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Two Studies at AACE 2009 Annual Meeting Highlight Effects of Welchol® (colesevelam HCl) on Blood Glucose and LDL-C in Patients with Type 2 Diabetes

- Welchol Added to Metformin Significantly Reduced A1C and LDL-C in Patients with Type 2 Diabetes
- Open-Label Extension Study Demonstrated the Safety and Durability of Welchol for up to 78 Weeks of Treatment

Parsippany, NJ (May 15, 2009) – Daiichi Sankyo, Inc. (DSI) announced today that data from a 16-week, randomized, open-label pilot study demonstrated that Welchol® (colesevelam HCl) significantly improved glycemic control and reduced mean LDL cholesterol (LDL-C) when added to metformin monotherapy in patients with type 2 diabetes. In this study, Januvia® (sitagliptin) and Avandia® (rosiglitazone) also significantly improved glycemic control, but LDL-C increased in patients on both of these treatment regimens. In total, 169 patients were randomized to receive either Welchol (n=57), Januvia (n=56) or Avandia (n=56).[1]

"Seventy percent of patients with type 2 diabetes have elevated LDL cholesterol and are not at the recommended goal of less than 100 mg/dL, which greatly increases their risk for cardiovascular disease," said Yehuda Handelsman, MD, FACP, FACE, Medical Director of the Metabolic Institute of America in Tarzana, Calif. and principal investigator of the study. "These new data further support that Welchol reduces these two risk factors for cardiovascular disease in patients with type 2 diabetes by significantly lowering A1C and LDL or 'bad' cholesterol, thereby offering physicians a unique therapeutic option."*

Data derived from a separate study, a post-hoc analysis of the metformin arm of a 52-week open-label extension study (n=146) were also presented. The results demonstrated that Welchol was well-tolerated and effective for up to 78 weeks when added to metformin-based therapy, which is important considering the chronic and progressive nature of type 2 diabetes.[3]

"The safety of Welchol® (colesevelam HCl) has been established through an extensive clinical trial program and more than nine years as an approved treatment option for patients with high LDL

cholesterol," said Harold E. Bays, MD, Medical Director of Louisville Metabolic and Atherosclerosis Research Center Inc., Louisville, KY and principal investigator of the open-label extension study. "I'm encouraged to see that the safety and durability of Welchol also extends to patients with type 2 diabetes, which is a significant finding given that patients with type 2 diabetes need sustained control of both blood glucose and LDL-C, two important metabolic parameters."

Findings from both studies were presented today at the American Association of Clinical Endocrinologists' (AACE) 18th Annual Meeting and Clinical Congress in Houston.

About the Studies

Abstract #220 – Effect of Colesevelam HCl (Welchol®), Rosiglitazone (Avandia®), or Sitagliptin (Januvia®) in Patients with Type 2 Diabetes Mellitus Inadequately Controlled with Metformin Monotherapy

In this 16-week, open-label, multi-center pilot study, 169 patients were randomized to receive Welchol 3.75 g/d (n=57), rosiglitazone 4 mg/d (n=56) or sitagliptin 100 mg/d (n=56). This study was designed to evaluate the effects of these three oral diabetes medications on glycemic control and lipid profiles when added to metformin monotherapy across demographically similar patients with type 2 diabetes. Patients in the study included both men and women, aged 18-80 years, with inadequately controlled type 2 diabetes (A1C of 7-10 percent), on a stable metformin regimen with LDL-C ≥ 60 mg/dL and triglycerides of <500 mg/dL. The primary efficacy variable was the change in A1C from baseline to week 16 with last observation carried forward (LOCF).

At baseline, there were no significant differences in A1C between the groups. Welchol, rosiglitazone and sitagliptin each significantly reduced mean A1C ($p<0.05$, <0.0001 and <0.01, respectively), with considerable overlap among the 95 percent confidence intervals (-0.27 percent [-0.52,-0.02], -0.58 percent [-0.83,-0.32] and -0.38 percent [-0.64,-0.13], respectively). When evaluating the effects on lipid levels, a significant mean reduction in LDL-C of 12 percent was obtained in patients treated with Welchol, whereas an 8 percent mean increase of LDL-C was observed in patients treated with either sitagliptin or rosiglitazone ($p <0.05$ for both). In the study, 42 percent (n=22) of patients in the Welchol group, 24 percent (n=12) of patients in the rosiglitazone group, and 25 percent (n=13) of patients in the sitagliptin group attained or maintained LDL-C <100 mg/dL at week 16. Median triglyceride levels increased from baseline for both Welchol (14.9 percent) and rosiglitazone (24.2 percent) ($p\leq = 0.001$). Further, mean reductions in fasting plasma glucose (FPG) and 2-hour postprandial glucose (PPG) were observed in all groups. In patients treated with Welchol or sitagliptin, mean body weight decreased by 1.41 pounds ($p=0.022$) and 2.54 pounds ($p=0.0008$), respectively, and was unchanged in patients treated with rosiglitazone (increase of 0.57 pounds; $p=0.594$).

