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U.S. FDA approves first-in-class Glyxambi® (empagliflozin/linagliptin) tablets for adults with type 2 diabetes

Only prescription medication in U.S. to combine the dual mechanisms of action of SGLT2 and DPP-4 inhibitors to improve glycemic control as an adjunct to diet and exercise
As an add-on to metformin, GLYXAMBI was superior in reducing A1C when compared with either empagliflozin or linagliptin alone

RIDGEFIELD, Conn. and INDIANAPOLIS, Feb. 2, 2015 /PRNewswire/ -- The U.S. Food and Drug Administration (FDA) has approved Glyxambi® (empagliflozin/linagliptin) tablets, from Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) and Eli Lilly and Company (NYSE: LLY), as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes (T2D) when both empagliflozin and linagliptin are appropriate treatments.

GLYXAMBI is not recommended in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. GLYXAMBI has not been studied in patients with a history of pancreatitis, and it is unknown if using GLYXAMBI increases the risk of developing pancreatitis in these patients.

GLYXAMBI is the first and only diabetes treatment in the U.S. to combine the dual mechanisms of action of a sodium glucose co-transporter-2 (SGLT2) inhibitor and a dipeptidyl peptidase-4 (DPP-4) inhibitor in a once-daily tablet taken in the morning. GLYXAMBI combines 10 mg or 25 mg of empagliflozin with 5 mg of linagliptin. SGLT2 inhibitors remove glucose through the urine by blocking blood glucose re-absorption in the kidney. DPP-4 inhibitors work by increasing hormones that stimulate the pancreas to produce more insulin and stimulate the liver to produce less glucose.

"Today's medical community recognizes the need to treat type 2 diabetes from multiple fronts to help patients improve glycemic control," said Paul Fonteyne, president and CEO, BIPI. "With GLYXAMBI, the dual inhibition of DPP-4 and SGLT2 — two proven targets in the treatment of type 2 diabetes — now provides U.S. physicians and patients with an option to simultaneously address multiple pathways to improve glycemic control. For patients uncontrolled on metformin, phase III trial results showed GLYXAMBI provided significantly greater reductions in blood glucose levels compared with either empagliflozin or linagliptin alone."

GLYXAMBI should not be taken by patients with severe renal impairment, end-stage renal disease or dialysis; a history of hypersensitivity reaction to linagliptin, such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity; or history of serious hypersensitivity reaction to empagliflozin. There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis, in patients taking linagliptin, a component of GLYXAMBI. Take careful notice of potential signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue GLYXAMBI and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using GLYXAMBI.

"Half of people with type 2 diabetes do not achieve recommended blood sugar control, making new treatment options more important than ever," said Mike Mason, vice president, U.S., Lilly Diabetes. "The approval of GLYXAMBI gives U.S. physicians and patients a first-in-class prescription medicine to help manage this condition. The approval is also a testament to our alliance's commitment to adults living with type 2 diabetes."

About the Phase III Clinical Trial
The FDA approval was based on a phase III clinical trial that evaluated the efficacy and safety of GLYXAMBI (10/5 mg and 25/5 mg) compared with the individual components of empagliflozin (10 mg or 25 mg) or linagliptin (5 mg) in adults with T2D who were also taking high-dose metformin (mean dose 1889 mg daily). The study, which randomized 686 adults with T2D and hemoglobin A1C (a measure of average blood glucose over the past two to three months) between 7.0 and 10.5 percent, examined the change from baseline in A1C at 24 weeks.

In the study, as an add-on to metformin, GLYXAMBI showed statistically significant reductions in A1C compared with empagliflozin and linagliptin alone at 24 weeks. Starting from a mean baseline of approximately 8.0 percent, adults in this trial achieved a mean A1C of 6.9 and 6.7 percent with GLYXAMBI 10/5 mg and 25/5 mg, respectively, compared with a mean A1C of 7.3 and 7.4 percent for empagliflozin 10 mg and 25 mg, respectively, and 7.3 percent for linagliptin 5 mg.

The percentage of patients achieving an A1C less than 7 percent with GLYXAMBI 10/5 mg or 25/5 mg was 58 percent and 62 percent, respectively, compared with 28 percent, 33 percent and 36 percent for empagliflozin 10 mg, empagliflozin 25 mg and linagliptin 5 mg, respectively.

Although not approved for lowering weight, GLYXAMBI provided significant weight loss at 24 weeks compared with linagliptin alone.

