Tegaserod (ZELNORM) – Limited Use Permitted by FDA (USA)
Preliminary DRAFT

Highlights

- Patients taking ZELNORM 12mg/day are 1.2 times more likely to experience relief from global IBS symptoms compared to those who are not (NNT=14).
- Diarrhea is the most common side effect and is 3 times more likely to occur in patients on ZELNORM, versus those on placebo (NNH=20).
- A retrospective analysis reported that 13 patients (0.1%) on ZELNORM experience a cardiovascular ischemic event compared to 1 patient (0.01) in the placebo group (p=0.024), resulting in the removal of ZELNORM from the market.
- The FDA is now allowing the use of ZELNORM in female constipation-predominant IBS patients who are <55 years old with no history of heart problems. August 2007

Safety Concerns & Update

In the spring of 2007, tegaserod (ZELNORM) was removed from the market due to safety concerns involving an increased incidence of cardiovascular ischemic events. This decision was based on a retrospective analysis of pooled data from twenty-nine short-term (1-3 months in duration) randomized controlled placebo-controlled trials. Collectively, a total of 11,614 patients received ZELNORM and 7,031 patients were on placebo (mean age 43 years old, 88% female). A total of thirteen patients (0.1%) taking ZELNORM experienced a cardiovascular ischemic event, compared to only one patient (0.01%) in the placebo group (p=0.024). Of the thirteen patients, four had myocardial infarctions (one of which was fatal), six experienced unstable angina episodes, and three had strokes. The one patient from the placebo group developed the beginning symptoms of a stroke, which resolved without complications. The majority of the events occurred in patients with cardiovascular disease and cardiovascular risk factors, however not all had been diagnosed or identified prior to starting ZELNORM.[1, 2]

The FDA announced in August, 2007, that ZELNORM would be available with restricted access. The medication would be limited to women who are less than 55 years of age with no history of heart problems, for the treatment of irritable bowel syndrome with constipation and chronic idiopathic constipation.[1]

ZELNORM & Irritable Bowel Syndrome

Tegaserod, as a partial 5-HT_4 agonist, increases gastrointestinal motility and decreases visceral sensitivity.[3] Taking 12mg/day has been shown to relieve global IBS symptoms (RR 1.19, 95% CI 1.09-1.29) when compared to placebo, with a NNT of 14.

One of the most common side effects of the medication is diarrhea. Patients are 3 times more likely to experience diarrhea compared to those on placebo (RR 2.75, 95% CI 1.90-3.97; NNH=20).[4]

In contrast to the bulk of IBS trials, the studies evaluating ZELNORM were relatively well designed.[5, 6] The primary limitation with the trials has been the patient population. Over 80% of the patients were Caucasian females. The mean age was 45 years old and mean duration of IBS was 10 years. Patients met the ROME I criteria and the majority met the criteria for constipation-predominant IBS – although, some had alternating IBS. Due to the lack of evidence in patients with diarrhea-predominant or alternating IBS, and the associated risk of developing or exacerbating diarrhea, ZELNORM is only recommended in patients suffering from constipation-predominant IBS.[5]

It is suggested that ZELNORM be used for short-term, intermittent courses as the original trials were only 12 weeks in duration.[4, 5] However, a more recent trial assessed the safety of ZELNORM over a 12 month period (see below for summary). During this study, 48% withdrew from the trial – 11% due to adverse events. Those who completed one year of therapy experienced mild and transient adverse events.[7]

Only the 6mg tablet of ZELNORM was marketed in Canada, prior to its removal in spring of 2007. The suggested dose is 6mg po twice daily, given 30 minutes before a meal. If a patient responds to a first course of therapy, ZELNORM may be beneficial for subsequent recurrences of IBS symptoms.[5]

Tougas G, Snape WJ, Otten MH, Earnest DL, Langaker KE, Pruitt RE, Pecher E, Nault B, and Rojavin MA. *Long-term safety of tegaserod in patients with constipation-predominant IBS.* Aliment Pharmacol Ther 2002; 16:1701-1708.

- Assessed the safety of tegaserod over a 12 month period. Efficacy not reported as not a placebo-controlled trial, and high placebo response rate
- Population: n=579, male and non-pregnant females (90.3%, n=523), mean age 44.2 (age 18-70), CP-IBS (ROME I), 92.9% (n=538) Caucasian, 23.8% (n=138) previously treated with tegaserod
- Open-label study, tegaserod 2mg bid x 1 month and 6mg bid thereafter depending on therapeutic effect (assessed months 1,2,4,6,8,10)
- 48% (n=275) withdrew from the study (12%, n=72 ineffective, 11%, n=65 adverse events, others – withdrew consent, lost to follow-up, protocol violation, other)
- Majority of patients were increased to 12mg/day within the first 3 months. By month 12 – 82% were on 12mg/day. Mean duration on 12mg/day 209.7 days (+/- 122)
- Chest pain occurred in 2 patients (0.4%). No reports of MI or stroke.
- GI side effects affected 46% of the population. Most common – mild and transient diarrhea (10.1%), headache (8.3%), abdominal pain (7.4%) and flatulence (5.5%)

Additional Information – Zelnorm - Comparison Chart
(if needed – from Micromedex, CPS)

Column #1
- Strength/Formulation: 6 mg tablet
- Coverage: non-formulary, not covered by NIHB
- Symbols: pregnancy category B, kidney for renal insufficiency

Column #2
- Class: partial 5-HT_4 agonist

Column #3
- Side effects: MI, stroke, chest pain, ischemic colitis, severe diarrhea (hypotension, hypovolemia), alopecia, abdominal pain, flatulence, nausea, vomiting, elevated liver enzymes, dizziness, headache, cholecystitis
- Contraindications: bowel obstruction, gallbladder disease, liver disease, renal impairment, abdominal adhesions

Column #4
- Drug Interactions: digoxin
- Comments/Safety: information about withdrawal and return (if happens) to market

Column #5
- Dose: 6mg po bid 30 minutes before meals

Column #6
- Cost: ~$140/month

Prepared by: Lynette Kolodziejak

References:

1. FDA. FDA Permits Restricted Use of Zelnorm for Qualifying Patients; 2007. Links: http://fdanews.com/newsletter/article?issueId=10540&articleId=96755 (http://factsandcomparisons.com/News/ArticlePage.aspx?id=7748)
2. Canada N. Health Canada Endorsed Important Safety Information on Zelnorm: Health Canada; 2007.
3. Abramowicz M. Treatment Guidelines: Drugs for Irritable Bowel Syndrome. *The Medical Letter.* March 2006;4(43):11-16.
4. Evans BW, Clark WK, Moore DJ, Whorwell PJ. Tegaserod for the treatment of irritable bowel syndrome. *Cochrane Database Syst Rev.* 2004(1):CD003960.
5. Brandt LJ, Bjorkman D, Fennerty MB, et al. Systematic review on the management of irritable bowel syndrome in North America. *Am J Gastroenterol.* Nov 2002;97(11 Suppl):S7-26.
6. Tack J FM, Houghton LA, Spicak J, and Fisher G. Systematic review: the efficacy of treatments for irritable bowel syndrome - a European perspective. *Alimentary Pharmacology and Therapeutics.* 2006;24:183-205.
7. Tougas G, Snape WJ, Jr., Otten MH, et al. Long-term safety of tegaserod in patients with constipation-predominant irritable bowel syndrome. *Aliment Pharmacol Ther.* Oct 2002;16(10):1701-1708.