Study: Sibutramine Linked to Cardiac Events

BY ELIZABETH MECHCATIE

The Food and Drug Administration is looking at recent data suggesting that the cardiovascular event rate among patients on the weight-loss drug sibutramine was higher than among those on placebo.

"The analysis of these data is ongoing and FDA is making no conclusions about the preliminary findings at this time," according to a statement posted on the agency's MedWatch site. These findings, the statement adds, "highlight the importance of avoiding the use of sibutramine" in patients with a history of coronary artery disease, congestive heart failure, arrhythmias, or stroke, which is recommended in the current sibutramine label.

Sibutramine is an orally administered drug marketed as Meridia by Abbott Laboratories. Its therapeutic effects result from norepinephrine, serotonin, and dopamine reuptake inhibition, according to the label. It was approved in 1997 for the management of obesity in conjunction with a reduced-calorie diet, and is recommended only for obese patients with an initial body mass index at or above 30 kg/m^2 or a BMI at or above 27 kg/m^2 in patients with other risk factors such as diabetes, hypercholesterolemia, or controlled hypertension.

The FDA reported results from a study of about 10,000 overweight or obese patients aged 55 years or older who had a history of heart disease or type 2 diabetes and one additional cardiovascular risk factor. The preliminary results of the study's primary end point—MI, stroke, resuscitated cardiac arrest, or death—were reported in 11.4% of those on sibutramine, compared with 10% of those on placebo. The difference was "higher than expected, suggesting that sibutramine is associated with an increased cardiovascular risk in the study population," the FDA noted.

Recent data highlight the importance of avoiding sibutramine in patients with a history of coronary artery disease, congestive heart failure, arrhythmias, or stroke.

Abbott started the study, Sibutramine Cardiovascular Morbidity/Mortality Outcomes in Overweight or Obese Subjects at Risk of a Cardiovascular Event (SCOUT), in 2002 at the request of the FDA's European counterpart, the European Medicines Agency (EMEA), as one of the conditions for keeping the drug on the market in Europe after serious cardiovascular events were reported in the early 2000s. The study's aim was to evaluate the safety and efficacy of sibutramine in overweight and obese people.

The FDA was apprised of the results in mid-November. On Dec. 3, Public Citizen's Health Research Group, a health advocacy organization, filed a citizen's petition calling on the FDA to withdraw the drug from the market immediately, because of the new data indicating that it increases the risk of MI, stroke, resuscitated cardiac arrest, or death.

In 2005, the FDA denied a previous petition by the group requesting that sibutramine be taken off the market because of concerns over its safety arising from preapproval clinical studies.

In an interview, Dr. Sidney Wolfe, director of the Washington-based Health Research Group, said that the preliminary results of the SCOUT trial are a concern. The group continues to support the withdrawal of sibutramine from the market and is analyzing sibutramine-related reports in the FDA's adverse event reporting system database, he said.

Despite the label's recommendation that patients with risk factors such as cardiovascular disease not be treated with sibutramine, the drug is still prescribed to patients who are obese and have some of these risk factors, he noted. ■

Report adverse events to the FDA's MedWatch program at 800-332-1088 or www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm. For more information, visit www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm191655.htm.

Novel Lipid-Lowering Drug Effective, but Raises Liver Fat

BY BRUCE JANCIN

ORLANDO — Lomitapide is a powerful lipid-lowering agent with a potentially serious drawback, according to interim results of an ongoing phase III study in patients with homozygous familial hypercholesterolemia.

Lomitapide is first in a new class of investigational lipid-lowering drugs known as microsomal triglyceride transfer protein inhibitors. These agents reduce LDL cholesterol levels by inhibiting apolipoprotein B lipidation, a novel mechanism that results in reduced secretion of atherogenic apo B–containing lipoproteins, Dr. Marina Cuchel said at the annual scientific sessions of the American Heart Association.

Homozygous familial hypercholesterolemia is a rare but daunting therapeutic challenge. Affected patients have extraordinarily severe dyslipidemia from birth that often is resistant to lipid-lowering drugs. They typically develop clinical cardiovascular disease before reaching adulthood.

