Maker of Weight-Loss Drug Pulls Application

BY ALICIA AULT
Associate Editor, Practice Trends

Soon after the Food and Drug Administration's Endocrinologic and Metabolic Drugs Advisory Committee voted unanimously against recommending approval of the weight-loss drug Zimulti, Sanofi-Aventis withdrew its new drug application, saying it needed time to discuss the panel's findings with the FDA.

The agency had been required to act on the Zimulti (rimonabant) application by July 26, and the likely result would have been a "nonapprovable" letter. The committee's recommendations are not binding, but the FDA generally follows its advice.

The panel members said at their June 13 meeting in Silver Spring, Md., that although they believed that the drug effectively helped patients lose about 5% of body weight, questions about psychiatric and neurologic side effects were too numerous. The advisory committee also expressed concerns about a high number of drop-outs in the company's four pivotal studies and about whether Zimulti was safe for long-term use.

Sanofi said Zimulti would have to be taken daily for a lifetime to combat what it called a chronic condition.

"There's much good about rimonabant," said obesity expert Dr. Jules Hirsch of the Rockefeller University in New York, a temporary member of the FDA panel. He lauded the drug's ability to help patients lose weight and to improve triglyceride, HDL-cholesterol, and hemoglobin A_{1c} levels. "But I wouldn't in any way suggest that it be approved at the present time for use," he added, citing safety concerns.

Sanofi repeatedly told the panel it would insist that Zimulti only be prescribed to patients who were prepared to comply with diet and exercise counseling, and who did not have a history of depression or epilepsy and were not currently receiving therapy for either of those conditions. The company also said it would ask physicians to administer a two-question depression screen to patients before prescribing Zimulti, and that it would monitor doctors' prescribing habits through regular surveys that would tell the company if depressed or epileptic patients were getting the drug.

Panelists were impressed but not swayed. "This is a real quandary for me," said Dr. Wayne Goodman, chairman of psychiatry department at the University of Florida, Gainesville. "There are very few effective treatments for obesity out there …I don't want to deny this option." However, Dr. Goodman said he could not vote for approval because of concerns about higher rates of depression, anxiety, and suicidality among Zimulti patients.

Panel members had cited concerns about higher rates of depression, anxiety, suicidality, and neurologic side effects among patients on Zimulti.

Zimulti is approved in 37 countries, but is currently only marketed in 18, according to Sanofi. It is indicated as an adjunct to diet and exercise for obese patients (those with a body mass index greater than 30 kg/m^2) or overweight patients (those with a BMI greater than 27 kg/m^2) with associated risk factors such as type 2 diabetes.

Sanofi initially sought the same indication in the United States, along with using it in combination with metformin or a sulfonylurea to improve glycemic control and reduce weight in type 2 diabetes. The company later dropped the diabetes indication.

Although it voted against recommending approval, the advisory committee said it was willing to reconsider the issue after Sanofi completes the 17,000-patient Comprehensive Rimonabant Evaluation Study of Cardiovascular Endpoints and Outcomes (CRESCENDO) in 2010; that study will have 5-year follow-up data on patients.

In announcing its NDA withdrawal, Sanofi did not say whether it would wait until those results are in. But the company did acknowledge that duration of treatment was a major concern of the panel. The reason for withdrawal was "our difficulty [in understanding] some points raised by the advisory panel and written in the minutes of the advisory committee from the FDA, such as the duration of treatment requested for a chronic disease like obesity," said Marc Cluzel, Sanofi's senior vice president of scientific and medical affairs, in a June 29 conference call. "We thought that we have not enough time up to the [Prescription Drug User Fee Act] date to discuss this point with the FDA."

The company will continue with its clinical program in rimonabant and will "quickly approach the FDA in order to determine together the most suitable label for Zimulti and the activities to be performed in order to resubmit," he said.

The pivotal data came from four international multicenter studies that were part of the Rimonabant in Obesity and Related Metabolic Disorders (RIO) trials: RIO-North America, which involved 3,040 obese or overweight patients without comorbidities who were randomized to drug (5 mg or 20 mg) or placebo for a year, followed by having half of each group randomized to placebo for another year; RIO-Europe, a 2-year study with 1,507 patients similar to those in RIO-North America; RIO-Lipids, a 1-year trial involving 1,033 obese patients with untreated dyslipidemia; and RIO-Diabetes, a 1-year trial involving 1,045 obese or overweight patients with type 2 diabetes who were taking either metformin or a sulfonylurea.

