</li> <li>➤ Assuming a responder rate of 30% for placebo and 42% responder rate for at least one tegaserod group, 395 patients per treatment group were deemed sufficient to achieve 90% power in detecting a treatment difference, based on a two-sided chi-square test without correction at a significance level of 0.025</li> <li>➤ Efficacy analyses were performed using the intent-to-treat population, defined as all randomized patients, irrespective of whether or not the actually took study medication.</li> </ul> </li> <li>• <b>Efficacy Measures</b> <ul style="list-style-type: none"> <li>➤ Primary Efficacy Measure               <ul style="list-style-type: none"> <li>○ Responder rate for CSBM during weeks 1-4 of treatment</li> <li>○ Patients with a mean increase of <math>\geq 1</math> CSBM/week compared with the last 14 days of baseline were defined as responders, provided that they had completed at least 7 days of treatment.</li> </ul> </li> <li>➤ Secondary Efficacy Measures               <ul style="list-style-type: none"> <li>○ Responder rate for CSBM during the entire 12 weeks of treatment and at each weekly time point</li> <li>○ Change from baseline in the scores for individual constipation symptoms</li> <li>○ Percentage of spontaneous bowel movements (SMB) with a sensation of complete evacuation</li> <li>○ Number of days with too much straining</li> <li>○ Days of laxative use</li> <li>○ Median time to first CSBM and SBM</li> <li>○ Percentage of patients recording <math>\geq 3</math> CSBM/week during weeks 1-4 and weeks 1-12 were calculated for each group</li> <li>○ Percentages of patients experiencing a CSBM or SBM within 24 and 48 hours of starting treatment were calculate post hoc</li> </ul> </li> </ul> </li> </ul>



**Criteria**

- **Patient Population**

Table 1. Baseline Characteristics

Demographic/Baseline Variable	Tegaserod 2mg bid (n=417)	Tegaserod 6mg bid (n=431)	Placebo (n=416)
Age, yr (+/- SD)	46.5 (15.9)	46.2 (14.7)	46.0 (15.6)
Aged <65 yr, n (%)	351 (84.2)	384 (89.1)	358 (86.1)
Female, n (%)	359 (86.1)	369 (85.6)	363 (87.3)
Race, n (%)			
- Caucasian	410 (98.3)	423 (98.1)	409 (98.3)
- Black	2 (0.5)	2 (0.5)	2 (0.5)
- Asian	1 (0.2)	4 (0.9)	1 (0.2)
- Other	4 (1.0)	2 (0.5)	4 (1.0)

Table 2. Duration of Symptoms and Constipation History for 6 months Prior to Study

Variable	Tegaserod 2mg bid (n=417)	Tegaserod 6mg bid (n=431)	Placebo (n=416)
Mean duration of symptoms, years (+/-SD)	14.1 (12.4)	15.5 (14.6)	14.5 (13.5)
Main Complaint, n (%)			
- Abdominal distension/bloating	122 (29.3)	128 (29.7)	131 (31.5)
- Infrequent defecation	69 (16.5)	67 (15.5)	65 (15.6)
- Abdominal pain	62 (14.9)	74 (17.2)	58 (13.9)
- Feeling of incomplete evacuation	60 (14.4)	49 (11.4)	64 (15.4)
- Straining	50 (12.0)	58 (13.5)	47 (11.3)
- Hard stools	53 (12.7)	48 (11.1)	46 (11.1)
- Other	1 (0.2)	6 (1.4)	5 (1.2)
Patients Using Treatment for constipation, n (%)			
- Laxatives/enemas	243 (58.3)	247 (57.3)	240 (57.7)
- Diet	165 (39.6)	166 (38.5)	165 (39.7)
- Natural remedies	116 (27.8)	106 (24.6)	110 (26.4)
- Bulk forming agents	103 (24.7)	118 (27.4)	104 (25.0)
- Other	154 (36.9)	137 (31.8)	167 (40.1)

- The majority of the subjects were Caucasian females with a median age of 46 yr.
- Treatment groups were comparable with respect to demographic characteristics
- 86.4% of subjects had previously used at least one treatment for constipation in the preceding 6 months prior to the study
- 33 patients (2.6%) had a previous medical diagnosis IBS

- **Inclusion Criteria**

- ≥18 years of age (≥19 years of age in Australia)
- Minimum of 6 month history of constipation
- Average of <3 CSBM per week with at least one of the following 25% of the time:
  - Straining
  - Incomplete evacuation
  - Very hard and/or
  - Hard stools

- **Exclusion Criteria**

- Constipation caused by organic disease of the colon or pelvic floor dysfunction.
- Metabolic, neurologic or other significant disease that may have prevented the completion of the study.
- Pregnant or breast feeding women
- Those who planned to use concomitant medications affecting gastrointestinal function
- History of laxative abuse
- If constipation was not confirmed by diary during baseline period
- ≥3 days of loose or watery stools during baseline period
- Noncompliant in completing daily or weekly diary
- >2 days of laxative use during baseline period



**Results**

- **Primary End Point**
  - Both doses of tegaserod were significantly superior to placebo during the first 4 weeks of treatment
  - Responder rates in terms of CSBM in weeks 1-4 are as follows:
    - Tegaserod 2mg po bid = 35.6% (P=0.0001 vs. placebo)
    - Tegaserod 6mg po bid = 40.2% (P=0.0001 vs. placebo)
    - Placebo = 26.7%
  - The number needed to treat (NNT) in terms of CSBM responders are as follows:
    - Tegaserod 2mg po bid = 11.1
    - Tegaserod 6mg po bid = 7.3
  
- **Secondary Endpoints**
  - Responder rates in terms of CSBM in weeks 1-12 were only significantly higher in the 6mg bid group when compared to placebo (43.2% vs 30.6%, respectively; p<0.0001)
  - The NNT over weeks 1-12 are as follows:
    - Tegaserod 2mg po bid = 18.4
    - Tegaserod 6mg po bid = 7.8
  - Treatment with tegaserod 6mg bid improved the number of CSBM, SBM and BM/week compared with placebo (p<0.0001), whereas tegaserod 2mg bid only improved SBM/week and BM/week (p<0.0001 for both), but not of CSBM/week.