- GLYXAMBI 10/5 mg: average body weight reduction of 3.1 percent from an average baseline of 191 lbs
- GLYXAMBI 25/5 mg: average body weight reduction of 3.4 percent from an average baseline of 187 lbs
- Linagliptin 5 mg: average body weight reduction of 0.7 percent from an average baseline of 187 lbs

Through 52 weeks, the overall incidence of hypoglycemia with GLYXAMBI was 2.2 percent and 3.6 percent for GLYXAMBI 10/5 mg and 25/5 mg, respectively, and there were no cases of severe hypoglycemia reported in the trial. A lower dose of an insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with GLYXAMBI.

Through 52 weeks, the safety profile of GLYXAMBI was demonstrated in a pooled analysis, and the most common adverse reactions were:

- Urinary tract infection (UTI): 12.5 percent and 11.4 percent for GLYXAMBI 10/5 mg and 25/5 mg, respectively; through 52 weeks, no patient discontinued GLYXAMBI due to UTIs
- Nasopharyngitis: 5.9 percent and 6.6 percent for GLYXAMBI 10/5 mg and 25/5 mg, respectively
- Upper respiratory tract infection: 7.0 percent for GLYXAMBI 10/5 mg and 25/5 mg

What is GLYXAMBI?
GLYXAMBI is a prescription medicine that contains 2 diabetes medicines, empagliflozin and linagliptin. GLYXAMBI can be used along with diet and exercise to lower blood sugar in adults with type 2 diabetes when treatment with both empagliflozin and linagliptin is appropriate.

GLYXAMBI is not for people with type 1 diabetes or for diabetic ketoacidosis (increased ketones in the blood or urine). If you have had pancreatitis (inflammation of the pancreas) it is not known if you have a higher chance of getting pancreatitis while taking GLYXAMBI.

IMPORTANT SAFETY INFORMATION

What is the most important information I should know about GLYXAMBI?

Serious side effects can happen to people taking GLYXAMBI, including:

- **Inflammation of the pancreas** (pancreatitis), which may be severe and lead to death. Before you start taking GLYXAMBI, tell your doctor if you have ever had pancreatitis, gallstones, a history of alcoholism, or high triglyceride levels.

  Stop taking GLYXAMBI and call your doctor right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

- **Dehydration.** GLYXAMBI can cause some people to have dehydration (the loss of body water and salt). Dehydration may cause you to feel dizzy, faint, light-headed, or weak, especially when you stand up. You may be at higher risk of dehydration if you have low blood pressure, take medicines to lower your blood pressure, including water pills (diuretics), are on a low salt diet, have kidney problems, or are 65 years of age or older.

- **Vaginal yeast infection.** Women who take GLYXAMBI may get vaginal yeast infections. Talk to your doctor if you experience vaginal odor, white or yellowish vaginal discharge (discharge may be lumpy or look like cottage cheese), and/or vaginal itching.

- **Yeast infection of the penis.** Men who take GLYXAMBI may get a yeast infection of the skin around the penis, especially uncircumcised males and those with chronic infections. Talk to your doctor if you experience redness, itching or swelling of the penis, rash of the penis, foul smelling discharge from the penis, and/or pain in the skin around penis.

Who should not take GLYXAMBI?

Do not take GLYXAMBI if you have severe kidney problems or are on dialysis.

Do not take GLYXAMBI if you are allergic to empagliflozin and linagliptin or any of the ingredients in GLYXAMBI.

Symptoms of a serious allergic reaction to GLYXAMBI may include skin rash, itching, flaking or peeling; raised red patches on your skin (hives); difficulty swallowing or breathing; or swelling of your face, lips, tongue, and throat that may cause difficulty breathing or swallowing. If you have any of these symptoms, stop taking GLYXAMBI and call your doctor or go to the emergency room right away.

What should I tell my doctor before using GLYXAMBI?

Tell your doctor if you:

- have kidney problems. Your doctor may do blood tests to check your kidneys before and during your treatment with GLYXAMBI
- have liver problems
- have a history of inflammation of your pancreas (pancreatitis)
- have a history of infection of the vagina or penis
- have a history of urinary tract infections or problems with urination
- have any other medical condition
- are pregnant or plan to become pregnant. It is unknown if GLYXAMBI will harm your unborn baby. Tell your doctor right away if you become pregnant during treatment with GLYXAMBI
- are breastfeeding, or planning to breastfeed. It is unknown if GLYXAMBI passes into your breast milk.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. GLYXAMBI may affect the way other medicines work, and other medicines may affect how GLYXAMBI works.

Especially tell your doctor if you take:

- insulin or other medicines that can lower your blood sugar
- diuretics (water pills)
- rifampin (Rifadin®, Rimactane®, Rifater®, Rifamate®)*, an antibiotic that is used to treat tuberculosis

*These trademarks are owned by third parties not affiliated with GLYXAMBI.