The 14 participants in the phase III open-label lomitapide study who have been on the drug for at least 6 months had a baseline mean LDL cholesterol level of 351 mg/dL, a total cholesterol level of 444 mg/dL, a non-HDL cholesterol level of 404 mg/dL, and an apo B level of 278—while on maximum tolerated doses of statins and other standard lipid-lowering drugs as well as apheresis and a low-fat diet. At a mean age of 33 years, 12 of the 14 (86%) had cardiovascular disease.

At week 26 of the phase III study, patients on lomitapide at a median dose of 40 mg/day—the most effective dose—along with concomitant maximal background lipid-lowering therapies, showed a mean 57% reduction in LDL from baseline. Ten of the 14 patients had an LDL level below 165 mg/dL, including 6 with an LDL level of less than 100 mg/dL, reported Dr. Cuchel of University of Pennsylvania Institute for Translational Medicine, Philadelphia.

Total cholesterol was down by 53% from baseline, non-HDL cholesterol by 56%, and apo B by 53%. Triglycerides dropped from a mean baseline of 112 to 57 mg/dL, and HDL decreased from 40 to 32 mg/dL.

The most common side effects with lomitapide were mild to moderate diarrhea, abdominal discomfort, and nausea and vomiting. To date, three patients have dropped out of the study because of GI side effects before reaching the 6-month mark on lomitapide. Two of 14 patients developed transient elevations in liver function tests of at least five times the upper limit of normal. Both responded to temporary reductions in lomitapide dosing.

The most problematic adverse effect associated with lomitapide is accumulation of liver fat. Hepatic fat content climbed from a mean baseline of 1.3% to 7.9% after 26 weeks on the investigational drug.

The long-term clinical implications of this adverse effect remain unclear. It appears to be intrinsic to inhibition of microsomal triglyceride transfer protein. In the six patients who have been on lomitapide for 1 year or longer, liver fat content stabilized or retreated from its 6-month high to a mean value of 3.7% at 56 weeks, Dr. Cuchel continued.

To date, the phase III study has enrolled 22 of a planned 25 subjects. The trial is funded by the Food and Drug Administration's Office of Orphan Drug Development and Aegerion Pharmaceuticals Inc.

Dr. Cuchel said she has no conflicts of interest to disclose. ■

Premeal Exenatide Improved Postprandial Endothelial Function

VITALS

Major Findings: Premeal exenatide injections significantly improved postprandial serum triglyceride levels and endothelial function in patients with impaired glucose tolerance or type 2 diabetes.

Source of Data: Double-blinded crossover trial of 35 patients

Disclosures: The study was funded in part by Amylin Pharmaceuticals and Lilly USA, which jointly market exenatide.

BY SHERRY BOSCHERT

SAN FRANCISCO — A premeal injection of exenatide significantly reduced postprandial serum triglyceride levels compared with placebo in a randomized, double-blinded crossover trial in 35 patients with impaired glucose tolerance or recent-onset type 2 diabetes mellitus.

In 28 patients who also underwent endothelial function tests, postprandial endothelial function was significantly better after premeal exenatide compared with placebo, and after researchers controlled for preinjection endothelial function values, Dr. Gerald Reaven said at the Sixth Annual World Congress on the Insulin Resistance Syndrome.

Further analysis suggested that the effects on postprandial triglyceride levels explained about 60% of the effects on endothelial function, added Dr. Reaven, director of the diabetes program at the Veterans Affairs Medical Center, Phoenix.

Investigators are hoping that acute therapy with exenatide or other incretin mimetics may alter metabolic factors to favorably affect endothelial dysfunction, which occurs in the early stages of diabetes. Endothelial dysfunction has been associated with cardiovascular disease, the No. 1 cause of morbidity and mortality in patients with type 2 diabetes. More research is needed to see if acute therapy can improve endothelial function.

Exenatide injection also significantly improved postprandial serum levels of apolipoprotein B48, remnant lipoprotein cholesterol, and remnant lipoprotein triglycerides compared with placebo injection, he reported.

Twenty patients with impaired glucose tolerance and 15 with type 2 diabetes diagnosed within the past 3 years whose hemoglobin A_{1c} levels were well controlled on diet without medication were randomized to receive a premeal subcutaneous injection of 10 mcg exenatide or saline before eating a calorically dense meal consisting of 45% fat, 40% carbohydrates, and 50% protein. After a 1- to 2-week washout period, the exenatide and saline groups switched therapies. Endothelial function was measured by peripheral arterial tonometry. ■