

**Food and Drug Administration
Center for Drug Evaluation and Research**

**Summary Minutes of the
Gastrointestinal Drugs Advisory Committee**

June 26, 2000

Marriott Washington Center
9751 Washington Blvd.
Gaithersburg, MD

Members Present

Stephen Hanauer, M.D., Chair
Loren Laine, M.D.
George D. Ferry, M.D.
Christina M. Surawicz, M.D.
Joanne A.P. Wilson, M.D.
Joel Richter, M.D.
Michael M. Wolfe, M.D.

FDA Participants

Florence Houn, M.D.
Lilia Talarico, M.D.
Hugo Gallo-Torres, M.D., Ph.D.
Raymond Joseph, M.D., F.A.C.P.
Sonia Castillo, Ph.D.

Consumer Representative

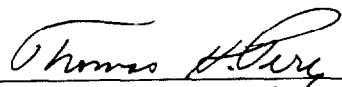
Richard J. Hammes, R.Ph

Guest Experts to the GIDAC

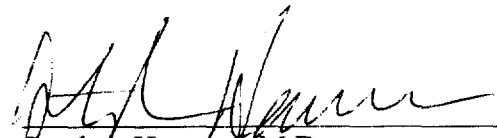
Samuel Smith, M.D.
Richard Buyalos, M.D.

These summary minutes for the June 26 meeting of the Gastrointestinal Drugs Advisory Committee were approved on November 9, 2000.

I certify that I attended the June 26 meeting of the Gastrointestinal Drugs Advisory Committee and that these minutes accurately reflect what transpired.



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



Stephen Hanauer, M.D.
Chair

This report contains public information that has not been reviewed by the agency or the Gastrointestinal Drugs Advisory Committee. The official summary minutes will be prepared, circulated, and certified as usual. Transcripts will be available in about 12 days. External requests should be submitted to the Freedom of Information office.

The Gastrointestinal Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on June 26 and 27, 2000 at the Marriott Washington Center, 9751 Washington Blvd., Gaithersburg, MD.

On June 26, 2000 the committee discussed new drug application (NDA) 21-200, Zelmac™ (tegaserod), Novartis Pharmaceuticals Corporation, for the treatment of abdominal pain and discomfort, bloating and altered bowel function in patients with irritable bowel syndrome who have predominant symptoms of pain, discomfort, and constipation.

The Committee had received a briefing document from the Novartis Pharmaceuticals Corporation, and the FDA.

There were approximately 250 persons in the audience. The meeting was called to order at 8:30am by the Chair, Stephen Hanauer, M.D. Thomas H. Perez, Executive Secretary of the Gastrointestinal Drugs Advisory Committee read the Meeting Statement. The Committee members and discussants introduced themselves.

The Novartis Pharmaceuticals Corporation presentation began at 8:45 am and proceeded as follows.

Introduction	Mathias Hukkelhoven, Ph.D., Vice President, US Drug Regulatory Affairs, Novartis
Irritable Bowel Syndrome	Arnold Wald, M.D., University of Pittsburgh Medical Center
5HT ₄ Receptor Activation	Michael Camilleri, M.D., Mayo Clinic
Efficacy and Safety of Tegaserod	Martin Lefkowitz, M.D., Director, Clinical Research, Novartis
Review of Data on Ovarian Cysts	Bruce Carr, M.D., The University of Texas Southwestern Medical Center
Closing Remarks	Sidney Cohen, M.D., Temple University School of Medicine

At approximately 11:00 the FDA, CDER presentation was made by

Statistical Reviewer	Sonia Castillo, Ph.D.
Medical Reviewer	Raymond Joseph, M.D., F.A.C.P., F.A.C.G.

The Open Public Hearing portion of the meeting included one participant, Nancy Norton, representing the International Foundation for Functional Gastrointestinal Disorders

The Committee discussed the following questions:

Novartis Pharmaceuticals Corporation has requested approval for Zelmac™ (tegaserod) Tablets for the treatment of irritable bowel syndrome (IBS) in patients who identify abdominal pain/discomfort and constipation as their predominant symptoms. The sponsor recommends a dose of 6 mg by mouth, twice a day, within 30 minutes prior to a meal.

3.

1. Has efficacy been demonstrated in both men and women with constipation-predominant IBS?

Men: Yes 0 No 8 Women: Yes 6 No 2

(a) If not, in which gender was efficacy demonstrated? Answer: Only in Women

(b) If yes (for both genders or one), which of the following dose(s) demonstrated efficacy?

(i) 4 mg/day Yes 1
(ii) 12 mg/day Yes 4
(iii) titrated dose regimen from 4 mg/day to 12 mg/day Yes 3

2. Please comment on the following findings of the carcinogenicity studies.

(a) Mucosal hyperplasia and adenocarcinoma of the small intestine were observed in (CD-1) mice at the tegaserod dose of 600 mg/kg/day but not at 200 or 60 mg/kg/day.

Answer: Not Prohibitive

(b) An apparent increased incidence of ovarian follicular cysts at 110 weeks of age was observed in (HanIbm Wistar) rats.

Answer: Not Prohibitive

3. In the clinical trials, diarrhea was seen in greater proportion in patients receiving Zelmac™. Please comment on this finding.

Answer: Diarrhea in trials was confined and mild, and clears up upon discontinuation of medication.

4. In the clinical trials, lower abdominal pain leading to laparotomy occurred in greater proportion in patients receiving Zelmac™. Please comment on this finding.

Answer: The Committee viewed this as not a problem. A number of these are due to constipation, and some are the result of adhesions.

5. On the basis of your benefit-risk evaluation, do you recommend that Zelmac™ be approved for the indication requested by the sponsor?

Yes 1 No 7

(a) If yes,

i) what labeling recommendations do you have to reduce the potential risks of Zelmac™?

Answers: Limit to women; short term treatment (up to 12 weeks); and exclude patients prone to diarrhea.

- ii) what recommendations do you have for post-marketing studies or risk management programs to address any remaining concerns?

Answers: Long-term open label trial; Randomized dose-ranging maintenance trial in good responders; Pediatric trial that includes dose-ranging, pharmacokinetics, and dosage in both genders.

6. If not, what additional efficacy and/or safety data should the sponsor provide?

Answer: Higher dose trial in men; Adjunctive therapy to other therapies (i.e. fiber); As needed vs. Continuous use; Pregnancy registry.