September 18, 2014

FDA Approves Trulicity™ (dulaglutide), Lilly's Once-Weekly Therapy for Adults with Type 2 Diabetes

- Trulicity, a weekly glucagon-like peptide-1 (GLP-1) receptor agonist, is indicated for adults with type 2 diabetes as an adjunct to diet and exercise
- The single-dose pen does not require mixing nor measuring and comes with a no-see, no-handle needle

INDIANAPOLIS, Sept. 18, 2014 /PRNewswire/ -- Trulicity™ (dulaglutide), approved today by the U.S. Food and Drug Administration, is the latest Eli Lilly and Company (NYSE: LLY) treatment option for adults with type 2 diabetes.

Trulicity is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. Trulicity is not recommended as first-line therapy for patients inadequately controlled on diet and exercise. It has not been studied in patients with a history of pancreatitis, and other antidiabetic therapies should be considered for patients with a history of pancreatitis. Trulicity is not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. Trulicity is not a substitute for insulin and has not been studied in combination with basal insulin. Trulicity has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and is not for patients with pre-existing severe gastrointestinal disease.

Lilly plans to make Trulicity 0.75 mg and 1.5 mg single-dose pens available for adults in the United States later this year. This marks the first approval for Trulicity anywhere in the world. It has also been submitted to the European Medicines Agency and other regulatory bodies.

"We are delighted with the approval of Trulicity. Lilly now has treatment options in several classes of diabetes medications: orals, GLPs and insulin," said Enrique Conterno, president, Lilly Diabetes. "Trulicity will help grow the GLP-1 receptor agonist class as a new choice for adults with type 2 diabetes."

The labeling for Trulicity contains a Boxed Warning regarding increased risk for thyroid C-cell tumors based on studies in rats. In rats, dulaglutide caused a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure. It is unknown whether Trulicity causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance could not be determined from clinical or nonclinical studies. Trulicity is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with Trulicity. Patients should be counseled regarding the risk factors and symptoms of thyroid tumors. See the Important Safety Information at the end of this press release, Prescribing Information and Medication Guide.

The biologics license application to the FDA was based on a number of studies of Trulicity used alone or in combination with commonly prescribed diabetes medications, including metformin, pioglitazone, glimepiride and insulin lispro. These studies included five large Phase 3 clinical trials from the Assessment of Weekly AdministRation of LY2189265 in Diabetes (AWARD) clinical development program. The efficacy of Trulicity was compared to four commonly used type 2 diabetes medicines: metformin, Januvia®, Byetta® and Lantus®.

Trulicity comes in a single-dose pen that does not require mixing, measuring or needle attachment. Trulicity is administered once a week, any time of day, independent of meals, and should be injected subcutaneously in the abdomen, thigh or upper arm. The recommended starting dose is 0.75 mg, which can be increased to 1.5 mg dose for patients who need additional blood sugar control.

"Type 2 diabetes is a progressive disease, and many patients have not reached their treatment goals," said Dr. David Kendall, vice president, medical affairs, Lilly Diabetes. "Trulicity is a new, non-insulin, injectable option that was designed with the patient in mind. It will be available in a once-weekly pen and does not require mixing, measuring nor needle handling."

Diabetes remains one of society's most prevalent diseases. More than 380 million people around the world have diabetes.[1] In the U.S., the disease affects more than 29 million people.[2] Type 2 diabetes is the most common, and the number of people with the disease is quickly growing.[1]

About Trulicity
Trulicity is a once-weekly, glucagon-like peptide-1 (GLP-1) receptor agonist injectable prescription medicine indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. Trulicity is not insulin. It acts like GLP-1, a natural hormone, helping the body release its own insulin when patients eat.

Trulicity comes in a pen that does not require the patient to mix, measure or handle the needle. It can be taken any time of day, with or without meals, and should be injected subcutaneously in the abdomen, thigh or upper arm.

Indication and Limitations of Use for Trulicity
Trulicity is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.

Trulicity is not recommended as first-line therapy for patients inadequately controlled on diet and exercise. It has not been studied in patients with a history of pancreatitis, and other antidiabetic therapies should be considered for patients with a history of pancreatitis. Trulicity is not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. Trulicity is not a substitute for insulin and has not been studied in combination with basal insulin. Trulicity has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and is not for patients with pre-existing severe gastrointestinal disease.

Important Safety Information for Trulicity

WARNING: RISK OF THYROID C-CELL TUMORS

In male and female rats, dulaglutide causes dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure. It is unknown whether Trulicity causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance could not be determined from clinical or nonclinical studies.

