NEWS FROM THE FDA

Panel Split on Pulling Sibutramine Off Market

BY ELIZABETH MECHCATIE

FROM THE FDA'S ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

ADELPHI, MD. – A Food and Drug Administration advisory panel split on whether to recommend that sibutramine, the norepinephrine reuptake inhibitor approved as a weight-loss agent in 1997, be withdrawn from the market because of concerns over its cardiovascular safety, at a meeting last month held to review the results of a cardiovascular outcomes study of the drug.

At a meeting of the committee, held to discuss the results of a large cardiovascular outcomes study of the drug, 8 of the 16 panelists recommended that sibutramine be withdrawn from the U.S. market because of concerns over cardiovascular safety, its modest weight loss effect, and lack of evidence of health benefits associated with treatment. Another two panelists recommended that it remain on the market, with the addition of a boxed warning to the label warning that treatment is associated with an increased risk for cardiac events and that blood pressure and pulse need to be monitored in patients during treatment.

ELIZABETH MECHATIE/ELSEVIER GLOBAL MEDICAL NEWS

The panelists were split into three groups, including one that recommended withdrawing the drug because of safety concerns.

The remaining six panelists recommended that it be allowed to remain on the market with this boxed warning – as well as limiting the drug's use by restricting its distribution which could include only allowing specialists to prescribe the drug to patients.

"I have yet to see any positive benefit of the weight loss on this drug," remarked Dr. Lamont Weide, chief, diabetes and endocrinology, and professor of internal medicine, University of Missouri, Kansas City. What is needed is some "identifiable, quantifiable benefit" to counteract the risks of the drug, "and we can't identify patients at risk," added Dr. Weide, who voted to withdraw the drug.

Sibutramine, which has sympathomimetic effects, is marketed as Meridia by Abbott Laboratories as a weight-loss agent in obese or overweight people.

The modest increases in heart rate and blood pressure associated with sibutramine treatment have been a concern since it was approved, and, in 2002, contraindications were added to the label for the following populations: patients with a history of cardiovascular disease, heart failure, tachycardia, peripheral artery disease, arrhythmias, and cerebrovascular disease; patients with inadequately controlled hypertension; and patients older than 65 years. These additions were made because of concerns over data indicating that the risk of MIs and strokes was increased in patients with cardiovascular disease treated with sibutramine.

These concerns prompted the Sibutramine Cardiovascular Outcomes (SCOUT) trial, a randomized, double-blind trial that compared placebo to sibutramine in almost 10,000 obese men and women, aged 51-88 years, with preexisting cardiovascular disease, type 2 diabetes, or both. The study was conducted at the request of European health authorities and was the focus of the meeting.

Over a mean 3.4 years, the risk of nonfatal MI, nonfatal stroke, resuscitation after cardiac arrest, or cardiovascular death (the primary end point) was increased by 16% among those treated with sibutramine over those on placebo. The increased risk was driven by the greater rate of nonfatal MIs (4.1%) and nonfatal strokes (2.6%) among those on sibutramine, compared to those on placebo (3.2% and 1.9%, respectively); the risk of cardiovascular mortality was not increased. The risk of the nonfatal events was increased among sibutramine users with preexisting cardiovascular disease and with cardiovascular disease and type 2 diabetes, but not among those with type 2 diabetes alone.

Abbott officials maintained that it was difficult to extrapolate the results of SCOUT, which enrolled mostly patients with contraindications to sibutramine, to use of the drug in patients who meet the labeled criteria for treatment. They also pointed out that cardiovascular event rates in "real world" sibutramine users, who reflect on-label population, are low compared to the rates in SCOUT.

The company also proposed a risk management plan to address the risks, which would include a single pharmacy and a boxed warning to reinforce the contraindications in people with a CVD history and dispensing of the drug from a single pharmacy, to ensure treatment is started only in appropriate patients.

The FDA usually follows the recommendations of its advisory panels. ■

Disclosures: Members of advisory panels have been cleared of having conflicts related to the topic of meetings. Occasionally, the agency grants a waiver to a panelist who has conflicts, but not at this meeting.

Naltrexone Is Safe but Needs Stronger Label, Panel Advises

BY MARTIN BERMAN-GORVINE

"The Pink Sheet"

Naltrexone is safe and effective for the treatment of opioid abuse, but the company should build on existing labeling that calls for monitoring and support as essential parts of therapy, a Food and Drug Administration advisory panel said.

Lingering concerns about the applicability of the results from the single clinical trial, which was conducted in Russia, to the U.S. population were not enough to stem the tide of support. The Psychopharmacologic Drugs Advisory Committee voted 11-2 with no abstentions in middle September that data from the trial were sufficient to demonstrate efficacy, 10-1 with 2 abstentions that the data could be applied to the U.S. population, 12-0 with 1 abstention that the safety data were adequate, and 12-1 that the supplemental indication should be approved.

Alkermes Inc., maker of naltrexone under the name Vivitrol, has a head start on the monitoring and support question from the drug's current label for alcohol abuse treatment, which states: "Alcohol-dependent patients, including those taking Vivitrol, should be monitored for the development of depression or suicidal thinking. Families and caregivers of patients being treated with Vivitrol should be alerted to the need to monitor patients for the emergence of symptoms of depression or suicidality, and to report such symptoms to the patient's health care provider."

The label also says that "patients should be advised that Vivitrol has been shown to treat alcohol dependence only when used as part of a treatment program that includes counseling and support."

Citing a presentation delivered on behalf of Alkermes by Dr. Paul Earley, medical director of the Talbott Recovery Campus, panel member Chung-yui Betty Tai, Ph.D., of the National Institute on Drug Abuse, said that Vivitrol "is a good medication for young [patients with a] short addiction history [who are] highly motivated, such as addicted professionals, and also with strong social and family support. Based on those, I think that's comparable to the Russian population in the study, based on the report I have reviewed."

"I am of the belief that no one piece of treatment decides totally what the outcome is," Louis Baxter, executive medical director of the Professional Assistance Program of New Jersey, said. "So using this medicine in conjunction with the other elements of addiction treatment, I believe that we will actually be able to observe those same results [as in the Russian trial] and perhaps even better."

Data from an intent-to-treat analysis of the 250 patients enrolled in the study showed that the 126 patients treated once monthly with Vivitrol had 90% opioid-free urine screens, compared with 35% for the 124 patients taking a placebo. "It's rare to see data this robust to show the efficacy, although it's from a single trial," Dr. Tai said, citing her long experience doing clinical trials for drug addiction treatments.

The FDA's official view going into the meeting was almost unequivocally positive as well. "I think we've made it clear that we agreed with the sponsor that they have demonstrated efficacy and that there are no particularly concerning new safety signals with this formulation. And really, we did not find any concerns related to the data integrity from the one study," Dr. Bob Rappoport, director of the division of anesthesia and analgesia products, said. However, he added, "the single study done in Russia still raises questions. … I think we feel that we've adequately addressed those questions to our level of comfort, but we want to hear from [the advisory committee]."

This apparently refers to a concern raised in background materials released before the meeting that there was a lower rate of adverse events in the Russian study than in prior studies conducted in the United States, and there might be a "cultural norm" in Russia of underreporting adverse events.

However, this question was addressed in a presentation by Dr. Tejashri Purohit-Sheth, branch chief for Good Clinical Practice 2 at the FDA's division of scientific investigations, who said that the agency found in its inspection of 4 of the 13 Russian sites that "adverse event and serious adverse event reporting [were] adequate," and that there was "no evidence of underreporting."

The data are "reliable in support of the application," she said.

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