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Will A CV Warning On Meridia Alter FDA Views On Obesity Drugs?

The FDA’s cardiovascular safety warning on Abbott’s obesity drug *Meridia* (sibutramine) – which was issued in light of early results from a 10,000 patient strong outcomes study – could mean higher regulatory risk for up-and-coming obesity drugs.

Preliminary data from Abbott’s Sibutramine Cardiovascular Outcomes Trial shows that patients using the drug had a slightly higher rate of cardiovascular events, including heart attack, stroke, resuscitated cardiac arrest, or death than those on placebo (11.4 percent versus 10 percent), according to a Nov. 20 agency warning sent to health care professionals and patients. To date, the adverse events do not include deaths, said an FDA spokesperson.

The finding is another blow to a drug that initially emerged as a salve amid the controversy over the 1997 withdrawal of the fen-phen diet-pill combination. Approved the same year by FDA and in Europe two years later, sibutramine was the second largest global player in obesity after Roche’s *Xenical* (orlistat) by 2008, with a 20 percent market share. Nonetheless, the product generated only modest sales that year of \$359 million, while sitting on the back burner of Abbott’s sales and marketing efforts.

The drug actually began its decline seven years ago, when 50 adverse events and two deaths in Italy led European regulators to suspend approval. The EU European Medicines Agency Committee for Medicinal Products for Human Use required a CV outcomes study in at-risk patients as a condition for returning the pill to the marketplace (“The Pink Sheet,” June 17, 2002). Around the same time, the U.S. consumer advocacy group Public Citizen was lobbying for the drug’s withdrawal and the FDA issued a warning letter about Abbott’s adverse event reporting practices (“The Pink Sheet,” Aug. 12, 2002).

SCOUT is believed to be the first formal clinical trial documenting the impact of modest weight loss on cardiovascular events and mortality. It took seven years to gather the necessary number of CV events to answer questions about the drug’s long-term efficacy and safety, the FDA spokesperson explained. Although sibutramine is known to raise blood pressure and heart rate, some analysts nevertheless said results were somewhat surprising.

“The SCOUT trial was intended to demonstrate that sibutramine, or more precisely, weight loss, would translate into reduced rate of cardiovascular events so the data (as judged by the FDA’s comment) have to be disappointing,” wrote Lazard analyst William Tanner in a Nov. 23 note.

Adverse events were more common in the treatment arm, but it’s unclear whether they occurred in patients who were actually losing weight and/or in a subgroup of the sickest patients, said Louis Aronne, director of the Comprehensive Weight Control Program at Weill-Cornell Medical College. Adherence rates in the trial are also unknown. A full dataset is needed to understand the implications, Aronne said.

Enrolled patients were 55 years of age or older, overweight or obese, and had a history of heart disease or type 2 diabetes, plus one additional cardiovascular risk factor. In its warning letter, the FDA stated: “These findings highlight the importance of avoiding the use of sibutramine in patients with a history of coronary artery disease, congestive heart failure, arrhythmias, or stroke, as recommended in the current sibutramine labeling.”

Abbott points out the drug is not approved or recommended for 90 percent of patients who were in the SCOUT study. Furthermore, a data monitoring safety board never stepped in to stop the study, the company said.

“Abbott’s assessment of the data is that they do not indicate a change in safety profile of sibutramine when used in the approved patient population,” said Abbott spokesman Kurt Ebenhoch in an interview.

Adverse event reporting system records suggest that there has been off-label use of sibutramine in patients with coronary artery disease and other risk factors, the FDA spokesperson said.

Implications for Vivus, Arena and Orexigen?

The findings from SCOUT had been eagerly awaited as a sign of the long-term safety of prescription drugs for such a common, chronic disease as obesity (“The Pink Sheet,” June 1, 2009). Instead of offering reassurance about the prospects for the pills, the release spurred questions about whether the agency will react by asking for cardiovascular outcomes studies for obesity drugs, similar to what is required in diabetes.

