DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

John R. Cutt, Ph.D.
Director, Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

RE: **NDA# 21-200**
Zelnorm (tegaserod maleate) Tablets
MACMIS# 11577

Dear Dr. Cutt:

This letter objects to Novartis Pharmaceuticals Corporation's (Novartis) dissemination of a direct-to-consumer (DTC) print advertisement (ad) for Zelnorm (tegaserod maleate) Tablets that is false or misleading, in violation of the Federal Food, Drug, and Cosmetic Act (Act) and implementing regulations. Specifically, the Division of Drug Marketing, Advertising, and Communications (DDMAC) reviewed the DTC advertisement for Zelnorm that appeared in the March 10, 2003, issue of *The New Yorker* magazine and the March 16, 2003, issue of *The New York Times Magazine* and finds it to be in violation of the Act for the following reasons.

Misleading Product Claim Ad

While not using the name of the Novartis drug—Zelnorm (tegaserod maleate) Tablets— the ad effectively promotes this drug product. In particular, the ad discusses irritable bowel syndrome (IBS) with constipation and its cure ("Her pain and suffering are over") in "just three days" ("Beating IBS. Novartis and Gloria ended 30 years of debilitating abdominal pain, bloating and constipation in just 3 days.") because of **a** "**treatment from Novartis**." (emphasis added) Consequently, this presentation is a product-specific prescription drug ad for Zelnorm that is misleading because it omits important information about the drug's safety and effectiveness.

The print ad is misleading and lacks fair balance because it fails to disclose <u>any</u> risk information in the body of the ad about Zelnorm. The print ad is also misleading because it fails to include a true statement of information in brief summary relating to side effects, contraindications (including warnings, precautions, etc.) and effectiveness, commonly referred to as the "brief summary." Finally, the print ad is misleading because it fails to clearly communicate the indication and limitations of use for Zelnorm. These omissions are of particular concern because Zelnorm has serious safety concerns that pose a considerable risk to public health and safety. Specifically:

1. According to the Indications and Usage section of the Zelnorm approved product labeling (PI):

   "Zelnorm is indicated for the **short-term treatment** of **women** with irritable bowel syndrome (IBS) **whose primary bowel symptom is constipation. The safety and effectiveness of Zelnorm in men have not been established**" (emphasis added).

   Omission of this information, especially the limitations to the indication, implies a broader use for Zelnorm than has been demonstrated by substantial evidence or substantial clinical experience.

2. According to the Contraindications section of the Zelnorm PI:

   "Zelnorm is contraindicated in those patients with **severe renal impairment; moderate or severe hepatic impairment; a history of bowel obstruction, symptomatic gallbladder disease, suspected sphincter of Oddi dysfunction, or abdominal adhesions; [or] a known hypersensitivity to the drug or any of its excipients."**

   Additionally, the Precautions section of the PI states:

   "Zelnorm should not be initiated in patients who are **currently experiencing or frequently experience diarrhea**.…Zelnorm should be discontinued **immediately in patients with new or sudden worsening of abdominal pain**" (emphasis added)

   Omission of this information, as well as omission of important adverse reactions (e.g.,. abdominal pain, headache, diarrhea) implies that there are no risks to the patient who takes Zelnorm.

Overstatement of Efficacy

The ad contains misleading claims that overstate the efficacy and clinical benefit of Zelnorm. The ad shows a picture of a smiling woman and man in a swimming pool. The ad text states (emphasis added):

"**Beating IBS**. (headline)

Novartis and Gloria ended 30 years of debilitating abdominal pain, bloating and constipation in just 3 days. (subheadline)
Ever since Gloria Swanson was nineteen—and that was over thirty years ago—she's missed out on a large part of life. Trips, time with her family, promotions at work. Gloria doesn't have a life-threatening disease. She has Irritable Bowel Syndrome (IBS) with constipation. The abdominal pain, bloating and constipation were often crippling. But **today, we see a new Gloria. Her pain and suffering are over**, thanks to her doctor and a treatment from Novartis. Together, **they stopped her 30 years of pain in just three days**. Now she and her husband Charles are making up for a lot of lost time. Novartis is proud to be the innovative force that's bringing real help to patients and their families. Millions of women suffer from IBS with constipation, and their symptoms vary from mild to severe. In Gloria's case, we're happy **her thirty years of pain have ended**. **Think what's possible**."