Table 3. Comparison of baseline data with weeks 1-12 of treatment with tegaserod 6mg, 2mg or placebo.

Variable Mean (+/- SD)	Tegaserod 2mg bid		Tegaserod 6mg bid		Placebo	
	Baseline	Weeks 1-12	Baseline	Weeks 1-12	Baseline	Weeks 1-12
# of CSBM/wk	0.5 (+/-0.9)	1.6 (+/-2.0)	0.5 (+/-0.9)	1.9 (+/-2.1)	0.5 (+/-0.8)	1.3 (+/-1.6)
# of SBM/wk	3.1 (+/-2.7)	4.7 (+/-3.1)	3.1 (+/-2.9)	5.1 (+/-3.3)	3.2 (+/-3.2)	4.1 (+/-3.2)
# of BMs/wk	3.9 (+/-2.6)	5.3 (+/-3.0)	4.0 (+/-2.7)	5.7 (+/-3.0)	4.1 (+/-3.0)	4.9 (+/-2.9)

- The proportion of patients who experienced  $\geq 3$  CSBM/wk during weeks 1-4 was significantly greater in the tegaserod groups when compared with placebo:
  - Tegaserod 2mg po bid = 18.8% (p=0.025)
  - Tegaserod 6mg po bid = 22.2% (p=0.0002)
  - Placebo = 12.9%
- The proportion of patients who experienced  $\geq 3$  CSBM/wk during weeks 1-12:
  - Tegaserod 2mg po bid = 17.1% (p=unknown)\*
  - Tegaserod 6mg po bid = 25.2% (p=0.0001)
  - Placebo = 14.3%

\*Not statistically different
- Median time until first CSBM after initiation of treatment:
  - Tegaserod 2mg po bid = 174.3 hours (p=0.007)
  - Tegaserod 6mg po bid = 98.0 hours (p=0.007)
  - Placebo = 286.3 hours
- Median time until first SBM after initiation of treatment:
  - Tegaserod 2mg po bid = 21.3 hours (p=0.0001)
  - Tegaserod 6mg po bid = 18.4 hours (p=0.0001)
  - Placebo = 37.2 hours
- Laxative use during the 2-week baseline period was similar in all groups. Fifty-three percent of the patients took laxatives during the baseline period and the mean number of days /week with laxative use was similar across all treatment groups (1.2, 1.3, and 1.3 with tegaserod 2mg bid, 6mg bid, and placebo, respectively).
- During the double-blind treatment period, the mean number of days /week of laxative use among the aforementioned patients decreased to:
  - Tegaserod 2mg po bid = 0.8 days/week (p=0.01)
  - Tegaserod 6mg po bid = 0.5 days/week (p=0.01)
  - Placebo = 1.0 days/week

- **Withdrawal of Treatment:**

- A total of 1,633 patients were screened, of these 1,264 patients were included, with 1,048 (82.9%) completing the study.

Table 4. Reasons subjects withdrew from study.

Reason for Discontinuation	Tegaserod 2mg (n=417)	Tegaserod 6mg (n=431)	Placebo (n=416)
- Adverse events (AE)	15	32	21
- Unsatisfactory response	17	13	22
- Withdrew consent	13	15	12
- Lost to follow-up	18	8	10
- Protocol violation	6	3	8
- Abnormal lab value	1	1	0
- Administrative problems	0	0	1
Total Number to Complete	347	359	342

- **Safety and Tolerability**

- Overall, the proportion of patients reporting an AE was not statistically different between the groups.
- Diarrhea was the only AE shown to have a higher occurrence in the tegaserod 6mg group when compared to placebo\*.
- Severe adverse events (SAE) were reported in 21 patients during the study, with a comparable frequency across the groups (<3% in any group).
- One SAE was suspected to be due to tegaserod 2mg (severe abdominal pain). This patient withdrew from the study.
- There were no clinically relevant changes observed in any of the treatment groups for hematology, biochemistry, urinalysis, vital signs or ECG parameters.

Table 5. Number (%) of patients with AEs during treatment:

N (%)	Tegaserod 2mg (N=413)	Tegaserod 6mg (N=431)	Placebo (n=415)
Total Reported AEs	211 (51.1)	223 (51.7)	234 (56.4)
- Headache	46 (11.1)	53 (12.3)	57 (13.7)
- Lower Abdominal Pain	25 (6.1)	21 (4.9)	31 (7.5)
- Diarrhea	16 (3.9)	25 (5.8)*	9 (2.2)
- Nasopharyngitis	10 (2.4)	25 (5.8)	14 (3.4)
- Nausea	15 (3.6)	19 (4.4)	13 (3.1)
- Abdominal distension	9 (2.2)	17 (3.9)	17 (4.1)
- Influenza	12 (2.9)	12 (2.8)	17 (4.1)
- Upper abdominal pain	8 (1.9)	14 (3.2)	12 (2.9)
- Back pain	9 (2.2)	10 (2.3)	15 (3.6)

