US FDA accepts supplemental New Drug Application for Jardiance® for children 10 years and older with type 2 diabetes

March 8, 2023

- The application is based on phase III results from the DINAMO trial showing Jardiance® (empagliflozin) tablets significantly reduced A1c (a marker of average blood sugar) versus placebo in participants aged 10-17 living with type 2 diabetes
- If approved, Jardiance would be the first SGLT2 inhibitor indicated for this vulnerable population

RIDGEFIELD, Conn. and INDIANAPOLIS, March 8, 2023 /PRNewswire/ -- The U.S. Food and Drug Administration (FDA) accepted a supplemental New Drug Application (sNDA) for Jardiance® (empagliflozin) investigating a potential new indication to lower blood sugar along with diet and exercise in children 10 years and older with type 2 diabetes, Boehringer Ingelheim and Eli Lilly and Company (NYSE: LLY) announced.

"There are clear unmet needs for young people living with type 2 diabetes, which has nearly doubled in prevalence in people aged 10-19 over the past two decades," said Mohamed Eid, M.D., M.P.H., M.H.A., vice president, Clinical Development & Medical Affairs, Cardio-Renal-Metabolism & Respiratory Medicine, Boehringer Ingelheim Pharmaceuticals, Inc. "We look forward to working closely with the FDA during the review process and while we await a decision on our efforts to bring another potential treatment option to children 10 years and older with type 2 diabetes."

The sNDA is based on the results from the DINAMO phase III trial, in which Jardiance was associated with a statistically significant reduction in the primary endpoint of change from baseline in A1c at 26 weeks compared with placebo in participants aged 10-17 years with type 2 diabetes. When added to other baseline treatments (diet, exercise, metformin and/or insulin), Jardiance 10 mg and 25 mg pooled doses reduced A1c by 0.84% compared with placebo at week 26 (95% CI −1.50 to −0.19; P=0.012). Reduction in A1c in participants treated with Tradjenta® (linagliptin) was not statistically significant when compared with placebo. A numerical reduction of 0.34% (P=0.2935) was observed. Results were presented during the International Diabetes Federation World Diabetes Congress 2022.

Overall, the safety data in DINAMO was consistent with the previously known safety profile of Jardiance.

Initially approved in 2014, Jardiance is a once-daily tablet used along with diet and exercise to lower blood sugar in adults with type 2 diabetes; and to reduce the risk of cardiovascular death in adults with type 2 diabetes and known cardiovascular disease. Jardiance is also indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure. Jardiance is not for patients with type 1 diabetes, or to improve glycemic control in adults with type 2 diabetes with an eGFR <30 mL/min/1.73 m^2. Jardiance is contraindicated in people with hypersensitivity to empagliflozin or any of the excipients in Jardiance, and in patients on dialysis. **Please see additional Important Safety Information below.**

"Impacting an estimated 39,000 people under the age of 20, type 2 diabetes is a growing health issue for young people in the U.S.," said Jeff Emmick, M.D., Ph.D., vice president, Product Development, Lilly. "If approved, Jardiance would be a new oral treatment option for type 2 diabetes in children 10 years and older in the U.S., making this application acceptance an important step forward as we add to the body of knowledge for this vulnerable patient population, for whom oral treatment options have been limited."

About DINAMO: DIabetes study of liNAgliptin and eMpagliflozin in children and adOlescents
DINAMO (NCT03429543) is a multicenter, randomized, double-blind, parallel group phase III trial that enrolled participants aged 10-17 years with type 2 diabetes (A1c 6.5% to 10.5%) previously treated with metformin or insulin. The primary endpoint was change from baseline in A1c at 26 weeks. Of the 262 participants screened, 158 were randomly assigned to treatment with Jardiance (10 mg) (n=52), Tradjenta (5 mg) (n=53) or placebo (n=53) once daily. Participants in the Jardiance group who did not have A1c below 7.0% by week 12 were re-randomized to either remain on 10 mg or increase to 25 mg. Participants in the placebo group were reassigned at week 26 to Tradjenta 5 mg or Jardiance 10 mg or 25 mg. All participants were treated with diet and exercise plus metformin and/or insulin (or no background if metformin intolerant). Safety was assessed until week 52.