Earlier this year, FDA officials confirmed they were considering such a move, but acknowledged it would be difficult because obesity trials are typically done in women in their 40s, a population generally not at risk for cardiovascular events (“The Pink Sheet” DAILY, April 15, 2009). The agency said its analysis of the SCOUT data is ongoing and that it was making no conclusions about the preliminary findings at this time.

Obesity is already fraught with risk. Big Pharma has adopted a cautious stance on the therapeutic category since Sanofi-Aventis withdrew a marketing application for cannabinoid-1 antagonist *Acomplia* (rimonabant) from FDA in 2007, due to suicide risk (“The Pink Sheet” DAILY, June 29, 2007).

Extensive pivotal data were released for three compounds this year by three companies, none of which have found a partner to take their drugs forward: Arena, which is developing lorcaserin; Vivus, which is developing *Qnexa* (topiramate/phentermine); and Orexigen, which is developing *Contrave* (naltrexone/bupropion).

Writing in a Nov. 20 note, Leerink Swann analyst Joshua Schimmer noted that Qnexa showed a statistically significant reduction in both systolic and diastolic blood pressure, and “therefore, CV issues should not be a problem.”

Lorcaserin showed decreases in systolic and diastolic blood pressure, but this outcome achieved statistical significance in only one of the two Phase III trials.

Contrave did show an increase in heart rate and blood pressure in Phase III trials but not by as much as Meridia, the analyst noted: “We believe Contrave is still approvable given the efficacy and safety profile ... FDA may require post-marketing CV outcomes studies, but Orexigen was already planning on conducting them. This may be a subject to review at an advisory panel meeting.”

Weighing Safety Against Need For Options

New data could “increase regulatory scrutiny of obesity drugs,” wrote Tanner. “We suspect that data from the SCOUT trial, in conjunction with previous data for rimonabant, for example, may heighten concerns about obesity drugs and their side effects in patients with complicated medical issues.”

While the FDA has exercised more caution over safety signals, there is also reason to believe the agency would not want to unnecessarily delay development of obesity drugs, considering that few treatment options are available, according to Kelly Close, president of the diabetes consultancy Close Concerns, of San Francisco, Calif. Drugs now in development have different profiles and it might be possible to base requirements for approval on signs of cardiovascular risk, such as increased blood pressure seen with sibutramine, she said.

Sibutramine is a serotonin/norepinephrine reuptake inhibitor. A number of drugs in development also work on serotonin, but in a different way. For example, Arena's lorcaserin selectively stimulates the serotonin 5HT(2c) receptors. In theory, this avoids valvulopathy risks experienced with fenfluramine, which was one-half of the fen-phen cocktail.

REMS Are Another Option, Could Hurt Combos

Restrictive labeling or a requirement for a risk evaluation and mitigation strategy as a condition for approval seem likely in obesity, because potential for overuse or misuse is a major concern, Cowen & Company analyst Ian Sanderson said in an interview.

For example, the selected dose of J&J's anticonvulsant topiramate, one-half of the combination pill Qnexa, will be kept low enough to cause minimal effects on the central nervous system. Three controlled release doses were tested in Phase III Qnexa trials: 23 mg, 46 mg and 92 mg. In a randomized, double-blind study of overweight patients with diabetes sponsored by J&J, a 175 mg CR dose had an unacceptable CNS and psychiatric adverse event profile. J&J dropped its topiramate obesity program some time ago, but results concluding the drug was "unsuitable for treatment of diabetes and obesity," were recently published (*Diabetes Care* 30:1480-1486, 2007).

If approved, there would be a risk that Qnexa could be misused at a double dose to spur more weight loss.

"FDA is going to be extremely vigilant; they know all the drugs might be overused if they get to the market. The safety bar is raised here," Sanderson said.

A REMS would present a hurdle in prescribing and in the case of the generic combination drugs like Qnexa and Contrave, doctors may have more of an incentive to use cheaper generics instead, Sanderson said.

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