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# Colesevelam HCl Lowered LDL Cholesterol in Pediatric Patients with Heterozygous Familial Hypercholesterolemia

*First Presentation of Pivotal Study Data in Pediatric Patients Presented at the American Heart Association's Annual Scientific Sessions 2008*

**Parsippany, NJ (November 11, 2008)** – Daiichi Sankyo, Inc. (DSI), announced today that results from the pivotal study supporting the use of colesevelam HCl in pediatric patients with heterozygous familial hypercholesterolemia (heFH), were presented for the first time at the American Heart Association's (AHA) Annual Scientific Sessions 2008. According to the findings, colesevelam HCl was well-tolerated and produced a significant reduction in low density lipoprotein (LDL) or "bad" cholesterol when used as monotherapy or in combination with a statin.

Familial hypercholesterolemia (FH) is a genetic disorder resulting in elevated LDL cholesterol and increased risk of cardiovascular disease (CVD).[1] There are 10 million people with FH worldwide, the majority of whom have heterozygous FH.[2] Early identification of FH is critical, as is proper diet, exercise and medication to help lower LDL cholesterol.[3]

The efficacy of colesevelam HCl 3.75 g/day as monotherapy or in combination with a statin was evaluated in an eight-week, multi-center, randomized, double-blind, placebo-controlled study of pediatric patients with heFH, followed by an 18-week, open-label treatment period. At week eight, patients with heFH who were given colesevelam HCl 3.75 g/day showed a significant, placebo-adjusted mean reduction of 13 percent in LDL cholesterol ($p \leq 0.0001$). The reductions in LDL cholesterol in pediatric patients who received colesevelam HCl 3.75 g/day during the double-

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blind period were maintained through the 18-week open-label treatment period. Additional findings from the eight-week study showed that patients in the colesevelam HCl 3.75 g/day study group demonstrated a clinically and statistically significant, placebo-adjusted mean six percent increase in high density lipoprotein (HDL) or "good" cholesterol ($p<0.01$). These study arm findings also produced statistically significant placebo-corrected reductions from baseline in total cholesterol (7 percent; $p<0.01$), apolipoprotein B (8 percent; $p<0.01$) and non-HDL cholesterol (11 percent; $p\leq0.0001$) as well as an increase in apolipoprotein A-I (7 percent; $p<0.01$). There was a non-significant, placebo-adjusted, 5.1 percent median increase in triglyceride levels. Compliance rates for patients receiving colesevelam HCl 3.75 g/day in the study at the completion of the double-blind period was 87 percent.

"Treatment with colesevelam HCl in pediatric patients with inherited high cholesterol significantly reduced their LDL or 'bad' cholesterol and increased the HDL or 'good' cholesterol. This was seen in children who received colesevelam HCl alone or combined with a statin, demonstrating the additive effect on LDL-cholesterol reduction that is offered by colesevelam HCl therapy," said Evan A Stein MD PhD, Director, Metabolic & Atherosclerosis Research Center, Cincinnati, OH. "Current guidelines support the need for and benefits of lowering LDL cholesterol in children with heterozygous familial hypercholesterolemia."

According to the American Academy of Pediatrics (AAP), high cholesterol is a growing problem among children in the United States. In the AAP's Child and Adolescent Trial for Cardiovascular Health, 13.3 percent of children in the fourth grade had total cholesterol concentrations of greater than 200 mg/dL.[4] The current NCEP guidelines for total cholesterol in children ages 2 to 18 years of age is less than 170 mg/dL, with high cholesterol identified as greater than 200 mg/dL.[5] The AAP also recently published a statement recommending that cholesterol lowering medications should be considered for children who are more than eight years old and have high LDL concentrations.[6]

Colesevelam HCl, marketed as Welchol®, is the first and only medication indicated as an adjunct to diet and exercise to improve both glycemic control in adults with type 2 diabetes mellitus, and to reduce elevated LDL-C in adults with primary hyperlipidemia (Fredrickson Type IIa) as monotherapy or in combination with a hydroxymethyl-glutaryl-coenzyme A (HMG CoA) reductase inhibitor (a statin).[9] Welchol should not be used for the treatment of type 1 diabetes or diabetic ketoacidosis. Welchol has not been studied in type 2 diabetes as monotherapy or in combination with a DPP-4 inhibitor and has not been extensively studied in combination with thiazolidinediones. Welchol has not been studied in Fredrickson Type I, III, IV, and V dyslipidemias. Welchol is not currently approved for use in pediatric patients and has not been studied in children nine years of age and younger or in pre-menarchal girls.