What is JARDIANCE?

JARDIANCE is a prescription medicine used to:

- reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure, when the heart cannot pump enough blood to the rest of your body
- reduce the risk of cardiovascular death in adults with type 2 diabetes who also have known cardiovascular disease
- lower blood sugar along with diet and exercise in adults with type 2 diabetes

JARDIANCE is not for people with type 1 diabetes. It may increase their risk of diabetic ketoacidosis (increased ketones in the blood or urine).

JARDIANCE is not for use to lower blood sugar in adults with type 2 diabetes who have severe kidney problems, because it may not work.

IMPORTANT SAFETY INFORMATION
Do not take JARDIANCE if you are allergic to empagliflozin or any of the ingredients in JARDIANCE.

Do not take JARDIANCE if you are on dialysis.

JARDIANCE can cause serious side effects, including:

- **Ketoacidosis (increased ketones in your blood or urine).** Ketoacidosis is a serious condition which needs to be treated in the hospital. Ketoacidosis may lead to death. Ketoacidosis occurs in people with type 1 diabetes and can also occur in people with type 2 diabetes taking JARDIANCE, **even if blood sugar is less than 250 mg/dL**. Ketoacidosis has also happened in people with diabetes who were sick or who had surgery during treatment with JARDIANCE. **Stop taking JARDIANCE and call your healthcare provider right away or go to the nearest hospital emergency room if you get any of the following symptoms,** and if possible, check for ketones in your urine:
    - nausea
    - vomiting
    - stomach-area (abdominal) pain
    - tiredness
    - trouble breathing
- **Dehydration.** JARDIANCE can cause some people to become dehydrated (the loss of body water and salt). Dehydration may cause you to feel dizzy, faint, light-headed, or weak, especially when you stand up. Sudden worsening of kidney function has happened in people who are taking JARDIANCE.

You may be at a higher risk of dehydration if you:

- take medicines to lower your blood pressure, including water pills (diuretics)
- are on a low salt diet
- have kidney problems
- are 65 years of age or older

Talk to your healthcare provider about what you can do to prevent dehydration, including how much fluid you should drink on a daily basis, and if you reduce the amount of food or liquid you drink, if you are sick or cannot eat, or start to lose liquids from your body from vomiting, diarrhea, or being in the sun too long.

- **Serious urinary tract infections.** Serious urinary tract infections can occur in people taking JARDIANCE and may lead to hospitalization. Tell your healthcare provider if you have symptoms of a urinary tract infection, such as a burning feeling when passing urine, a need to urinate often or right away, pain in the lower part of your stomach or pelvis, or blood in the urine. Sometimes people also may have a fever, back pain, nausea or vomiting.

- **Low blood sugar** (hypoglycemia): If you take JARDIANCE with another medicine that can cause low blood sugar, such as sulfonylurea or insulin, your risk of low blood sugar is higher. The dose of your sulfonylurea or insulin may need to be lowered. Symptoms of low blood sugar may include:
    - headache
    - drowsiness
    - weakness
    - dizziness
    - confusion
    - irritability
    - hunger
    - fast heartbeat
    - sweating
    - shaking or feeling jittery
- **Necrotizing fasciitis. A rare but serious bacterial infection that causes damage to the tissue under the skin in the area between and around your anus and genitals (perineum).** This bacterial infection has happened in women and men who take JARDIANCE, and may lead to hospitalization, multiple surgeries, and death. **Seek medical attention immediately if you have a fever or are feeling very weak, tired or uncomfortable (malaise), and you develop any of the following symptoms in the area between and around your anus and genitals: pain or tenderness, swelling, and redness of skin (erythema).**

- **Vaginal yeast infection.** Talk to your healthcare provider if you have 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.** Swelling of an uncircumcised penis may develop that makes it difficult to pull back the skin around the tip of the penis. Talk to your healthcare provider if you have redness, itching or swelling of the penis, rash of the penis, foul smelling discharge from the penis, and/or pain in the skin around the penis.

