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by Lynne Peterson

Quick Pulse

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Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

NOVARTIS DRUG WITHDRAWN FROM U.S. MARKET

At the FDA's request, Novartis is voluntarily withdrawing Zelnorm (tegaserod maleate) from the U.S. market. The decision was based on a meta-analysis of 29 trials which found Zelnorm is associated with an unacceptably high risk of heart attack, stroke, and angina.

Zelnorm, or Zelmac as it is called in some countries, is sold in 55 countries other than the U.S., including Australia and Canada. The outlook in those countries has not been determined. The FDA has communicated with international regulators, and Novartis reportedly is in discussions with other countries on what the appropriate action might be in those countries.

Dr. John Jenkins, director of the FDA's Office of New Drugs in the Center for Drug Evaluation and Research (CDER), said the pooled data from 29 short-term, randomized, placebo-controlled trials found a 0.1% incidence of cardiovascular (CV) ischemic events – myocardial infarction (MI), stroke, and angina – with Zelnorm vs. 0.01% with placebo, a statistically significant difference between the two groups. Out of 11,614 patients taking Zelnorm, 13 had serious and life-threatening adverse cardiac events (4 heart attacks, 6 unstable angina, 3 strokes), and one of these died. In comparison, only one placebo-treated patient (out of 7,031) had an adverse event – symptoms suggesting the beginning of a stroke that went away without complication.

Dr. Jenkins said, "It is important to emphasize the actual number of adverse events were small. However, patients treated with Zelnorm were more likely to have these events than patients treated with placebo…The absolute risk of a cardio-vascular event in Zelnorm patients was quite small…(but) the relative risk compared to placebo was significantly greater."

FDA officials had no estimate of how many Americans are taking or have taken Zelnorm. Public Citizen's Health Research Group estimated that 2.13 million prescriptions were written for Zelnorm in 2005 alone, making it one of the 200 most-prescribed drugs in the U.S.

Zelnorm was first approved in July 2002 for the short-term treatment of women with irritable bowel syndrome (IBS) whose primary symptom was constipation (IBS-C). It was subsequently approved in August 2004 for the treatment of chronic constipation for men and women <age 65. The label for Zelnorm warned of a small (but not statistically significant) incidence of angina since the drug was approved. In April 2004, the label was changed to include a new warning about the serious consequences of diarrhea and a new precaution about ischemic colitis and other forms of intestinal ischemia.

An earlier gastrointestinal drug, Johnson & Johnson's Propulsid (cisapride), a partial 5-HT4 receptor agonist, was taken off the market in 2000 because of cardiac arrhythmias. Before Zelnorm was first approved, Public Citizen Health Research Group urged the FDA not to approve the drug, contending it was "only marginally effective" and had "serious safety concerns," including an "increased incidence of ovarian cysts and a five-fold increase in fainting (syncope) compared to placebo." Dr. Sidney Wolfe said he warned the FDA that Zelnorm also acted on 5-HT4 receptors, which occur in the heart as well as in the intestinal tract.

Dr. Jenkins said that when the FDA reviewed Zelnorm in 2002 and again in 2004 there wasn't a clear signal of a problem, "There were imbalances between Zelnorm and placebo, but they were not such that you could draw inferences. It really took pulling together all 29 studies conducted over the life of the product to see this level of signal…The AERS (Adverse Event Reporting System) database had eight reports of this type with Zelnorm, and Novartis had 19 reports worldwide…It is very difficult to ascertain causality or understand adverse events in AERS because there is a high background rate of heart attacks, stroke, etc., so that is not the best place to look for what is a fairly common adverse event." Dr. Gerald Dal Pan, director of the FDA's Office of Surveillance and Epidemiology in CDER, added, "The spontaneous reporting system is not very sensitive for events that are common in the background. We had eight CV reports in AERS. All those patients had an underlying risk factor for cardiac disease, and many of them actually had pre-existing cardiac disease itself …so it is difficult to make any inferences from that…All had prior CV events, most commonly prior heart attacks."

The meta-analysis was performed by Novartis at the request of Swiss regulators, who asked for the study after the FDA added ischemic colitis to the Zelnorm labeling in 2004. Dr. Jenkins explained, "As part of their interest in looking at ischemic colitis, they apparently asked Novartis to broaden the look at the database to look at all ischemic events, and that led to the findings on which we based our decision."

