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NOVARTIS

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Dear Health Care Professional:

Novartis is writing to inform you of an important drug warning and important prescribing information which has been incorporated into the labeling for Zelnorm® (tegaserod maleate) tablets. Zelnorm is a serotonin 5-HT_4 receptor partial agonist indicated for the short-term treatment of women with irritable bowel syndrome (IBS) whose primary bowel symptom is constipation. This new information relates to a Warning for serious consequences of diarrhea and a Precaution for rare reports of ischemic colitis in post marketing use of Zelnorm.

IMPORTANT DRUG WARNING

Novartis has updated the package insert to include a Warning on diarrhea. This reflects rare cases where serious consequences of diarrhea (including hypovolemia, hypotension, and syncope) have been reported in clinical trials and during marketed use of Zelnorm.

WARNINGS

Serious consequences of diarrhea, including hypovolemia, hypotension, and syncope have been reported in the clinical studies and during marketed use of Zelnorm. In some cases, these complications have required hospitalization for rehydration. Zelnorm should be discontinued immediately in patients who develop hypotension or syncope. Zelnorm should not be initiated in patients who are currently experiencing or frequently experience diarrhea (see ADVERSE REACTIONS).

In addition, the section of the package insert titled "Zelnorm-Induced Diarrhea" in the Adverse Reactions section has also been revised to include a new sentence (see underlined text).

ADVERSE REACTIONS

Zelnorm-Induced Diarrhea

In the Phase 3 clinical studies, 8.8% of patients receiving Zelnorm reported diarrhea as an adverse experience compared to 3.8% of patients receiving placebo. The majority of the Zelnorm patients reporting diarrhea had a single episode. In most cases, diarrhea occurred within the first week of treatment. Typically, diarrhea resolved with continued therapy. Overall, the discontinuation rate from the studies due to diarrhea was 1.6% among the Zelnorm-treated patients. <u>In clinical studies, a small number of patients (0.04%) experienced clinically significant diarrhea including hospitalization, hypovolemia, hypotension and need for intravenous fluids.</u> Patients who experience severe diarrhea during therapy with Zelnorm should be directed to consult their physician. Diarrhea can be the pharmacologic response to Zelnorm.

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In two clinical studies of 4-8 weeks of duration designed to assess the safety and tolerability of Zelnorm in IBS patients with diarrhea as a predominant symptom (N=162), no serious adverse events were observed; 6% of Zelnorm-treated patients discontinued treatment due to diarrhea or abdominal pain.

Accordingly, the patient prescribing information, "Information for the Patient", has also been revised to include the following information:

What is the most important information I should know about Zelnorm?

If you get new or worse abdominal pain with or without blood in your stools, stop taking Zelnorm right away and tell your doctor. Your doctor may need to do tests to find out if you have a serious problem.

Sometimes Zelnorm causes diarrhea. Stop taking Zelnorm and call your doctor right away if you get so much diarrhea that you get light-headed, dizzy, or faint.

IMPORTANT PRESCRIBING INFORMATION

Rare post marketing reports of ischemic colitis and other forms of intestinal ischemia have been reported during marketed use of Zelnorm. Placebo-controlled clinical trials of 7,000 patients for 3-month duration showed no cases of these events and would suggest the rate of these events is low. Novartis has updated the package insert to include a Precaution that includes information on these safety reports. A causal relationship between Zelnorm use and these events has not been established.

The Precautions section of the labeling has been revised as follows:

PRECAUTIONS

Ischemic Colitis

Ischemic colitis and other forms of intestinal ischemia have been reported in patients receiving Zelnorm during marketed use of the drug (see ADVERSE REACTIONS: Post Marketing Experience). A causal relationship between Zelnorm use and these events has not been established. Placebo-controlled clinical trials of 7,000 patients for 3-month duration showed no cases of these events and would suggest the rate of these events is low. Zelnorm should be discontinued immediately in patients who develop symptoms of ischemic colitis, such as rectal bleeding, bloody diarrhea, or new or worsening abdominal pain. Patients developing these symptoms should be evaluated promptly and have appropriate diagnostic testing performed. Treatment with Zelnorm should not be resumed in patients who develop findings consistent with ischemic colitis.

Accordingly, a new sentence has also been added to the Precautions section titled "Information for Patients".

Information for Patients

Patients should stop Zelnorm treatment and consult their physician if they experience new or worsening abdominal pain with or without rectal bleeding.

In addition, the section of the package insert titled "Post Marketing Experience" in the Adverse Reactions section has been revised to include new information on safety reports received during marketed use of Zelnorm (see underlined text).

ADVERSE REACTIONS

Post Marketing Experience

Voluntary reports of adverse events occurring with the use of Zelnorm include the following: ischemic colitis (see PRECAUTIONS), mesenteric ischemia, gangrenous bowel, rectal bleeding, syncope, suspected sphincter of Oddi spasm, bile duct stone, and cholecystitis with elevated transaminases. Because these cases are reported voluntarily from a population of unknown size estimates of frequency cannot be made. No causal relationship between these events and Zelnorm use has been established. Hypokalemia secondary to diarrhea has also been reported.

Healthcare professionals should report all serious adverse events suspected to be associated with the use of Zelnorm to Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, New Jersey 07936 by phone (888) NOW-NOVARTIS or (888-669-6682) or the internet at http://www.novartis.com.

Alternatively, this information may be reported to FDA's MedWatch Reporting System by phone at 1-800-FDA-1088, by facsimile 1-800-FDA-0178, by mail using the Form 3500 at http://www.fda.gov/medwatch/index.html.

Please see the enclosed revised package insert for complete prescribing information.

Sincerely,

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