

Questions for the Gastrointestinal Drugs Advisory Committee

NDA: 21-200/S-005

Drug: Zelnorm[®] (tegaserod maleate) Tablets

Applicant: Novartis Pharmaceuticals Corporation

Indication: treatment of chronic constipation

1. Efficacy

- a. Discuss the appropriateness of a primary efficacy endpoint of an increase of =1 complete spontaneous bowel movement per week vs. a total of =3 complete spontaneous bowel movements per week.
- b. Only 9 to 16% of subjects were =65 years of age and the treatment effect was significantly smaller in older patients. Are these data adequate for an indication that is common in the elderly?
- c. Only 9 to 14% of the subjects were male and the treatment effect was smaller in males than females. Are these data adequate to support approval of Zelnorm[®] for use in the treatment of chronic constipation in males?
- d. Is the population studied representative of patients with chronic constipation? If not, how do the populations differ?
- e. Are the clinical trial data adequate with respect to the population with chronic constipation that is likely to be treated with Zelnorm[®]?
- f. Is Zelnorm[®] effective for the treatment of chronic constipation?

2. Safety

- a. Post-marketing cases of ischemic colitis and serious complications of diarrhea were not limited to patients with irritable bowel syndrome. What are the implications of these adverse events for patients with chronic constipation?
- b. The incidence of diarrhea and discontinuations due to diarrhea was higher in patients =65 years of age. Is there sufficient information that Zelnorm[®] is safe for use in this age group?
- c. Do the adverse event data from the clinical trials and post-marketing surveillance provide adequate evidence of safety of Zelnorm[®] for the treatment of chronic constipation?
- d. Should the information on the post-marketing cases of ischemic colitis and intestinal ischemia be moved from the PRECAUTIONS section to the WARNINGS section of the package insert?

3. Should Zelnorm be approved for the proposed indication of *the treatment of patients with chronic constipation and relief of the associated symptoms of straining, hard or lumpy stools, and infrequent defecation?*