<b>Conclusions</b>	<ul style="list-style-type: none"> <li>• In the first 4 weeks of treatment, tegaserod 2mg and 6mg taken twice daily was shown to be superior to placebo in regards to responder rates of CSBMs in patients suffering from chronic constipation.</li> <li>• Beyond 4 weeks, however, only tegaserod 6mg taken twice daily was shown to significantly improve responder rates of CSBMs in subjects.</li> <li>• Although there was a similar response in using both tegaserod doses, tegaserod 6mg twice daily generally produced greater therapeutic response.</li> <li>• Both doses of tegaserod were shown to be safe and well tolerated in comparison to placebo, with the exception of the occurrence of diarrhea in the tegaserod 6mg group.</li> </ul>
<b>Critique</b>	<ul style="list-style-type: none"> <li>• <b>Limitations</b> <ul style="list-style-type: none"> <li>➤ Over 86% of the study subjects were female with an average age of 46 years.</li> <li>➤ It is not known what percentage of men finished the study.</li> <li>➤ Over 98% of the subjects were Caucasian</li> <li>➤ Study was performed in South Africa, Europe and Australia with marked differences in diet and life-style compared to typical VA populations.</li> <li>➤ Another confounding factor is that bisacodyl was allowed to be used by subjects during the study.</li> <li>➤ There are limited data available supporting the validity and clinical usefulness of CSBM as an efficacy measure.</li> <li>➤ As seen in other studies involving constipation, placebo alone showed significant improvement over several baseline variables.</li> <li>➤ Because patients with pelvic floor dysfunction due to causes not related to bowel or gynecological surgery were not excluded and patient's transit time was not assessed, it is not known what proportion of patients had constipation due to slow transit time or pelvic floor dysfunction. It is difficult to determine, therefore, which population best benefits from tegaserod.</li> </ul> </li> </ul>
<b>Sponsor</b>	<b>Novartis Pharma</b>

<b>Citation</b>	<b>Johansen J, Wald A, Tougas G, Chey W, Novick J, Lembo A, et al. Effect of tegaserod in chronic constipation: a randomized, double blind, controlled trial<sup>30</sup></b>
<b>Study Goals</b>	To evaluate the efficacy, safety, and tolerability of tegaserod in patients with chronic constipation.
<b>Methods</b>	<ul style="list-style-type: none"> <li>• <b>Study Design</b> <ul style="list-style-type: none"> <li>➤ Prospective, randomized, double-blind, placebo-controlled trial</li> <li>➤ 12-week, 3-arm study (preceded by 2-week baseline washout period and followed by a 4-week withdrawal period) <ul style="list-style-type: none"> <li>○ Tegaserod 2mg po bid (n=450)</li> <li>○ Tegaserod 4mg po bid (n=451)</li> <li>○ Placebo po bid (n=447)</li> </ul> </li> <li>➤ Patients not experiencing a bowel movement (BM) for more than 96 hours were instructed to use bisacodyl as a rescue medication</li> <li>➤ Subjects were seen by study investigator on day 1, and following 4, 8, 12 and 16 week of treatment, when efficacy data and information on adverse events were collected.</li> <li>➤ Patients recorded their constipation symptoms in a paper diary, during baseline and throughout the 12-week treatment period and following 4-week withdrawal. <ul style="list-style-type: none"> <li>○ The time of any BM, and whether this was associated with any straining or a feeling of incomplete evacuation (yes/no).</li> <li>○ They also recorded the form of each stool using the 7-point Bristol Stool Form Scale (1= separate hard lumps, to 7= watery no solid pieces).</li> <li>○ Time of intake of any bisacodyl taken as rescue medication.</li> <li>○ Time of intake of study medication.</li> <li>○ Satisfaction with bowel habits (0=great deal satisfied, 4=not satisfied at all)</li> <li>○ Bothersomeness of constipation, abdominal distension/bloating, abdominal pain/discomfort (0=not at all bothersome, 4=very great deal bothersome)</li> <li>○ Quality of life surveys were taken at baseline and weeks 4 and 12.</li> </ul> </li> </ul> </li> <li>• <b>Data Analysis</b> <ul style="list-style-type: none"> <li>➤ Sample size calculations were based on the responder rate for complete spontaneous bowel movement (CSBM) during weeks 1-4.</li> <li>➤ Assuming a responder rate of 30% for placebo and 42% responder rate for at least one tegaserod group, 395 patients per treatment group were deemed sufficient to achieve 90% power in detecting a treatment difference, based on a two-sided chi-square test without correction at a significance level of 0.025.</li> <li>➤ Efficacy analyses were performed using the intent-to-treat population, defined as all randomized patients, irrespective of whether or not the actually took study medication.</li> </ul> </li> <li>• <b>Efficacy Measures</b> <ul style="list-style-type: none"> <li>➤ <b>Primary Efficacy Measure</b> <ul style="list-style-type: none"> <li>○ Responder rate for CSBM during weeks 1-4 of treatment</li> <li>○ Patients with a mean increase of <math>\geq 1</math> CSBM/week compared with the last 14 days of baseline were defined as responders, provided that they had completed at least 7 days of treatment.</li> </ul> </li> <li>➤ <b>Secondary Efficacy Measures</b> <ul style="list-style-type: none"> <li>○ Responder rate for CSBM during the entire 12 weeks of treatment and at each weekly time point</li> <li>○ Change from baseline in the scores for individual constipation symptoms</li> <li>○ Percentage of spontaneous bowel movements (SMB) with a sensation of complete evacuation</li> <li>○ Number of days with too much straining</li> <li>○ Days of laxative use</li> <li>○ Median time to first CSBM and SBM</li> <li>○ Percentage of patients recording <math>\geq 3</math> CSBM/week during weeks 1-4 and weeks 1-12 were calculated for each group</li> <li>○ Percentages of patients experiencing a CSBM or SBM within 24 and 48 hours of starting treatment were calculate post hoc</li> </ul> </li> </ul> </li> </ul>