Trulicity is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with Trulicity. Counsel regarding the risk factors and symptoms of thyroid tumors.

Trulicity is contraindicated in patients with a prior serious hypersensitivity reaction to dulaglutide or any of the product components.

Risk of Thyroid C-cell Tumors: Counsel patients regarding the risk of medullary thyroid carcinoma and the symptoms of thyroid tumors (e.g. a mass in the neck, dysphasia, dyspnea, persistent hoarseness). Patients with elevated serum calcitonin (if measured) and patients with thyroid nodules noted on physical examination or neck imaging should be referred to an endocrinologist for further evaluation.

Pancreatitis: Has been reported in clinical trials. Observe patients for signs and symptoms including persistent severe abdominal pain. If pancreatitis is suspected discontinue Trulicity promptly. Do not restart if pancreatitis is confirmed. Consider other antidiabetic therapy.

Hypoglycemia: The risk of hypoglycemia is increased when Trulicity is used in combination with insulin secretagogues (e.g., sulfonylureas) or insulin. Patients may require a lower dose of the sulfonylurea or insulin to reduce the risk of hypoglycemia.

Hypersensitivity Reactions: Systemic reactions were observed in clinical trials in patients receiving Trulicity. Instruct patients who experience symptoms to discontinue Trulicity and promptly seek medical advice.

Renal Impairment: In patients treated with GLP-1 RAs there have been postmarketing reports of acute renal failure and worsening of chronic renal failure, sometimes requiring hemodialysis. A majority of reported events occurred in patients who had experienced nausea, vomiting, diarrhea or dehydration. In patients with renal impairment, use caution when initiating or escalating doses of Trulicity and monitor renal function in patients experiencing severe adverse gastrointestinal reactions.

Severe Gastrointestinal Disease: Use of Trulicity may be associated with gastrointestinal adverse reactions sometimes severe. Trulicity has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and is therefore not recommended in these patients.

Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Trulicity or any other antidiabetic drug.

The most common adverse reactions reported in ≥5% of Trulicity-treated in placebo-controlled trials (placebo, Trulicity 0.75 mg and 1.5 mg) were nausea (5.3%, 12.4%, 21.1%), diarrhea (6.7%, 8.9%, 12.6%), vomiting (2.3%, 6.0%, 12.7%), abdominal pain (4.9%, 6.5%, 9.4%), decreased appetite (1.6%, 4.9%, 8.6%), dyspepsia (2.3%, 4.1%, 5.8%) and fatigue (2.6%, 4.2%, 5.6%).

Gastric emptying is slowed by Trulicity, which may impact absorption of concomitantly administered oral medications. Use caution when oral medications are used with Trulicity. Drug levels of oral medications with a narrow therapeutic index should be adequately monitored when concomitantly administered with Trulicity. In clinical pharmacology studies, Trulicity did not affect the absorption of the tested, orally administered medications to a clinically relevant degree.

Pregnancy: There are no adequate and well-controlled studies of Trulicity in pregnant women. Use only if potential benefit outweighs potential risk to fetus.

Nursing Mothers: It is not known whether Trulicity is excreted in human milk. A decision should be made whether to discontinue nursing or to discontinue Trulicity taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of Trulicity have not been established and use is not recommended in patients less than 18 years of age.

Please click to access Full Prescribing Information, including Boxed Warning about possible thyroid tumors including thyroid cancer, and Medication Guide for Trulicity.

Please see Instructions for Use that accompany the pen.
DG HCP ISI 18SEP2014

About the AWARD Studies
AWARD-1 was a 52-week, randomized, placebo-controlled study evaluating the effects of Trulicity 1.5 mg (N=279; baseline A1C 8.1%) or 0.75 mg (N=280; baseline A1C 8.1%) and Byetta (N=276; baseline A1C 8.1%) versus placebo (N=141; baseline A1C 8.1%) on glycemic control in adults with type 2 diabetes on maximally tolerated metformin and Actos. Patients were excluded based on previous use of a GLP-1 receptor agonist or chronic insulin therapy. The primary objective was to demonstrate superiority of once-weekly Trulicity 1.5 mg versus placebo at 26 weeks (change from baseline). At the 26-week primary endpoint, mean A1C reductions were Trulicity 1.5 mg: 1.5%; Trulicity 0.75 mg: 1.3%; Byetta: 1.0%; placebo: 0.5%.

