

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 test-

ed 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.

Now Approved

In addition to diet and exercise to improve glycemic

ONCE A DAY
kombiglyze XR
 (saxagliptin and metformin HCl
 extended-release) tablets

1
 ONE DAILY DOSE

The first and only once-a-day metformin XR + DPP-4 inhibitor* combination tablet.

Generally taken once-daily with evening meal; gradually titrate dose to reduce GI side effects associated with metformin. Maximum daily recommended dose is 5 mg saxagliptin and 2000 mg metformin XR that can be taken as two 2.5 mg/1000 mg tablets once a day.

*saxagliptin

Indication and Important Limitations of Use

KOMBIGLYZE XR is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate. KOMBIGLYZE XR should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. KOMBIGLYZE XR has not been studied in combination with insulin.

Important Safety Information

WARNING: LACTIC ACIDOSIS

Lactic acidosis is a rare, but serious, complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure.

The onset of lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress.

Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate.

If acidosis is suspected, KOMBIGLYZE XR should be discontinued and the patient hospitalized immediately.

[See Warnings and Precautions]

Contraindications

- Renal impairment (e.g., serum creatinine levels ≥ 1.5 mg/dL for men, ≥ 1.4 mg/dL for women, or abnormal creatinine clearance)
- Hypersensitivity to metformin hydrochloride
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis
- KOMBIGLYZE XR should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials because use of such products may result in acute alteration of renal function.

Warnings and Precautions

- The reported incidence of lactic acidosis in patients receiving metformin is very low (approximately 0.03 cases/1000 patient-years). When it occurs, it is fatal in approximately 50% of cases. Reported cases of lactic acidosis have occurred primarily in diabetic patients with significant renal insufficiency.
- Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis.
- Lactic acidosis risk increases with the degree of renal dysfunction and patient age. The risk may be significantly decreased by use of minimum effective dose of metformin and regular monitoring of renal function. Careful renal monitoring is particularly important in the elderly. KOMBIGLYZE XR should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.
- Withhold KOMBIGLYZE XR in the presence of any condition associated with hypoxemia, dehydration, or sepsis.
- Before initiation of KOMBIGLYZE XR, and at least annually thereafter, renal function should be assessed and verified as normal.
- KOMBIGLYZE XR is not recommended in patients with hepatic impairment.
- Metformin may lower vitamin B12 levels. Measure hematological parameters annually.
- Warn patients against excessive alcohol intake.
- KOMBIGLYZE XR should be suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids), and should not be restarted until patient’s oral intake has resumed and renal function is normal.
- Use of saxagliptin or metformin with medications known to cause hypoglycemia
 - Saxagliptin: Insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia if used in combination with KOMBIGLYZE XR.

Please see adjacent Brief Summary of US Full Prescribing Information including **Boxed WARNING** about lactic acidosis.