While the FDA does not use meta-analyses for approval of a drug, meta-analyses are useful for studying safety. Dr. Jenkins said, "We are very skeptical of a meta-analysis as the basis for approval for effectiveness…We commonly use them to strengthen the signal for safety findings. This is an example where pooled data can be useful for safety, but we are skeptical and don't use a meta-analysis as the primary basis for approval on effectiveness."

The FDA said it was first informed of the findings on February 27, 2007, and immediately requested additional information from Novartis. After reviewing the information, the FDA met with Novartis on March 28 and informed the company that "the risk:benefit profile was no longer favorable," requesting that Novartis discontinue marketing. The next day, Novartis agreed.

Patients using Zelnorm should contact their healthcare advisor to discuss alternate treatment. Patients should seek emergency medical care if they experience severe chest pain, dizziness, shortness of breath, sudden onset of weakness, difficulty walking or talking, or other symptoms of a heart attack or stroke.

Although all of Zelnorm patients with CV side effects had pre-existing CV disease and/or CV risk factors, FDA officials insisted causality is not definitely established. Dr. Jenkins said, "We don't know at this time whether the relative risk of these events is different in people who do or don't have the risk factors. We didn't see events in patients without risk factors, but we don't know if that means the risk is different in patients without risk factors…We have not proven causality. The data are very concerning…There may be hypothetical mechanisms by which someone might speculate that Zelnorm might cause vasospasm of the arteries. That has not been well-proven, particularly not in humans…So, we don't have an answer if this is a mechanistic finding…We don't have to have causality on safety to take action."

Novartis is not giving up on Zelnorm. Dr. Stephen Cunningham, vice president and head of U.S. clinical development and medical affairs at Novartis, said, "Zelnorm provides unique benefits to patients by treating the multiple symptoms of abdominal pain, bloating, and constipation that are associated with IBS with constipation. Although we have complied with the FDA's request and are collaborating with the Agency, we continue to believe that Zelnorm provides important benefits for appropriate patients."

The FDA is leaving the door open a crack for Zelnorm. The Agency plans to approve access to the drug under a "Treatment Investigational New Drug Application (IND)." Dr. Jenkins said, "FDA does recognize that Zelnorm is the only drug for the treatment of IBS-C, and there may be some patients with severe symptoms who do not have other effective treatment options. The FDA has agreed to work to open a "treatment IND" to allow access to Zelnorm for patients with no other treatment options where the benefits may outweigh the risk. Novartis and FDA will work as quickly as possible to get the treatment IND up and running."

However, Dr. Jenkins estimated it will take at least several weeks to get this program working. He said, "Novartis needs to submit a proposed protocol and the parameters of that program…We will review it as expeditiously as possible, and then Novartis will be the contact point for physicians who want to enter patients into the treatment IND for access. The program is not set up yet, and it will take at least several weeks before something will be in place."

In addition, the FDA may consider letting Zelnorm back on the market for a subgroup of patients – but not before there is more data and an FDA Advisory Committee meeting. Dr. Jenkins said, "There may be a population of patients where Zelnorm is the only treatment option and where the benefits

may outweigh the cardiovascular event risk…FDA has agreed to consider a limited…reintroduction of Zelnorm at a later date…That would require data to identify a patient population where the benefit may outweigh the risk…Before any such proposal it would be presented to a public advisory committee meeting."

Asked if it was coincidental that the withdrawal of Zelnorm came just one day after pergolide was also withdrawn from the market for safety reasons, Dr. Jenkins said, "We are focusing on drug safety as we always have…The withdrawals today and yesterday are coincidental. The Permax (Valeant Pharmaceuticals, pergolide) work was ongoing for the last several weeks to evaluate the data and make a decision. The information on Zelnorm came in a few weeks ago, and we worked to evaluate it rapidly and make the decision we are communicating (now)."

In the future, the FDA may require annual safety reports for many drugs. The FDA has proposed a requirement for periodic safety update reports (PSURs), which Dr. Jenkins described as "an opportunity or a requirement for a company to once a year do a comprehensive analysis of all post-marketing data." He said that is not yet required, but some companies are already submitting annual PSURs.

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