**Criteria**

- **Patient Population**

Table 6. Baseline Characteristics

Demographic/Baseline Variable	Tegaserod 2mg bid (n=450)	Tegaserod 6mg bid (n=451)	Placebo (n=447)
Age, yr	46.7	46.7	47.2
Aged <65 yr, n (%)	391 (86.9)	410 (90.9)	387 (86.6)
Female, n (%)	400 (88.9)	406 (90.0)	407 (91.1)
- Premenopausal	212 (53.0)	211 (52.0)	209 (51.4)
Caucasian, n (%)	381 (84.7)	385 (85.4)	376 (84.1)
Black, n (%)	35 (7.8)	30 (6.7)	31 (6.9)
Oriental, n (%)	2 (0.4)	3 (0.7)	1 (0.2)
Other, n (%)	32 (7.1)	33 (7.3)	39 (8.7)
Mean Body Mass Index	25.6	25.8	25.8

Table 7. Duration of Symptoms and Constipation History for 6 months Prior to Study

Variable	Tegaserod 2mg bid (n=450)	Tegaserod 6mg bid (n=451)	Placebo (n=447)
Mean duration of symptoms, years	19.0	19.3	20.2
Main Complaint, n (%)			
- Abdominal distension/bloating	123 (27.3)	118 (26.2)	108 (24.2)
- Infrequent defecation	116 (25.8)	121 (26.8)	107 (23.9)
- Feeling of incomplete evacuation	58 (12.9)	70 (15.5)	71 (15.9)
- Straining	58 (12.9)	50 (11.1)	66 (14.8)
- Hard stools	46 (10.2)	53 (11.8)	46 (10.3)
- Abdominal pain/discomfort	46 (10.2)	35 (7.8)	44 (9.8)
- Other	3 (0.7)	4 (0.9)	5 (1.1)
SBM that were hard/very hard (%)	74.7	78.9	77.4
Mean number of days of laxative use	2.8	2.4	2.6

- The majority of the subjects were Caucasian females with a median age of 47 yr.
- Treatment groups were comparable with respect to demographic characteristics.
- 4.2 % of randomized patients had a previous medical diagnosis of IBS

- **Inclusion Criteria**

- ≥18 years of age
- Minimum of 6-month history of constipation defined as stated below.
- Average of <3 CSBM per week with at least one of the following 25% of the time:
  - Straining
  - Incomplete evacuation
  - Very hard and/or
  - Hard stools

- **Exclusion Criteria**

- Constipation caused by organic disease of the colon or pelvic floor dysfunction secondary to bowel or gynecological surgery.
- Metabolic, neurologic or other significant disease that may have prevented the completion of the study.
- Those who planned to use concomitant medications affecting gastrointestinal function
- Nonpharmacologic therapies affecting the GI system (e.g., acupuncture, colonic irrigation) were not allowed
- If constipation was not confirmed by diary during baseline period
- ≥3 days of loose or watery stools during baseline period
- Noncompliant in completing daily or weekly diary
- ≥2 days of laxative use during baseline period



**Results**

- **Primary End Point**
  - Both doses of tegaserod were significantly superior to placebo during the first 4 weeks of treatment
  - Responder rates in terms of CSBM in weeks 1-4 are as follows:
    - Tegaserod 2mg po bid = 41.4% (P=0.0001 vs. placebo)
    - Tegaserod 6mg po bid = 43.2% (P=0.0001 vs. placebo)
    - Placebo = 25.1%
  - This effect was maintained through week 12 in both tegaserod groups.
  - Responder rates in terms of CSBM in weeks 1-4 are as follows:
    - Tegaserod 2mg po bid = 40.3% (P=0.0001 vs. placebo)
    - Tegaserod 6mg po bid = 44.8% (P=0.0001 vs. placebo)
    - Placebo = 26.9%
  
- **Secondary Endpoints**
  - Both tegaserod treatment groups showed a significant improvement in the number of CSBM, SBM and BM/week compared with placebo (p<0.0001).

Table 8. Comparison of baseline data with weeks 1-12 of treatment with tegaserod 6mg, 2mg or placebo.

Variable Mean (+/- SD)	Tegaserod 2mg bid		Tegaserod 6mg bid		Placebo	
	Baseline	Weeks 1-12	Baseline	Weeks 1-12	Baseline	Weeks 1-12
# of CSBM/wk	0.5 (+/- 0.8)	1.9 (+/- 2.3)*	0.6 (+/- 0.8)	1.9 (+/- 2.1)*	0.6 (+/- 0.9)	1.3 (+/- 1.7)
# of SBM/wk	3.6 (+/- 3.3)	5.5 (+/- 4.0)*	3.5 (+/- 3.4)	5.4 (+/- 3.8)*	3.7 (+/- 3.3)	4.6 (+/- 3.2)
# of BMs/wk	4.6 (+/- 3.2)	6.2 (+/- 3.7)*	4.7 (+/- 2.7)	6.1 (+/- 3.5)*	4.7 (+/- 3.1)	5.4 (+/- 3.0)

\*Change from baseline statistically significant vs. placebo

- The proportion of patients who experienced  $\geq 3$  CSBM/wk during weeks 1-4 was significantly greater in the tegaserod groups when compared with placebo:
  - Tegaserod 2mg po bid = 23.0% (p=0.0001)
  - Tegaserod 6mg po bid = 21.8% (p=0.0001)
  - Placebo = 12.9%
- The proportion of patients who experienced  $\geq 3$  CSBM/wk during weeks 1-12 was significantly greater in the tegaserod groups when compared with placebo:
  - Tegaserod 2mg po bid = 22.7% (p=0.0001)
  - Tegaserod 6mg po bid = 22.0% (p=0.0001)
  - Placebo = 13.1%
- Median time until first CSBM after initiation of treatment was significantly shorter with both tegaserod treatments (95% confidence intervals):
  - Tegaserod 2mg po bid = 117 +/- 66 hours (p<0.01)
  - Tegaserod 6mg po bid = 73 +/- 45 hours (p<0.0001)
  - Placebo 229 +/- 123 hours
- Median time until first SBM after initiation of treatment was significantly shorter with both tegaserod treatments (95% confidence interval):
  - Tegaserod 2mg and 6mg po bid = approximately 3.5 hours
  - Placebo = approximately 15 hours
- Laxative use during the 2-week baseline period was similar in all groups. Among the patients who took laxatives during the baseline period, the mean number of days/week with laxative use was similar across all treatment groups (1.2, 1.3, and 1.3 with tegaserod 2mg bid, 6mg bid, and placebo, respectively).
- During the double-blind treatment period, the mean number of days/week with laxative use decreased to:
  - Tegaserod 2mg po bid = 0.8 days/week (p=0.01)
  - Tegaserod 6mg po bid = 0.5 days/week (p=0.01)
  - Placebo 1.0 days/week