**About the Study**

The study was a 32 week, multi-center, controlled study, conducted with boys and post-menarchal girls 10-17 years of age, who were either treatment naïve or on stable background statin therapy. The primary efficacy measurement was percent change in LDL-C from baseline (beginning of double-blind period) to week eight (end double-blind period). There was an initial four-week, single-blind, placebo run-in, to measure compliance, followed by an eight-week, double-blind period in which patients were randomized to either placebo (n=65), colesevelam HCl 1.875 g/day (n=65) or colesevelam HCl 3.75 g/day (n=64). The eight-week, double-blind period was followed by an 18-week open-label treatment to goal (LDL-C <110 mg/dL) in which all patients received colesevelam HCl 3.75 g/day (and were eligible to receive a statin), concluding with a two-week follow-up period.

The most common adverse reactions in the eight-week, double-blind period were: nasopharyngitis (6.2 percent), headache (4.7 percent), fatigue (3.9 percent), vomiting (2.3 percent), rhinitis (2.3 percent) and creatine phosphokinase increase (2.3 percent). The most frequently reported adverse reactions during the additional 18-week open-label treatment period were similar to those during the double-blind period and also included upper respiratory tract infection (4.9 percent), influenza (3.8 percent) and nausea (3.8 percent). Colesevelam HCl was not observed to have an effect on growth, sexual maturation, hormone levels or fat-soluble vitamin levels during the course of the study.

**IMPORTANT INFORMATION ABOUT WELCHOL® (colesevelam HCl)**

Prescription Welchol lowers LDL or "bad" cholesterol in adults, along with diet and exercise. It can be taken alone or with other cholesterol-lowering medications known as statins.

Welchol, along with diet and exercise, also lowers blood sugar levels in adults with type 2 diabetes mellitus when added to other antidiabetic medications (metformin, sulfonylureas, or insulin).

Ask your doctor if Welchol is right for you.

Welchol is not for everyone, especially those with intestinal blockage, those with blood triglyceride levels of greater than 500 mg/dL, or a history of pancreatitis (inflammation of the pancreas) due to high triglyceride levels.

Welchol has not been determined to prevent heart disease or heart attacks.

Tell your doctor if you have high triglycerides (greater than 300 mg/dL).

Tell your doctor if you have stomach or intestinal problems, including gastroparesis (when the stomach takes too long to empty its contents), abnormal contractions of the digestive system, major gastrointestinal tract surgery, or if you have trouble swallowing.

Tell your doctor if you have vitamin A, D, E, or K deficiencies.

Welchol has known interactions with glyburide (a drug for diabetes), levothyroxine (a drug used to treat an underactive thyroid) and certain oral contraceptives. Welchol has not been studied with all combinations of drugs and supplements. Please tell your doctor about all medications and supplements you may be taking before beginning Welchol, as your doctor may tell you to take your other medications and supplements 4 hours before taking Welchol.

Remember to tell your doctor if you are pregnant, plan to become pregnant, or are breastfeeding. In patients with high LDL ("bad" cholesterol) side effects that occurred greater than placebo (a "sugar" pill) were constipation (11.0% vs. 7.0%), indigestion (8.3% vs. 3.5%), nausea (4.2% vs. 3.9%), accidental injury (3.7% vs. 2.7%), weakness (3.6% vs. 1.9%), sore throat (3.2% vs. 1.9%), flu-like symptoms (3.2% vs. 3.1%), runny nose (3.2% vs. 3.1%) and muscle aches (2.1% vs. 0.4%).

In patients with type 2 diabetes side effects that occurred greater than placebo were constipation (8.7% vs. 2.0%), inflamed nasal passages and throat (4.1% vs. 3.6%), indigestion (3.9% vs. 1.4%), low blood sugar (3.0% vs. 2.3%), nausea (3.0% vs. 1.4%) and high blood pressure (2.8% vs. 1.6%).

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

For more information on Welchol, call 877-4-DSPROD (877-431-7763), or go to the Welchol web site at www.Welchol.com.

**About Daiichi Sankyo, Inc.**

Daiichi Sankyo Inc., headquartered in Parsippany, New Jersey, is the U.S. subsidiary of Tokyo-based Daiichi Sankyo Co., Ltd. This global pharma innovator was established in 2005 through the

merger of two leading Japanese pharmaceutical companies. The integration created a more robust organization that allows for continuous development of novel drugs that enrich the quality of life for patients around the world. A central focus of Daiichi Sankyo's research and development is cardiovascular disease, including therapies for dyslipidemia, hypertension, diabetes, and acute coronary syndrome. Equally important to the company is the discovery of new medicines in the areas of infectious diseases, cancer, bone and joint diseases, and immune disorders. For more information, visit www.dsus.com.

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