AWARD-2 was a 78-week, randomized, open-label study evaluating the effects of Trulicity 1.5 mg (N=273; baseline A1C 8.2%) or 0.75 mg (N=272; baseline A1C 8.1%) and Lantus (N=262; baseline A1C 8.1%) on glycemic control in adults with type 2 diabetes on maximally tolerated doses of metformin and glimepiride. Patients were excluded based on previous use of a GLP-1 receptor agonist or chronic insulin therapy. The primary objective was to demonstrate the noninferiority of once-weekly Trulicity 1.5 mg versus Lantus titrated to target on A1C at 52 weeks (change from baseline). At the 52-week primary endpoint, mean A1C reductions were Trulicity 1.5 mg: 1.1%; Trulicity 0.75 mg: 0.8%; Lantus: 0.6%.

AWARD-3 was a 52-week, randomized, double-blind study evaluating the effects of Trulicity 1.5 mg (N=269; baseline A1C 7.6%) or 0.75 mg (N=270; baseline A1C 7.6%) and metformin (N=268; baseline A1C 7.6%) on glycemic control in adults with early type 2 diabetes. Patients were excluded based on previous use of a GLP-1 receptor agonist or chronic insulin therapy. The primary objective of the study was to demonstrate the noninferiority of monotherapy with once-weekly Trulicity 1.5 mg versus metformin on A1C at 26 weeks (change from baseline). At the 26-week primary endpoint, mean A1C reductions were Trulicity 1.5 mg: 0.8%; Trulicity 0.75 mg: 0.7%; metformin: 0.6%.

AWARD-4 was a 52-week randomized, open-label comparator study (double-blind with respect to Trulicity dose assignment) evaluating the effects of Trulicity 1.5 mg (N=295; baseline A1C 8.5%) or 0.75 mg (N=293; baseline A1C 8.4%) and Lantus (N=296; baseline A1C 8.5%), both in combination with insulin lispro, with or without metformin, in adults with type 2 diabetes. Patients had to be treated for three months previously with stable doses of a conventional insulin regimen and were excluded based on previous use of a GLP-1 receptor agonist. The primary objective was to demonstrate the noninferiority of once-weekly Trulicity 1.5 mg versus Lantus titrated to target, both in combination with insulin lispro, with or without metformin, on A1C at 26 weeks (change from baseline). At the 26-week primary endpoint, mean A1C reductions were Trulicity 1.5 mg: 1.6%; Trulicity 0.75 mg: 1.6%; Lantus: 1.4%.

AWARD-5 was a 104-week, placebo-controlled, randomized, double-blind study comparing the effects of Trulicity 1.5 mg (N=279; baseline A1C 8.1%), 0.75 mg (N=281; baseline A1C 8.2%) and Januvia (N=273; baseline A1C 8.0%) on glycemic control in adults with type 2 diabetes on metformin. Patients were excluded based on previous use of a GLP-1 receptor agonist or insulin therapy. The primary objective was to demonstrate the noninferiority of once-weekly Trulicity 1.5 mg versus Januvia on A1C at 52 weeks (change from baseline). At the 52-week primary endpoint, mean A1C reductions were Trulicity 1.5 mg: 1.1%; Trulicity 0.75 mg: 0.9%; Januvia: 0.4%.

About Lilly Diabetes
Lilly has been a global leader in diabetes care since 1923, when we introduced the world's first commercial insulin. Today we are building upon this heritage by working to meet the diverse needs of people with diabetes and those who care for them. Through research and collaboration, a broad and growing product portfolio and a continued determination to provide real

solutions—from medicines to support programs and more—we strive to make life better for all those affected by diabetes around the world. For more information, visit www.lillydiabetes.com.

About Eli Lilly and Company
Lilly is a global healthcare leader that unites caring with discovery to make life better for people around the world. We were founded more than a century ago by a man committed to creating high-quality medicines that meet real needs, and today we remain true to that mission in all our work. Across the globe, Lilly employees work to discover and bring life-changing medicines to those who need them, improve the understanding and management of disease, and give back to communities through philanthropy and volunteerism. To learn more about Lilly, please visit us at www.lilly.com, @LillyHealth on Twitter and http://newsroom.lilly.com/social-channels.

P-LLY

1. International Diabetes Federation. *IDF Diabetes Atlas, 6th edn*. Brussels, Belgium: International Diabetes Federation, 2013. http://www.idf.org/diabetesatlas.
2. Centers for Disease Control and Prevention. *National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States,* 2014. Atlanta, GA: U.S. Department of Health and Human Services; 2014.

Refer to: Candace Johnson, +1-317-755-9143, johnson_candace_a@lilly.com

Logo - http://photos.prnewswire.com/prnh/20031219/LLYLOGO

SOURCE Eli Lilly and Company