**Food and Drug Administration**
**Center for Drug Evaluation and Research**
Advisory Committee Conference Room, Rm. 1066, 5630 Fishers Lane, Rockville, MD.

# Summary Minutes of the July 14, 2004 meeting of the Gastrointestinal Drugs Advisory Committee

***New drug application 21-200/S-005, Zelnorm® (tegaserod maleate) Tablets, Novartis Pharmaceuticals Corp.***

*"for the proposed indication of the treatment of patients with chronic constipation and relief of associated symptoms of straining, hard or lumpy stools and infrequent defecation.."*

## Members Present

Ronald P. Fogel, M.D., Acting Chair
Robert Alan Levine, M.D.
Alan Buchman, M.D.
David Colin Metz, M.D.
John Thomas LaMont, M.D.
David Sachar, M.D.
Byron Cryer, M.D.

## Consultants

Allen Mangel, M.D.
Ralph D'Agostino, Ph.D.
Brian L. Strom, M.D.
Arthur A. Levin, M.P.H.
Curt Furberg, M.D.

## Federal Employee

Maria H. Sjogren, M.D.

## Industry Representative

Jose Vega, M.D.

## FDA Participants

Julie Beitz, M.D., M.P.H.
Robert Prizont, M.D.
Robert Justice, M.D.
Garry Della'Zanna, D.O., M.Sc.

These summary minutes for the July 14, 2004 meeting of the Gastrointestinal Drugs Advisory Committee were approved on July 23, 2004.

I certify that I attended the July 14, 2004 meeting of the Gastrointestinal Drugs Advisory, and that these minutes accurately reflect what transpired.

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Thomas H. Perez, M.P.H., R.Ph.
**Executive Secretary**

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Ronald P. Fogel, M.D.
**Acting Chair**

The Gastrointestinal Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met July 14, 2004 at the Advisory Committee Conference Room, Rm. 1066, 5630 Fishers Lane, Rockville, MD. Conference room D in the Parklawn building was used to accommodate the overflow of attendees to this meeting.

The Committee discussed new drug application (NDA) 21-200/S-005, Zelnorm® (tegaserod maleate) Tablets, Novartis Pharmaceuticals Corp., for the proposed indication of the treatment of patients with chronic constipation and relief of associated symptoms of straining, hard or lumpy stools and infrequent defecation.

The Committee had received a briefing document from the FDA, and a background package from Novartis Pharmaceutical Corp., in preparation for this meeting.

There were approximately 100 members of the public present in the meeting. Additionally Novartis brought 59 attendees to the meeting. The meeting was called to order at 8:35 a.m. by the Acting Chair, Ronald P. Fogel, M.D. The Committee members and discussants introduced themselves. Thomas H. Perez, Executive Secretary of the Gastrointestinal Drugs Advisory Committee read the Meeting Statement. Welcome and opening comments were provided by Robert Justice, M.D., Director, Division of Gastrointestinal and Coagulation Drug Products

Novartis Pharmaceutical Corp., representatives began their presentations at 8:45 a.m. The presentations proceeded as follows.

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| Introduction | John R. Cutt, Ph.D., Novartis Executive Director<br>Global Head GI, Drug Regulatory Affairs |
| Chronic Constipation: An Unresolved Problem for Many Patients | Charlene M. Prather, M.D.<br>St. Louis University School of Medicine |
| Zelnorm®: Efficacy and Safety in Chronic Constipation | Eslie Dennis, M.D., Novartis Senior Medical Director,<br>GI Clinical Development and Medical Affairs |
| Zelnorm: Safety Overview | Bo Joelsson, M.D., Novartis Head Gastroenterology<br>Clinical Research and Development |
| Benefit/Risk | Philip Schoenfeld, M.D.<br>University of Michigan School of Medicine |

The presentations were followed by a question and answer period. After a 15 minute break the Committee reconvened at 11:45 with the following two presentations from the FDA.

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|---|---|
| FDA Efficacy Presentation | Robert Prizont, M.D., Medical Officer<br>Division of Gastrointestinal and Coagulation Drug Products |
| FDA Safety Presentation | Gary Della'Zanna, D.O., M.Sc., Medical Officer<br>Division of Gastrointestinal and Coagulation Drug Products |

Each of the FDA presentations was followed by a question and answer period, and the Committee recessed for lunch at 1:15 p.m.

The meeting reconvened at 2:15 p.m., with the Open Public Hearing. There were three participants, Mr. Jeffrey Roberts, President of the IBS Association / IBS Self Help and Support Group, Ms. Constance Hill and Ms. Lynda K. Roepke.

At 2:40 the Committee continued with additional clarifying questions to the FDA and Sponsor on their presentations prior to a discussion of the meeting questions. The meeting was adjourned at 4:35 p.m.

The meeting transcript will be made available on the web in approximately three weeks. Transcripts may be accessed at the following web address www.fda.gov/ohrms/dockets/ac/acmenu.htm.
The Committee discussed the following questions.

## Gastrointestinal Drugs Advisory Committee
## Questions for NDA 21-200/S-005, Zelnorm® (tegaserod maleate) Tablets

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.
   ***The Committee felt that there is some improvement of constipation quantitatively in some subpopulation, but individuals remain constipated. Although ≥ 1 CSBM is a suitable endpoint it is not significant. Several committee members stated that there is a need for a global assessment metric. One suggestion was that in future studies, improvement be measured on such a global assessment that includes a quality of life assessment and considered this to be a better end point.***

   b. Is the population studied representative of patients with chronic constipation? If not, how do the populations differ?
   ***Yes 6 No 5 Abstain 2***
   ***Some of the comments offered by members included the following.***
   ***The population is not representative on age, gender, and ethnic or racial minorities.***
   ***IBS was not excluded from the population.***

   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?
   ***Yes 0 No 13***

   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?
   ***Yes 5 No 8***

   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®?
   ***Yes 9 No 3 Abstain 1***
   ***The yes votes included a number of caveats including:***
   ***Concern about patients being treated with other disease states. The use of direct to consumer advertising. Also concern that 50% of the patients did not have constipation, the small number of patients considered elderly, and the chronic use, > 12 weeks of therapy.***

   f. Is Zelnorm® effective for the treatment of chronic constipation and associated symptoms?
   ***Yes 8 No 4 Abstain 1***

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?
   ***The committee provided the following comments:***
   ***Concern that there will be an overuse and off-label use of the drug, and of potential serious complications. There may be a need for limited access to the drug and the use of proactive postmarketing surveillance efforts. Concern that there may be an increase in ischemic colitis in constipated patients. Concern that safety is not adequately established in patients that are at highest risk, such as patients over 65.***

   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?
   ***Yes 0 No 13***

   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?
   ***Yes 9 No 3 Abstain 1***

   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.*
   ***Yes 7 No 6***

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*?
   ***As Stated above Yes 0 No 13***

   ***The following proposals to the indication were provided by the panel members and each was subjected to a vote and tallied: (except for "No under any circumstances" exclusions are not mutually exclusive)***

   ***Exclude 65 or older - 10***
   ***Exclude males - - - 8***
   ***Limited to 12 weeks therapy - - - - - 6***
   ***Require a risk management plan***
   ***And/or medication guide - - - - 2***
   ***Only for functional or idiopathic constipation - - 1***
   ***No approval under any circumstances - - 3***