In this study, the most common drug-related adverse events were gastrointestinal disorders. Four patients experienced a severe adverse event: two (3.5 percent) in the Welchol group (thermal burn [n=1] and bronchopneumonia [n=1]), and one (1.8 percent) each in the rosiglitazone (transient ischemic

cerebrovascular accident) and sitagliptin (cholelithiasis) groups; none were considered related to the study drug.

Abstract #217– Long-Term Use of Colesevelam HCl in Subjects with Type 2 Diabetes Mellitus on Metformin Therapy

This post-hoc analysis evaluated the long-term glycemic effects of Welchol® (colesevelam HCl) 3.75 g/d when added to existing metformin-based therapy in patients with type 2 diabetes who completed a randomized, placebo-controlled, 26-week pivotal study and then elected to enter a 52-week open-label extension. In the open-label extension study, the dose of other anti-diabetic agents could be adjusted and additional anti-diabetic agents could be added to help achieve a target A1C <7.0 percent. Changes in A1C were calculated in the cohort of patients who completed the randomized phase and subsequently entered the open-label extension. Of the 316 subjects who entered the metformin-based pivotal study, 222 completed the randomized phase, and 146 (81 and 65 who previously received Welchol and placebo, respectively) entered the open-label extension. At baseline, prior to randomized treatment, the Welchol and placebo groups had comparable A1C levels (8.2 and 8.1 percent, respectively).

Results showed that patients on metformin-based therapy but naïve to Welchol (i.e., those treated with placebo during the 26-week randomized phase), who were subsequently treated with Welchol for 52 weeks (n=41) during the open label study, achieved a mean A1C reduction from baseline of 0.6 percent (8.0 percent to 7.4 percent). Patients on metformin-based therapy but treated with Welchol during the randomized phase and the 52-week open-label study (n=56) achieved a mean A1C reduction from baseline of 0.5 percent (8.2 percent to 7.7 percent), demonstrating that the efficacy of Welchol may be sustained for up to 78 weeks. Similar observations were observed for reductions in LDL-C achieved during the double-blind and open-label study periods.

In the study, Welchol was safe and well-tolerated. In total, nine subjects discontinued due to an adverse event, including three from a serious adverse event. Non-serious adverse events considered possibly or probably related to Welchol were wheezing, dyspnea, and cough (n=1), abnormal liver function test (n=1) and dyspepsia (n=2). Events considered unlikely or unrelated to Welchol were memory impairment (n=1) and increased sweating (n=1). Serious adverse events, all unrelated to Welchol, were breast cancer (n=2), and diabetic gastroparesis and unilateral blindness (n=1). In total, 15 patients had serious adverse events, which were considered not related (n=13) or unlikely related (n=2) to Welchol treatment. Hypoglycemia was reported by one subject; the episode was not severe and did not lead to discontinuation. Overall, compliance with Welchol during the open-label extension was 88.5 percent, including all subjects that entered the extension study from the three (metformin, insulin, sulfonylurea) pivotal trials.

About Type 2 Diabetes and Cholesterol

According to the American Diabetes Association (ADA), about 23.6 million, or 8 percent of people in the United States, have diabetes, and approximately 90 to 95 percent of people diagnosed with diabetes have type 2 diabetes.[4,5] In addition, 70 percent of adults with type 2 diabetes also have high LDL cholesterol, the “bad” cholesterol that can cause build-up in the arteries.[2]

The ADA and the American College of Cardiology emphasize that it is critical to reduce both A1C (measure of average blood glucose level) and LDL cholesterol.[6,7,8] The ADA recommends that patients with type 2 diabetes target an A1C level of <7 percent, and The National Cholesterol Education Program (NCEP) recommends that patients with type 2 diabetes target an LDL cholesterol goal of <100 mg/dL.[9,10]

As the first and only medication approved to reduce A1C and LDL-C, Welchol addresses both of these chronic health conditions and provides physicians with a unique therapeutic approach for treating patients with type 2 diabetes and high LDL cholesterol.*

*The effect on cardiovascular morbidity and mortality has not been determined.