- **Withdrawal of Treatment:**

- A total of 1,954 patients were screened, of these 1,348 patients were included, with 1,118 (82.9%) completing the double-blind treatment phase and 97.2% of those subjects completing the withdrawal period.

Table 9. Reasons for withdrawal from 12-week treatment phase:

Reason for Discontinuation	Tegaserod 2mg (n=450)	Tegaserod 6mg (n=451)	Placebo (n=447)
- Adverse events (AE)	13	15	11
- Unsatisfactory response	21	20	40
- Withdrew consent	16	23	14
- Lost to follow-up	11	14	11
- Protocol violation	5	4	8
- Administrative problems	1	1	2
Total Number to Complete	383	374	361

Table 10. Reasons for withdrawal from 4-week withdrawal phase:

Reason for Discontinuation	Tegaserod 2mg (n=380)	Tegaserod 6mg (n=375)	Placebo (n=361)
- Adverse events (AE)	1	4	1
- Unsatisfactory response	2	3	3
- Withdrew consent	1	4	0
- Lost to follow-up	3	2	6
- Protocol violation	1	0	0
Total Number to Complete	372	362	351

- **Safety and Tolerability**

- Overall, the proportion of patients reporting an AE was not statistically different between the groups.
- The placebo group showed a higher incidence of headache and nasopharyngitis.
- Tegaserod groups showed an increased incidence of diarrhea.
- Severe adverse events (SAE) were reported in 13 patients during the study, with a comparable frequency across the groups (1% overall, 4 in each tegaserod group and 5 in placebo group).
- None of the reported SAEs were suspected to be due to study treatment.
- There were no clinically relevant changes observed in any of the treatment groups for hematology, biochemistry, urinalysis, vital signs or ECG parameters.

Table 11. Number (%) of patients with adverse events during treatment:

	Tegaserod 2mg (n=413)	Tegaserod 6mg (n=431)	Placebo (n=415)
Reported ≥1 AE in 12-weeks, n (%)	252.8 (61.2)	268.1 (62.2)	259.8 (62.6)
- Headache, %	9.2	9.8	12.8
- Diarrhea, %	4.5	7.3	3.8
- Nasopharyngitis, %	7.6	8.4	10.8

<b>Conclusions</b>	<ul style="list-style-type: none"> <li>• For the entire 12-week duration of treatment, tegaserod 2mg and 6mg taken twice daily was shown to be superior to placebo in regards to responder rates of CSBM's in patients suffering from chronic constipation.</li> <li>• Significant benefits over placebo were observed for both doses of tegaserod across a wide range of symptoms associated with chronic constipation.</li> <li>• Both doses of tegaserod were shown to be safe and well tolerated in comparison to placebo, with a higher incidence of diarrhea among the tegaserod users.</li> <li>• No rebound effect was observed over the 4-week treatment withdrawal period.</li> </ul>
<b>Critique</b>	<ul style="list-style-type: none"> <li>• <b>Limitations</b> <ul style="list-style-type: none"> <li>➢ Over 90% of the study subjects were female with an average age of 47 years.</li> <li>➢ It is not known what percentage of men actually finished the study.</li> <li>➢ Another confounding factor was bisacodyl use by subjects during the study, although BMs due to laxative use were reportedly excluded from the data.</li> <li>➢ As seen in other studies involving constipation, placebo alone showed significant improvement over several baseline variables.</li> <li>➢ There are limited data available supporting the validity and clinical usefulness of CSBM as an efficacy measure.</li> <li>➢ Because patients with pelvic floor dysfunction due to causes not related to bowel or gynecological surgery were not excluded and patient's transit time was not assessed, it is not known what proportion of patients had constipation due to slow transit time or pelvic floor dysfunction. It is difficult to determine, therefore, which population best benefits from tegaserod.</li> </ul> </li> </ul>
<b>Sponsor</b>	<b>Novartis Pharma</b>