Patients had a mean BMI of 34-37 in those studies, and a mean age of 45-55. Overall, they lost 9-12 pounds, or about 5% of baseline weight, though there was a trend toward a plateauing and then weight increase at the 2-year mark. In RIO-Lipids, patients taking the 20-mg dose saw an increase in HDL cholesterol of about 8% and a decrease in triglycerides of 12%.

Neither the panel nor the FDA questioned Zimulti's effectiveness; instead, safety was the big concern.

Sanofi classified rimonabant as a selective and neutral antagonist of the cannabinoid-1 receptor. But some panelists questioned whether some of the psychiatric and neurologic side effects with Zimulti might indicate that it was acting as an inverse agonist on the endocannabinoid system, meaning the drug would lock the receptors into inactivity and lead to negative consequences.

The FDA estimated that the relative risk for psychiatric adverse events in patients taking Zimulti in the four trials was 1.9, compared with placebo, and for neurologic adverse events the relative risk was 1.7. Four completed suicides have been reported for all of the company's completed and ongoing trials, said Dr. Amy G. Egan of the FDA's division of metabolic and endocrine products.

Because of the high drop-out rate seen in the trials—32%-49% in the first year, and 23%-58% in the second year—the relative risk may be underestimated, said Dr. Egan.

Zimulti appeared to double the risk of psychiatric adverse events, increased a variety of neurologic events, and increased nausea and vomiting, said Dr. Egan, adding that many of the risks "appear to be more pronounced in diabetics."

The depression-obesity interrelationship gave pause to Dr. Sidney Wolfe, director of Public Citizen's Health Research Group. "The evidence for increased suicidality and depression is of particular concern for a drug targeted towards the obese, a population that has been shown to have a significantly higher incidence of depression," he told the advisory committee. ■

FDA Proposes New Limits on Advisers With Conflicts

BY ALICIA AULT
Associate Editor, Practice Trends

The Food and Drug Administration is proposing to beef up its conflict-of-interest guidelines for experts who serve on its advisory committees, the agency announced in a teleconference.

Proposed guidelines would bar experts with stock or other financial interests worth more than $50,000 in a particular company from reviewing that manufacturer's product and ban voting by those who receive or own less than $50,000.

The $50,000 rule would be applied to any holdings or interest within 12 months of an advisory panel meeting.

The proposal was billed by FDA officials as an upgrade of guidelines that have been in effect since 2000 and were made partly in response to public demands for more accountability, according to Randall Lutter, FDA acting deputy commissioner for policy.

"[The] FDA is committed to making the advisory committee process more rigorous and transparent so that the public has confidence in the integrity of the recommendations made by its advisory committees," said Mr. Lutter in a statement issued by the agency.

However, in the briefing, he said the FDA "was not aware of any instances where decision making has been adversely affected by conflicts members might have." The new guidance attempts to balance the quest for transparency with the need for qualified experts, Mr. Lutter said.

As in the past, the guidelines are not legally binding. They are offered as suggestions to staff evaluating potential conflicts of interest by both government and nongovernment employees. It is rare for staff to make decisions that fall outside of the guidance, though, and waivers will likely only rarely be granted, Mr. Lutter said. For instance, if a panel member has received an individual grant or other fee of less than $50,000 from a company for work in the hematology area, but is reviewing the company's cardiology drug or device, that person might be allowed to participate in the panel meeting.

Mr. Lutter and other agency officials would not say how they came up with the $50,000 threshold or how many current advisory panel members might be disqualified based on that figure. However, said Mr. Lutter, "our judgment is, it is a significant number."

The proposed restriction would apply to stocks and investments, primary employment, consulting work, contracts and grants, royalties, expert witness work, and speaking and writing fees. It would not apply to mutual funds. The $50,000 figure would be increased each year in line with the consumer price index, according to the proposal.

A critic of the FDA's conflict-of-interest policies said the new guidance is a significant step forward in part because it would bar participants from voting if they had a financial conflict.

They "will be identified as committee members with a taint," said Peter Lurie, deputy director of Public Citizen's Health Research Group. In the past, even nonvoting members could influence a panel's decision, he said, adding that the new proposal will act as a "countermeasure."

The proposed rules also could "drive the conflict rate lower," said Mr. Lurie, noting that when it comes to recruiting new advisory committee members, "there's going to be a premium on finding those who don't have conflicts."

To submit electronic comments on the draft guidance, visit www.regulations.gov or www.fda.gov/dockets/ecomments. Written comments may be sent to: Division of Dockets Management (HFA-305), U.S. Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD, 20852. Comments must include the docket number 2007D-0101. ■

Pages 70a—70b