FDA Seeks More Data on Qnexa Side Effects

BY LISA LAMOTTA

The Food and Drug Administration issued a "complete response" letter for Qnexa, the combination phentermine/topiramate pill.

The letter asked its manufacturer, Vivus Inc., for "a comprehensive assessment of topiramate's and phentermine/topiramate's teratogenic potential," including a plan to evaluate and mitigate the risks of birth defects in women of childbearing age. It also asked for the company to provide evidence that the elevated heart rate associated with the combination does not increase the risk for serious cardiovascular issues.

Beyond that, FDA requested that the company continue its discussion with the agency concerning its Risk Evaluation and Mitigation Strategy. Although the FDA did not demand new clinical trials, it could ask for further studies later on, if its concerns are not alleviated.

Vivus said in a press release that it plans to respond to the letter within 6 weeks. "As part of the written response, the company plans to compile analyses integrating existing nonclinical and clinical data to provide a comprehensive assessment of the teratogenic potential of topiramate. In addition, Vivus plans to provide several new analyses to demonstrate Qnexa "does not increase the risk for major cardiovascular events."

The letter and its contents were not a surprise, since the Endocrinologic and Metabolic Drugs Advisory Committee in mid-July voted 10-6 against approval of the drug. Panelists there agreed the combination was an effective weight-loss agent, but were concerned about the associated risks, including teratogenicity, psychiatric effects, neurocognitive effects, increases in heart rate, and drops in serum bicarbonate levels. A prominent concern was that if the drug were approved, it would be used widely in populations other than those in the proposed indication.

Since the advisory committee meeting, Vivus has released the data from a 2-year study, Sequel, a follow-up trial to an earlier study, Conquer. Sequel involved 675 patients who completed the first 56 weeks of Conquer as well as another 52 weeks. The FDA asked for the submission of the data in the complete response.

Sequel showed that patients taking the highest dose of Qnexa achieved and maintained weight loss of 11.4%, or about 26 pounds, throughout the 2 years, while placebo patients achieved about 2.5% weight loss. Beyond that, the trial showed patients without diabetes were 76% less likely to develop the disease while taking the highest doses of Qnexa. Patients also saw improvements in weight-related comorbidities such as hypertension.

The advisory committee that reviewed Qnexa was concerned that safety issues for phentermine and topiramate would also be characteristics of Qnexa, even though it is a controlled-release formulation, and given in much lower doses than for the earlier indications. (The tested doses are 3.75 mg of phentermine and 23 mg of topiramate, as the starting dose; 7.5 mg/46 mg, as the recommended dose; and 15 mg/92 mg for patients not reaching their weight-loss goal.)

Phentermine raises the heart rate in patients, yet patients taking Qnexa in clinical trials experienced only a modest increase in heart rate and did not have any cardiovascular adverse events. Meanwhile, topiramate has been shown to cause birth defects and suicidal thoughts, but Qnexa again exhibited no evidence of these issues during studies. Women who became pregnant during the clinical trials did not have problem pregnancies or babies with birth defects.

The difference in safety profile may be related to dosing or administration, but ultimately, the panel was most concerned about the lack of sufficient data to allay these fears, calling for trials that followed patients for a longer period of time. "When you listen to the no votes you get the sense that they just had a little bit of hesitancy," Dr. Eric Colman, deputy director of the FDA's Division of Metabolism and Endocrinology Products, said to reporters after the meeting. ■

Lisa LaMotta is with "The Pink Sheet," which along with this newspaper is owned by Elsevier.