<b>Citation</b>	<b>Muller-Lisner S, Kamm M, Haeck P, Musoglu A, Huorka M, Guillot J, et al. Long term safety and tolerability of tegaserod in chronic constipation<sup>31</sup></b>
<b>Goal</b>	To assess the long-term safety and tolerability of tegaserod in the treatment of CC.
<b>Study Design</b>	<ul style="list-style-type: none"> <li>• 13-month, single-blind, uncontrolled study, enrolling patients with CC who completed an initial 12-week randomized, double-blind, placebo-controlled core study.</li> <li>• Those who received tegaserod 2mg or 6mg bid in the core study continued, while those on placebo were switched to 6mg bid.</li> <li>• Safety and tolerability were assessed by physical exam and monitoring of adverse events, serious adverse events, laboratory parameters, vital signs and ECG.</li> </ul>
<b>Results</b>	<ul style="list-style-type: none"> <li>• Results reported included safety and tolerability data from both the core study (12-weeks) and the continuation study (13-months)</li> <li>• 842 patients (mean age 46 years, 87% women) were enrolled in the extension study and 451 (54%) completed.</li> <li>• Most common reasons for discontinuing the study are as follows <ul style="list-style-type: none"> <li>➢ Unsatisfactory therapeutic response (19%)</li> <li>➢ Withdrawal of consent (11%)</li> <li>➢ Adverse events (6%)</li> </ul> </li> <li>• The most common adverse events are as follows: <ul style="list-style-type: none"> <li>➢ Headache <ul style="list-style-type: none"> <li>○ Tegaserod 2mg bid = 24%</li> <li>○ Tegaserod 6mg bid = 19%</li> </ul> </li> <li>➢ Abdominal pain <ul style="list-style-type: none"> <li>○ Tegaserod 2mg bid = 15%</li> <li>○ Tegaserod 6mg bid = 11%</li> </ul> </li> <li>➢ Diarrhea <ul style="list-style-type: none"> <li>○ Tegaserod 2mg bid = 8%</li> <li>○ Tegaserod 6mg bid = 10%</li> </ul> </li> <li>➢ Headache <ul style="list-style-type: none"> <li>○ Tegaserod 2mg bid = 24%</li> <li>○ Tegaserod 6mg bid = 19%</li> </ul> </li> </ul> </li> <li>• Serious adverse events (SAE) were reported by 37 patients (15 in 2mg group and 22 in 6mg</li> </ul>

	<p>group) and were deemed to be unrelated to tegaserod.</p> <ul style="list-style-type: none"> <li>No clinically relevant changes were seen in other parameters.</li> </ul>
<b>Conclusion</b>	<ul style="list-style-type: none"> <li>Results were similar to two previous 12-week studies, indicating that long-term treatment does not represent an increased safety or tolerability risk.</li> </ul>
<b>Critique</b>	<ul style="list-style-type: none"> <li>The only available information on this study is found in abstract form and the research was never published in a peer-reviewed journal.</li> <li>This study does not show any efficacy data.</li> <li>While this study does not analyze efficacy, it is interesting to note that the leading cause of withdrawal from the study (54%) was lack of therapeutic effect (19%). Since this is exponentially higher than the previous 2 short-term studies, it creates doubt in the long-term efficacy of tegaserod in the treatment of CC.</li> <li>It is not known how many men dropped out of the study and if any men finished.</li> </ul>

### Cost Analysis

A true cost analysis was not able to be performed due to the lack of published data on consistent outcome measures such as ROME I vs. II criteria, complete vs. incomplete evacuation, feeling of complete vs. incomplete evacuation etc. In the 2 studies involving tegaserod in treating chronic constipation the primary outcome measure used was the response rate in regards to complete spontaneous bowel movements (CSBM). Published data suggests that tegaserod may be effective in treating chronic constipation in patients that are refractory to traditional treatment. A cost minimization was performed below to provide a glimpse of the relative costs of these agents.

### Acquisition Cost

- 60 tablet bottle of tegaserod 2mg = \$90.32
- 60 tablet bottle of tegaserod 6mg = \$90.38
- Manufacturer's recommended tegaserod dose (Idiopathic Chronic Constipation):
  - o Initial Dose: 6mg po bid
  - o Maintenance Dose: 6mg po bid

**Table 12. Cost Comparison of available treatments for chronic constipation.**

Medication	Packaging	Price/Pack	Dose Range	Cost/Day	Cost/Month	Cost/12-weeks	Cost/Year
Psyllium (Metamucil)	3.4g/5g	\$5.60/30 pack	1 po qd-tid	\$0.18 - 0.54	\$5.40 – 16.20	\$15.12 – 45.36	\$64.8-194
Psyllium (Konsel)**	10.6 oz	\$3.56/bottle	1 tsp qd – tid	\$0.07 – 0.21	\$2.10 – 6.30	\$5.74 – 17.22	\$25.6–76.7
Milk-of-Mg	480 ml	\$0.89/bottle	15-60 ml po qhs	\$0.003 - 0.11	\$0.08 – 3.30	\$0.23 – 9.24	\$1.00-39.60
Bisacodyl 5mg	100 tabs	\$0.82/bottle	10-15mg po qhs	\$0.025	\$0.50 – 0.74	\$1.38 – 2.07	\$5.90-8.86
Bisacodyl 10mg	500 supp	\$23.28/box	10mg pr prn	\$0.046	\$1.40	\$3.91	\$16.76
Senna 8.6mg	100 tabs	\$1.06/bottle	8.6-34.4 mg po bid	\$0.01 - 0.04	\$0.32 - 1.27	\$0.89 – 3.56	\$3.82-15.26
Docusate Na 250mg	100 caps	\$2.22/bottle	250mg po qd	\$0.022	\$0.67	\$1.86	\$8.00
PEG 3350**	255g	\$10.45/bottle	1 tablespoon po qd	\$0.69	\$20.70	\$62.10	\$248
Lactulose 10g/15ml	480 ml	\$2.80/bottle	15-60ml po qd	\$0.085 - 0.35	\$2.63 - 10.50	\$7.35	\$31.50-126
Tegaserod 2mg**	60 tabs	\$90.32/bottle	2mg po bid	\$3	\$90	\$252	\$1080
Tegaserod 6mg**	60 tabs	\$90.38/bottle	6mg po bid	\$3	\$90	\$252	\$1080
Tegaserod 6mg** (split-tablets)	60 tabs	\$90.38/bottle	3mg po bid	\$1.51	\$45.19	\$126.53	\$542.28

\*\*Non-Formulary Agents

### Pharmacoeconomic Data

A pharmacoeconomic analysis of use of tegaserod in the treatment of chronic constipation is difficult to perform due to the lack of published data available comparing tegaserod with traditional treatments. There are no head-to-head studies involving tegaserod and traditional constipation treatments and the end points in previous studies involving chronic constipation and traditional treatments differ significantly. Direct cost effectiveness comparisons between tegaserod and traditional constipation treatments, therefore, were not performed.