  Talk to your healthcare provider about what to do if you get symptoms of a yeast infection of the vagina or penis. Your healthcare provider may suggest you use an over-the-counter antifungal medicine. Talk to your healthcare provider

right away if you use an over-the-counter antifungal medication and your symptoms do not go away.

- **Allergic (hypersensitivity) reactions.** Symptoms of serious allergic reactions to JARDIANCE may include:
  - swelling of your face, lips, throat, and other areas of your skin
  - difficulty with swallowing or breathing
  - raised, red areas on your skin (hives)

If you have any of these symptoms, stop taking JARDIANCE and contact your healthcare provider or go to the nearest emergency room right away.

The most common side effects of JARDIANCE include urinary tract infections and yeast infections in females.

These are not all the possible side effects of JARDIANCE. For more information, ask your healthcare provider or pharmacist.

Before taking JARDIANCE, tell your healthcare provider about all of your medical conditions, including if you:

- have kidney problems
- have liver problems
- have a history of infection of the vagina or penis
- have a history of urinary tract infections or problems with urination
- are going to have surgery. Your healthcare provider may stop JARDIANCE before you have surgery. Talk to your healthcare provider about when to stop taking JARDIANCE if you are having surgery and when to start it again
- are eating less or there is a change in your diet
- have or have had problems with your pancreas, including pancreatitis or surgery on your pancreas
- drink alcohol very often, or drink a lot of alcohol in the short term ("binge" drinking)
- have type 1 diabetes. JARDIANCE should not be used to treat people with type 1 diabetes
- are pregnant or plan to become pregnant. JARDIANCE may harm your unborn baby. Tell your healthcare provider right away if you become pregnant during treatment with JARDIANCE
- are breastfeeding or are planning to breastfeed. JARDIANCE may pass into your breast milk and may harm your baby. Do not breastfeed while taking JARDIANCE

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

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, please see Prescribing Information and Medication Guide.

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What is TRADJENTA?

TRADJENTA is a prescription medicine that is used along with diet and exercise to lower blood sugar in adults with type 2 diabetes.

TRADJENTA is not for people with type 1 diabetes.

If you have had inflammation of the pancreas (pancreatitis) in the past, it is not known if you have a higher chance of getting pancreatitis while you take TRADJENTA.

IMPORTANT SAFETY INFORMATION

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

TRADJENTA can cause serious side effects, including inflammation of the pancreas (pancreatitis), which may be severe and lead to death. Before you start taking TRADJENTA, tell your healthcare provider if you have ever had pancreatitis, gallstones, a history of alcoholism, or high triglyceride levels.

Stop taking TRADJENTA and call your healthcare provider 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 through to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

Who should not take TRADJENTA?

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

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

What should I tell my healthcare provider before taking TRADJENTA?
Tell your healthcare provider about all your medical conditions, including if you have or have had inflammation of your pancreas (pancreatitis). Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. TRADJENTA may affect the way other medicines work, and other medicines may affect how TRADJENTA works. Especially tell your healthcare

provider if you take:

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

Tell your healthcare provider if you are pregnant or planning to become pregnant or are breastfeeding or plan to breastfeed.

What are the possible side effects of TRADJENTA?