The bolded claims above imply greater efficacy for Zelnorm than has been demonstrated by substantial evidence or substantial clinical experience of which FDA is aware. Claims such as "Novartis and Gloria ended 30 years of debilitating abdominal pain, bloating, and constipation in just 3 days" imply that the "treatment from Novartis" (i.e., Zelnorm) conferred complete relief of her symptoms, to the point that "Gloria's" IBS with constipation was cured. Zelnorm is not indicated as a cure for IBS with constipation and does not help everyone. In fact, the approved patient labeling (PPI) states "Zelnorm does not work for all women that use it…Zelnorm increases the movement of stools (bowel movement) through the bowels. Zelnorm does not cure IBS. For those who are helped, Zelnorm reduces pain and discomfort in the abdominal area, bloating and constipation. If you stop taking Zelnorm, your IBS symptoms may return within 1 or 2 weeks."

Moreover, FDA is not aware of any studies in which patients experienced complete relief within 3 days of starting treatment with Zelnorm. The Clinical Studies section of the PI states:

> "Each week of the 4-week placebo-free baseline period and the 12-week double-blind treatment period, patients were asked the question, 'Please consider how you felt this past week in regard to your IBS, in particular your overall well-being, and symptoms of abdominal discomfort, pain, and altered bowel habit'….The response variable consisted of the following 5 categories: completely relieved, considerably relieved, somewhat relieved, unchanged, or worse. Patients were classified as responders within a month if they were considerably or completely relieved for at least two of the four weeks, or if they were at least somewhat relieved for each of the four weeks."

The print ad claims of complete relief after 3 days of therapy are misleading because only a very small proportion of patients as shown in the Clinical Studies section of the PI (and, at that, only in one of the three studies) reported complete relief after one week. Moreover, the clinical trials were only designed to assess patient response after one week or longer of Zelnorm therapy, and among those patients studied who reported relief, not all experienced the same level of relief.

Conclusions and Requested Actions

Novartis should immediately cease publication and distribution of this and other similar promotional materials for Zelnorm that contain the same or similar claims or presentations. Novartis should submit a written response to DDMAC on or before July 14, 2003, describing its intent and plans to comply with the above. In its letter to DDMAC, Novartis should include the date on which this and other similarly violative materials were discontinued.

Novartis should direct its response to the undersigned by facsimile at (301) 594-6759, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, Maryland 20857.

In all future correspondence on this matter, please refer to MACMIS ID# 11577 as well as the NDA number. DDMAC reminds Novartis that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

Christine Hemler Smith, Pharm.D.
Consumer Promotion Analyst
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Christine Smith
6/27/03 10:56:03 AM

Beating IBS.

Novartis and Gloria ended 30 years of debilitating abdominal pain, bloating and constipation in just 3 days.

Ever since Gloria Swanson was nineteen–and that was over thirty years ago–she's missed out on a large part of life. Trips, time with her family, promotions at work. Gloria doesn't have a life-threatening disease. She has Irritable Bowel Syndrome (IBS) with constipation. The abdominal pain, bloating and constipation were often crippling. But today, we see a new Gloria. Her pain and suffering are over, thanks to her doctor and a treatment from Novartis. Together, they stopped her 30 years of pain in just three days. Now she and her husband Charles are making up for a lot of lost time. Novartis is proud to be the innovative force that's bringing real help to patients and their families. Millions of women suffer from IBS with constipation, and their symptoms vary from mild to severe. In Gloria's case, we're happy her thirty years of pain have ended.

Think what's possible.

"If you have abdominal pain and constipation like I did, please, don't suffer in silence. Talk to your doctor. Help is available."

— Gloria Swanson

To find a doctor for your IBS with constipation, visit **www.novartis.com/IBSDoctorLocator**

New Yorker

NOVARTIS

www.novartis.com