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New Guidelines From the American Association of Clinical Endocrinologists (AACE) Identify Welchol® (colesevelam HCl) for Lowering Both A1C and LDL-Cholesterol in Patients with Type 2 Diabetes

Parsippany, NJ (June 6, 2013) – Recent guidance from the American Association of Clinical Endocrinologists (AACE) highlight for the first time a cardiovascular risk factor management algorithm that identifies treatments of dyslipidemia in patients with type 2 diabetes.[1] In these new guidelines, Welchol® (colesevelam HCl) is the only therapy recognized that provides patients with a dual-benefit: it helps to lower both A1C and LDL cholesterol ("bad" cholesterol or LDL-C) levels in adult patients with type 2 diabetes and primary hyperlipidemia.[1] This new *AACE Comprehensive Diabetes Management Algorithm 2013* was published online and in the March/April 2013 issue of *Endocrine Practice*.[1]

Specifically, the new guidelines identify Welchol as part of both a dual and triple combination therapy regimen along with metformin or other first-line agents in adult patients with type 2 diabetes and A1C levels greater than or equal to 7.5 percent.[1] In treating dyslipidemia in patients with type 2 diabetes, the guidelines also identify Welchol as part of a statin-intensive regimen if patients are not at a desirable LDL cholesterol level.[1]

"This new guidance issued by AACE recognizes the importance of reducing cardiovascular risk factors such as LDL cholesterol in addition to tight glycemic control in patients with type 2 diabetes," said Oliseyenum M. Nwose, MBBS, MRCPath, Executive Medical Director, Medical Affairs, Therapeutic Areas Head, Hypertension and Metabolism at Daiichi Sankyo, Inc. "Welchol is an effective treatment option that physicians should consider prescribing to help adult patients with type 2 diabetes and primary hyperlipidemia reach both A1C and LDL cholesterol goals."

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

It is estimated that 25.8 million people in the United States (about 8.3 percent of the population) have diabetes.[2] Approximately 90 to 95 percent of these people have type 2 diabetes,[2] and about 58 percent of all adults with diabetes also have high cholesterol.[3]

About Welchol

Welchol (colesevelam HCl) along with diet and exercise lowers LDL or "bad" cholesterol. 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 adult patients with type 2 diabetes mellitus when added to other anti-diabetic medications (metformin, sulfonylureas, or insulin). Welchol was approved by the FDA to lower bad cholesterol in the year 2000 and to lower blood sugar levels in the year 2008. Welchol is available in two formulations – Welchol Tablets and Welchol for Oral Suspension. Welchol for Oral Suspension is sugar-free and can be mixed with water, diet soft drinks or fruit juice. It is important for phenylketonurics to know that Welchol for Oral Suspension contains 27 mg phenylalanine per 3.75 gram dose. In addition, Welchol has a pediatric indication, specifically approved to reduce LDL cholesterol levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia.

Welchol should not be used to treat type 1 diabetes or diabetic ketoacidosis, and it has not been studied with all anti-diabetic medications. Welchol is not for everyone, especially those with a history of 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 studied in children younger than 10 years of age or in premenarchal girls.

In clinical studies of adult patients with type 2 diabetes, Welchol lowered A1C and LDL-C. The most common adverse events seen in these studies with Welchol were constipation, nasal pharyngitis, and dyspepsia. In clinical studies of patients with elevated LDL-C, Welchol lowered LDL-C when used alone or when added to other cholesterol-lowering medications known as

statins (lovastatin, simvastatin, and atorvastatin). In these studies the most common adverse events with Welchol were constipation, dyspepsia, and nausea. Welchol has not been shown to prevent heart disease or heart attacks.

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 hydroxymethylglutaryl-coenzyme A (HMG CoA) reductase inhibitor (statin)
- reduce LDL-C levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia, as monotherapy or in combination with a statin after failing an adequate trial of diet therapy
- 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
- Welchol has not been studied in children younger than 10 years of age or in premenarchal girls

Contraindications
Welchol is contraindicated in individuals with a history of 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, a history of major gastrointestinal tract surgery, and when treating patients with dysphagia and swallowing disorders.

Welchol interacts with some drugs. Drugs with a known interaction with colesevelam (cyclosporine, glimepiride, glipizide, glyburide, levothyroxine, olmesartan medoxomil, oral contraceptives [ethinyl estradiol, norethindrone], and metformin extended release [ER]) 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.

To avoid esophageal distress, Welchol for Oral Suspension should not be taken in its dry form. Due to tablet size, Welchol for Oral Suspension is recommended for, but not limited to, use in the pediatric population as well as in any patient who has difficulty swallowing tablets.

Phenylketonurics: Welchol for Oral Suspension contains 27 mg phenylalanine per 3.75 gram dose.

Adverse Reactions
In clinical trials, the adverse reactions observed in ≥2% of patients, and more commonly with Welchol than placebo, regardless of investigator assessment of causality seen in:

- Adults with Primary Hyperlipidemia 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%)
- Pediatric patients with heFH primary hyperlipidemia were: nasopharyngitis (6.2% vs 4.6%), headache (3.9 vs 3.1%), fatigue (3.9% vs 1.5%), creatine phosphokinase increase (2.3% vs 0.0%), rhinitis (2.3% vs 0.0%), and vomiting (2.3% vs 1.5%)
- Adult patients with Type 2 Diabetes 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
- Elevated thyroid-stimulating hormone (TSH) has been reported in patients receiving thyroid hormone replacement therapy

- Dysphagia has been reported with both tablet and oral suspension formulations

Pregnancy
Welchol is Pregnancy Category B.

Please see full Prescribing Information for Welchol.

About Daiichi Sankyo

The Daiichi Sankyo Group is dedicated to the creation and supply of innovative pharmaceutical products to address the diversified, unmet medical needs of patients in both mature and emerging markets. While maintaining its portfolio of marketed pharmaceuticals for hypertension, hyperlipidemia, and bacterial infections, the Group is engaged in the development of treatments for thrombotic disorders and focused on the discovery of novel oncology and cardiovascular-metabolic therapies. Furthermore, the Daiichi Sankyo Group has created a "Hybrid Business Model," which will respond to market and customer diversity and optimize growth opportunities across the value chain. For more information, please visit www.daiichisankyo.com.

Daiichi Sankyo, Inc., headquartered in Parsippany, New Jersey, is a member of the Daiichi Sankyo Group. For more information on Daiichi Sankyo, Inc., please visit www.dsi.com.

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[1] AACE Comprehensive Diabetes Management Algorithm, *Endocr Pract*. 2013;19(No.2)
[2] Center for Disease Control. National Diabetes Fact Sheet 2011.
[3] Center for Disease Control, Diabetes Program – Data & Trends, Risk Factor for Complications. Age-Adjusted Percentage of Adults Aged 18 Years or Older with Diagnosed Diabetes Who Have High Cholesterol, United States, 1995-2009.