## Discussion Section

### ***1. Tegaserod as a safe, effective alternative for patients who have failed traditional treatment for chronic constipation.***

Based on the data provided in the 2 clinical trials involving tegaserod in the treatment of chronic constipation, tegaserod 6mg twice daily has been shown to be superior to placebo in increasing the number of complete spontaneous bowel movements (CSBM) in patients when compared to baseline. It is difficult to know, however, if there will be differences in response between patients who are refractory to traditional treatments and those found in these studies.

### ***2. Tegaserod as a safe, effective alternative for refractory chronic constipation patients in the VA population.***

Over 90% and 86% of the subjects in the 2 clinical trials published were female. The third and only study published as an abstract, demonstrated safety through 13 months. This was a continuation study of one of the previous trials and the author(s) did not publish the percentage of males or the age of those patients who continued.

### ***3. Tegaserod as an effective alternative for long-term treatment of refractory chronic constipation beyond 12-weeks.***

The only 2 studies showing efficacy of tegaserod in the treatment of chronic constipation were both 12-weeks in duration. The only data beyond 12-weeks was a continuation study analyzing safety of tegaserod over a 13-month time frame. During this time the drop out rate from the study was 52%, with the leading cause being lack of therapeutic effect at 19%. This dropout rate due to lack of efficacy is 5-fold to >20-fold higher than the 2 previous 12-week studies. This data suggests that the effectiveness of tegaserod beyond 12-weeks is uncertain.

### ***4. Can tegaserod 6mg tablet be split for 3mg po bid dosing?***

The safety and efficacy of split tablets of tegaserod has not been studied and is not recommended by the manufacturer. In regards to the dose, however, it seems reasonable to conclude that tegaserod 3mg taken twice daily would be safe and effective, at least up until week-4, considering 2 previous studies showed efficacy and safety of both 2mg and 6mg taken twice daily. This will be left to provider discretion.

### ***5. Tegaserod as a safe and effective alternative for the treatment of chronic constipation induced by medications or other co-morbid conditions?***

The safety and efficacy of tegaserod in the treatment of chronic constipation induced by medications or other co-morbid conditions has not been studied. These specific patient populations were excluded from the 2 trials studying tegaserod in chronic constipation. Due to the lack of safety and efficacy data, tegaserod is not recommended for the treatment of chronic constipation induced by medications or caused by other co-morbid conditions.

## Conclusions

The goals of therapy in the treatment of chronic constipation target alleviation of symptoms and improved quality of life. Prior to treating chronic constipation, however, a full work-up of each patient must be performed to try and identify the underlying cause. As previously mentioned, chronic constipation can be separated into 3 categories, pelvic floor dysfunction, slow transit and normal transit. While treatment modalities can differ between the different categories, it is common to have significant overlap in symptoms between the categories in any given individual. In general, however, it is recommended to begin therapy with bulk forming laxatives (i.e. dietary fiber, psyllium) followed by magnesium hydroxide or PEG-3350. Lactulose, neuromuscular drugs and occasional stimulant laxatives in addition to combination therapy are other alternatives. Docusate sodium is another adjunctive agent that can be employed in the treatment of chronic constipation.

Published data has shown that tegaserod is effective, safe and well tolerated when used in the treatment of chronic constipation. It is important to keep in mind that the two trials discussed in this addendum were trials involving mostly women (>86% and >90%) with an average of 46 and 47 years of age.<sup>29,30</sup> This study limitation, however, is consistent with the prevalence of chronic constipation. Both studies were of 12-week duration and both proved efficacy of the tegaserod 6mg taken twice daily. Both studies showed efficacy of tegaserod 2mg up to week 4, while only one study showed efficacy through week 12. While efficacy has not been studied beyond 12 weeks, one of the trials performed a continuation study spanning 13 months to analyze the safety of long-term use.<sup>31</sup> This study was only published in abstract form and the research was not published in a peer-reviewed journal, therefore only limited data is available. Of interest in this study is that the leading cause for withdrawal from the study (54% dropout overall), was due to lack of therapeutic effect with a rate of 19%. Since this dropout rate due to lack of efficacy is 5-fold to >20-fold higher than the 2 previous 12-week studies, it creates doubt in the long-term efficacy of tegaserod in the long-term treatment of CC.

**Appropriate Use:** For patients under the age of 65 years who have chronic idiopathic constipation.

The Non-Formulary use of tegaserod in patients under the age of 65 years with idiopathic chronic constipation should be restricted to:

- Patients who are under the age of 65 years.
- Use of tegaserod will be considered upon non-formulary request from a GI specialist, or other designated person with expertise in this area, upon documented failure of all current formulary treatment options.
  - o All of the above agents listed in table 12 excluding Konsel™ brand of psyllium, which is Non-Formulary
- Patients whose chronic idiopathic constipation is not due to pelvic floor dysfunction.
- Patients who are approved for tegaserod should:
  - o Keep a daily report or other deemed data relevant by provider of stool frequency and other data deemed relevant by provider.
  - o Started on the manufacturer recommended dose of 6mg orally twice a day.
  - o Be limited to a 30-day supply with no refills.
- At the end of the 30-day trial, the patient must be re-evaluated for efficacy and a new consult must be provided.
- Treatment with tegaserod beyond 12-weeks lacks efficacy data and is not recommended.