IMPORTANT INFORMATION ABOUT WELCHOL® (colesevelam HCl)

Indications

Welchol is indicated as an adjunct to diet and exercise to:

- reduce elevated low-density lipoprotein cholesterol (LDL-C) in patients with primary hyperlipidemia (Fredrickson Type IIa) as monotherapy or in combination with an hydroxymethyl-glutaryl-coenzyme A (HMG CoA) reductase inhibitor.
- improve glycemic control in adults with type 2 diabetes mellitus.

Important Limitations of Use

- Welchol should not be used for the treatment of type 1 diabetes or for the treatment of diabetic ketoacidosis.
- Welchol has not been studied in type 2 diabetes as monotherapy or in combination with a dipeptidyl peptidase 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.

Contraindications

Welchol is contraindicated in individuals with bowel obstruction, those with serum triglyceride (TG) concentrations of >500 mg/dL, or with a history of hypertriglyceridemia-induced pancreatitis.

Warnings and Precautions

The effect of Welchol on cardiovascular morbidity and mortality has not been determined.

Welchol can increase serum TG concentrations particularly when used in combination with sulfonylureas or insulin. Caution should be exercised when treating patients with TG levels >300 mg/dL.

Welchol may decrease the absorption of fat-soluble vitamins A, D, E, and K. Patients on vitamin supplements should take their vitamins at least 4 hours prior to Welchol. Caution should be exercised when treating patients with a susceptibility to vitamin K or fat soluble vitamin deficiencies.

Caution should also be exercised when treating patients with gastroparesis, gastrointestinal motility disorders, major gastrointestinal tract surgery, and when treating patients with dysphagia and swallowing disorders.

Welchol reduces gastrointestinal absorption of some drugs. Drugs with a known interaction with colesevelam (glyburide, levothyroxine, and oral contraceptives [ethinyl estradiol, norethindrone]) should be administered at least 4 hours prior to Welchol. Drugs that have not been tested for interaction with colesevelam, especially those with a narrow therapeutic index, should also be administered at least 4 hours prior to Welchol. Alternatively, the physician should monitor drug levels of the co-administered drug.

Adverse Reactions

Primary Hyperlipidemia: In clinical trials, the adverse reactions observed in ≥ 2% of patients – and more commonly with Welchol than placebo – regardless of investigator assessment of causality were constipation (11.0% vs. 7.0%), dyspepsia (8.3% vs. 3.5%), nausea (4.2% vs. 3.9%), accidental injury (3.7% vs. 2.7%), asthenia (3.6% vs. 1.9%), pharyngitis (3.2% vs. 1.9%), flu syndrome (3.2% vs. 3.1%), rhinitis (3.2% vs. 3.1%) and myalgia (2.1% vs. 0.4%).

Type 2 Diabetes: In clinical trials, the adverse reactions observed in ≥2% of patients – and more commonly with Welchol than placebo – regardless of investigator assessment of causality were constipation (8.7% vs. 2.0%), nasopharyngitis (4.1% vs. 3.6%) dyspepsia (3.9% vs. 1.4%), hypoglycemia (3.0% vs. 2.3%), nausea (3.0% vs. 1.4%) and hypertension (2.8% vs. 1.6%).

Post-marketing experience: Due to the voluntary nature of these reports it is not possible to reliably estimate frequency or establish a causal relationship.
Increased seizure activity or decreased phenytoin levels have been reported in patients receiving phenytoin concomitantly with Welchol.
Reduced International Normalized Ratio (INR) has been reported in patients receiving warfarin concomitantly with Welchol.

Pregnancy

Welchol is Pregnancy Category B.

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. Please visit http://www.welchol.com/pdf/Welchol_PI.pdf for full Prescribing Information on Welchol.

About Daiichi Sankyo, Inc.

Daiichi Sankyo Inc., headquartered in Parsippany, New Jersey, is the U.S. subsidiary of Tokyo-based Daiichi Sankyo Co., Ltd., which is a global pharmaceutical innovator. The headquarters company was established in 2005 from the merger of two leading Japanese pharmaceutical companies. This 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. Also 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.dsi.com.

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