Gastrointestinal Drugs Advisory Committee

July 14, 2004

Questions

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. Is the population studied representative of patients with chronic constipation? If not, how do the populations differ?

    c. 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?

    d. 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?

    e. Are the clinical trial data adequate with respect to the population of non-IBS patients with chronic constipation that is likely to be treated with Zelnorm®?

    f. Is Zelnorm® effective for the treatment of chronic constipation and associated symptoms?

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?

    The labeling regulations state that the PRECAUTIONS section of the labeling "shall contain information regarding any special care to be exercised by the practitioner for safe and effective use of the drug…" The WARNINGS section "shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved." In addition, the WARNINGS section should include any potentially fatal adverse reaction.

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*?