## **References:**

- 1) Everhart JE, Go VL, Johannes RS, et al. A longitudinal survey of self-reported bowel habits in the United States. *Dig Dis Sci* 1989;34(8):1153-62.
- 2) Connell, AM, Hilton, C, Irvine, G, et al. Variation of bowel habit in two population samples. *Br Med J* 1965; 5470:1095.
- 3) Sandler RS, Drossman DA. Bowel habits in young adults not seeking health care. *Dig Dis Sci* 1987 Aug;32(8):841-5.
- 4) Thompson WG, Longstreth GF, Drossman DA, et al. Functional bowel disorders and functional abdominal pain. *Gut* 1999;45 Suppl 2:II43-7.
- 5) Nyam DC, Pemberton JH, Ilstrup DM, et al. Long-term results of surgery for chronic constipation. *Dis Colon Rectum* 1997;40(3):273-9.
- 6) Wald A, Hinds JP, Caruana BJ. Psychological and physiological characteristics of patients with severe idiopathic constipation. *Gastroenterology* 1989; 97(4): 932-7.
- 7) Waldron D, Bowes KL, Kingma YJ, et al. Colonic and anorectal motility in young women with severe idiopathic constipation. *Gastroenterology* 1988; 95(5): 1388-94.
- 8) Bassotti G, Chiarioni G, Imbimbo BP, et al. Impaired colonic motor response to cholinergic stimulation in patients with severe chronic idiopathic (slow transit type) constipation. *Dig Dis Sci* 1993; 38(6):1040-5.
- 9) Talley NJ, Weaver AL, Zinsmeister AR, et al. Functional constipation and outlet delay: a population based study. *Gastroenterology* 1993; 105:781-790.
- 10) Martelli H, Devroede G, Arhan P, et al. Mechanisms of idiopathic constipation: outlet obstruction. *Gastroenterology* 1978; 75(4):623-31.
- 11) Read NW, Abouzekry L, Read MG, et al. Anorectal function in elderly patients with fecal impaction. *Gastroenterology* 1985; 89(5):959-66.
- 12) Turnbull GK, Bartram CI, Lennard-Jones JE. Radiologic studies of rectal evacuation in adults with idiopathic constipation. *Dis Colon Rectum* 1988; 31(3):190-7.
- 13) Read NW, Timms JM, Barfield LJ, et al. Impairment of defecation in young women with severe constipation. *Gastroenterology* 1986; 90(1):53-60.
- 14) Crowell, M. Pathogenesis of slow transit and pelvic floor dysfunction: From bench to bedside. *Rev Gastroenterol Dis* 2004;4(suppl 2):S17-S27.
- 15) Sandler RS, Drossman DA. Bowel habits in young adults not seeking health care. *Dig Dis Sci* 1987; 32:84-845.
- 16) Adeniji OA, DiPalma JA. Prevalence of medicine associated constipation. *Am J Gastroenterol* 2001; 96:S140.
- 17) Rao SS. Constipation: evaluation and treatment. *Gastroenterol Clin North Am.* 2003; 32:659-693.
- 18) Pare P, Ferrazzi S, Thompson WG, et al. An epidemiological survey of constipation in Canada: definitions, rates, demographics, and predictors of health care seeking. *Am J Gastroenterol* 1999; 94:3530-3540.
- 19) Voderholzer WA, Schatke W, Muhldorfer M, et al. Clinical response to dietary fiber treatment of chronic constipation. *Am J Gastroenterol* 1997; 92:95-98.
- 20) Di Palma JA, DeRidder PH, Orlando RC, et al. An epidemiological survey of constipation in Canada: definitions, rates, demographics, and predictors of health care seeking. *Am J Gastroenterol* 2000; 95:446-450.

- 21) Cleveland MB, Flavin DP, Ruben RA, et al. New polyethylene glycol laxative for treatment of constipation in adults: a randomized, double blind, placebo-controlled study. *South Med J.* 2001; 94:478-481.
- 22) DiPalma JA. Current treatment options for chronic constipation. *Rev Gastroenterol Disorders* 2004; 4(suppl. 2):S34-42.
- 23) Verne GN, Davis RH, Robinson ME, et al. Treatment of chronic constipation with colchicines: a randomized, double blind, placebo controlled, cross over trial. *Am J Gastroenterol* 2003; 98:1112-1116.
- 24) Scarpignato C, Pelosini I. Management of irritable bowel syndrome: novel approaches to the pharmacology of gut motility. *Can J Gastroenterol* 1999; 13(suppl A):50A-65A.
- 25) Product Information: Zelnorm™, tegaserod maleate. Novartis Pharmaceuticals Corporation, East Hanover, NJ, (PI revised 8/2004) reviewed 8/2004.
- 26) Lefkowitz M, Shi Y, Schmitt C, et al. The 5-HT<sub>4</sub> partial agonist, tegaserod, improves abdominal discomfort/pain and normalizes altered bowel function in irritable bowel syndrome. *Am J Gastroenterol* 1999; 94:266.
- 27) Fidelholtz J, Smith W, Rawls J et al: Safety and tolerability of tegaserod in patients with irritable bowel syndrome and diarrhea symptoms. *Am J Gastroenterol* 2002; 97; 1176-1181.
- 28) Lefkowitz MP, Ruegg P, Shi Y et al: Relief of overall GI symptoms and abdominal pain and discomfort as outcome measures in a clinical trial of irritable bowel syndrome with HTF 919 (abstract). *Gastroenterology* 1999; 116(part 2):1027.
- 29) Kamm MA, Muller-Lissner S, Talley NJ, et al. Tegaserod for the treatment of chronic constipation: a randomized, double-blind, placebo-controlled multinational study. *Am J Gastroenterol.* 2005; 100(2):362-372.
- 30) Johanson J, Wald A, Cervias T, Chey W, Novick J, Lembo A, et al. Effect of Tegaserod in chronic constipation: a randomized, double blind, controlled trial. *Clin Gastroenterol Hepatol.* 2004;2(9):796-805.
- 31) Muller-Lissner S, Kamm M, Haeck P, et al. Long-term safety and tolerability of tegaserod in chronic constipation. *Gastroenterology* 2004;126(suppl 2):A-642. Abstract W1468.

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