

MEMORANDUM  
SERVICES

DEPARTMENT OF HEALTH AND HUMAN

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CENTER FOR DRUG EVALUATION AND

RESEARCH

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To: Members of the Gastrointestinal Drugs Advisory Committee

From: Robert L. Justice, M.D., M.S.,

Director, Division of Gastrointestinal and Coagulation Drug Products

Subject: revisions to the FDA Briefing Document

Date: July 1, 2004

Please note the attached revisions on pages 2 and 15 of the FDA Briefing Document on Zelnorm<sup>®</sup> for the treatment of chronic constipation.

# **Gastrointestinal Drugs Advisory Committee on Zelnorm<sup>®</sup> for Treatment of Chronic Constipation**

## **FDA Briefing Document**

Novartis Pharmaceuticals Corporation submitted a Supplemental New Drug Application (21-200/S-005) on October 20, 2003 seeking approval of Zelnorm (6 mg bid) for the treatment of chronic constipation. Zelnorm is a 5-HT<sub>4</sub> partial agonist with moderate affinity for the 5-HT<sub>1</sub> receptor. It was first approved in July 2002 for the short-term treatment (4-6 weeks) of women with constipation predominant irritable bowel syndrome (c-IBS). The therapeutic mechanism of action is based primarily on its agonist action on 5-HT<sub>4</sub> receptors, resulting in augmented bowel motility, increased intestinal secretion and inhibition of visceral sensitivity. Two clinical studies were submitted in support of the chronic constipation indication.

This briefing document for the Gastrointestinal Drugs Advisory Committee meeting consists of three sections:

1. Clinical Summary of Efficacy (pages 4-16)
2. Clinical Summary of Safety (pages 17-64)
3. Draft Statistical Review and Evaluation (pages 65-118)

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### **Issues for Discussion:**

1. Efficacy
  - a. Discuss the appropriateness of a primary efficacy endpoint of an increase of =1 complete spontaneous bowel movement per week vs. =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 idiopathic constipation?

#### 4. Conclusion

At first glance, the results revealed significant therapeutic gain for tegaserod 6 mg over placebo ranging from as high as 13% to as low as 9% depending on the methodology applied for analysis. Dose response was shown only in one trial. Careful examination reveals deficiencies in study design, in study execution, and robustness of results. The design of the studies excluded patients considered laxative abusers, and lacked a provision to exclude patients with IBS-C, a subtype of constipation for which tegaserod is already approved for use under prescription. This lack of provision to exclude IBS-C led to contamination of the total enrolled patient population with almost 600 patients who met the criteria of IBS-C (a few of them met the criteria of IBS-diarrhea predominant). In the execution of the studies, men and the elderly were underrepresented (discussed in the draft statistical review in greater detail), and the studied patient population was young or middle age women, 46 years old. A large proportion (=63%) of these women exhibited severe constipation at the run-in baseline period (0 CSBM) coupled with abdominal symptoms. This latter clinical picture is reminiscent of the clinical picture encountered in outlet obstruction or slow transit constipation. It appears, therefore, idiopathic constipation patients, if present, constituted a minority (37% or only 15%) of enrollees. A further fundamental deficiency in the design, i.e. choice of primary efficacy endpoint, was subsequently manifested in the results. About 18% of patients with 0 CSBM/wk at baseline were declared responders with only 1 CSBM per week. *Responders to treatment were non-constipated for approximately 42% of the 12-week study treatment.*

In acknowledging the favorable statistics toward tegaserod, this reviewer ponders about the clinical significance of these efficacy results, in the lifelong treatment of chronic constipation, and rather pointedly, in the lifelong treatment of idiopathic, outlet obstruction or slow transit constipation.