What are the possible side effects of GLYXAMBI?

GLYXAMBI may cause serious side effects, including:

- **Low blood sugar (hypoglycemia)**, if you take GLYXAMBI with another medicine that can cause low blood sugar such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea or insulin may need to be lowered. Signs and symptoms of low blood sugar may include headache, drowsiness, weakness, confusion, irritability, hunger, fast heartbeat, sweating, or feeling jittery.
- **Urinary tract infections** are a common side effect of GLYXAMBI but can sometimes be serious. Symptoms may include burning feeling when passing urine, urine that looks cloudy, and/or pain in the pelvis or back.
- **Allergic (hypersensitivity) reactions** can happen after your first dose or up to 3 months after starting GLYXAMBI. Symptoms may include swelling of your face, lips, throat, and other areas on your skin; difficulty with swallowing or breathing; raised, red areas on your skin (hives); and/or skin rash, itching, flaking, or peeling. If you have any of these symptoms, stop taking GLYXAMBI and call your doctor or go to the emergency room right away.
- **Kidney problems**, especially in people 75 years and older and people who already have kidney problems
- **Increased fats in your blood (cholesterol).**

The most common side effects of GLYXAMBI include urinary tract infections, stuffy or runny nose and sore throat, and upper respiratory tract infections.

These are not all the possible side effects of GLYXAMBI. For more information, ask your doctor or pharmacist.

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.

Visit GLYXAMBI.com for full Prescribing Information and Medication Guide.

About Diabetes
Approximately 29 million Americans and an estimated 387 million people worldwide have type 1 or type 2 diabetes, and nearly

28 percent of Americans with diabetes—totaling 8 million people—are undiagnosed. In the U.S., approximately 12 percent of those aged 20 and older have diabetes. T2D is the most common type, accounting for an estimated 90 to 95 percent of all adult diabetes cases in the U.S. Diabetes is a chronic condition that occurs when the body either does not properly produce, or use, the hormone insulin.

Boehringer Ingelheim and Eli Lilly and Company
In January 2011, Boehringer Ingelheim and Eli Lilly and Company announced an alliance in diabetes that centers on compounds representing several of the largest diabetes treatment classes. This alliance leverages the strengths of two of the world's leading pharmaceutical companies. By joining forces, the companies demonstrate commitment in the care of patients with diabetes and stand together to focus on patient needs. Find out more about the alliance at www.boehringer-ingelheim.com or www.lilly.com.

About Boehringer Ingelheim
Boehringer Ingelheim Pharmaceuticals, Inc., based in Ridgefield, CT, is the largest U.S. subsidiary of Boehringer Ingelheim Corporation (Ridgefield, CT) and a member of the Boehringer Ingelheim group of companies.

The Boehringer Ingelheim group is one of the world's 20 leading pharmaceutical companies. Headquartered in Ingelheim, Germany, it operates globally with 142 affiliates and more than 47,400 employees. Since it was founded in 1885, the family-owned company has been committed to researching, developing, manufacturing and marketing novel medications of high therapeutic value for human and veterinary medicine.

Social responsibility is a central element of Boehringer Ingelheim's culture. Involvement in social projects, caring for employees and their families, and providing equal opportunities for all employees form the foundation of the global operations. Mutual cooperation and respect, as well as environmental protection and sustainability are intrinsic factors in all of Boehringer Ingelheim's endeavors.

In 2013, Boehringer Ingelheim achieved net sales of about $18.7 billion (14.1 billion euro). R&D expenditure in the Prescription Medicines business corresponds to 19.5% of its net sales.

For more information please visit www.us.boehringer-ingelheim.com.

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 and newsroom.lilly.com/social-channels.

This press release contains forward looking statements about GLYXAMBI for the treatment of type 2 diabetes along with diet and exercise. It reflects Lilly's current beliefs; however, as with any such undertaking, there are substantial risks and uncertainties in the process of drug development and commercialization. There is no guarantee that future study results and patient experience will be consistent with study findings to date, or that GLYXAMBI will be commercially successful, or that it will receive additional regulatory approvals. For further discussion of these and other risks and uncertainties, please see Lilly's latest Forms 10-Q and 10-K filed with the U.S. Securities and Exchange Commission. Lilly undertakes no duty to update forward-looking statements.

Glyxambi® is a trademark of Boehringer Ingelheim Pharmaceuticals, Inc.

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Glyxambi® (empagliflozin/linagliptin) tablet packaging 10/5 mg (left). Glyxambi® (empagliflozin/linagliptin) tablet packaging 25/5 mg (right)

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