TRADJENTA may cause serious side effects, including

- Inflammation of the pancreas (pancreatitis).
- If you take TRADJENTA 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 medicine or insulin may need to be lowered while you take TRADJENTA. Signs and symptoms of low blood sugar may include headache, drowsiness, weakness, dizziness, confusion, irritability, fast heartbeat, sweating, shaking or feeling jittery.
- Allergic (hypersensitivity) reactions have happened in people who are taking TRADJENTA. Symptoms may include swelling of your face, lips, tongue, throat, and other areas on your skin; difficulty with swallowing or breathing; raised, red areas on your skin (hives); skin rash, itching, flaking, or peeling.
- Joint pain. Some people who take medicines called dipeptidyl peptidase-4 (DPP-4) inhibitors like TRADJENTA, may develop joint pain that can be severe. Call your healthcare provider if you have severe joint pain.
- Skin Reaction. Some people who take medicines called DPP-4 inhibitors like TRADJENTA, may develop a skin reaction called bullous pemphigoid which can be serious and may need to be treated in a hospital. Tell your healthcare provider right away if you develop blisters.
- Heart failure. Heart failure means your heart does not pump blood well enough. Before you start taking TRADJENTA, tell your healthcare provider if you have ever had heart failure or have problems with your kidneys. Contact your healthcare provider right away if you have any of the following symptoms: increasing shortness of breath or trouble breathing, especially when you lie down; swelling or fluid retention, especially in the feet, ankles, or legs; an unusually fast increase in weight or unusual tiredness. These may be symptoms of heart failure.

The most common side effects of TRADJENTA include stuffy or runny nose and sore throat, cough, and diarrhea.

These are not all the possible side effects of TRADJENTA. For more information, ask your healthcare provider 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.

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Please see Prescribing Information and Medication Guide.

Boehringer Ingelheim and Eli Lilly and Company
In January 2011, Boehringer Ingelheim and Eli Lilly and Company announced an Alliance that centers on compounds representing several of the largest diabetes treatment classes. Depending on geographies, the companies either co-promote or separately promote the respective molecules each contributing to the Alliance. The Alliance leverages the strengths of two of the world's leading pharmaceutical companies to focus on patient needs. By joining forces, the companies demonstrate their commitment, not only to the care of people with diabetes, but also to investigating the potential to address areas of unmet medical need.

About Boehringer Ingelheim
Boehringer Ingelheim is working on breakthrough therapies that improve the lives of humans and animals. As a leading research-driven biopharmaceutical company, the company creates value through innovation in areas of high unmet medical need. Founded in 1885 and family-owned ever since, Boehringer Ingelheim takes a long-term perspective. Around 52,000 employees serve more than 130 markets in the three business areas, Human Pharma, Animal Health, and Biopharmaceutical Contract Manufacturing. Learn more at www.boehringer-ingelheim.com/us.

About Lilly
Lilly unites caring with discovery to create medicines that make life better for people around the world. We've been pioneering life-changing discoveries for nearly 150 years, and today our medicines help more than 47 million people across the globe. Harnessing the power of biotechnology, chemistry and genetic medicine, our scientists are urgently advancing new discoveries to solve some of the world's most significant health challenges, redefining diabetes care, treating obesity and curtailing its most devastating long-term effects, advancing the fight against Alzheimer's disease, providing solutions to some of the most debilitating immune system disorders, and transforming the most difficult-to-treat cancers into manageable diseases. With each step toward a healthier world, we're motivated by one thing: making life better for millions more people. That includes delivering innovative clinical trials that reflect the diversity of our world and working to ensure our medicines are accessible and affordable. To learn more, visit Lilly.com and Lilly.com/newsroom or follow us on Facebook, Instagram and LinkedIn.

Cautionary Statement Regarding Forward-Looking Statements

This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about Jardiance® as a treatment for adults with type 2 diabetes, to reduce the risk of cardiovascular death in adults with type 2 diabetes and known cardiovascular disease, to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure, and as a potential treatment for children 10 years and older with type 2 diabetes, and reflects Lilly's current beliefs and expectations. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of drug research, development and commercialization. Among other things, there is no guarantee that planned or ongoing studies will be completed as planned, that future study results will be consistent with study results to date or that Jardiance® will receive additional regulatory approvals. For further discussion of these and other risks and uncertainties that could cause actual results to differ from Lilly's expectations, see Lilly's Form 10-K and Form 10-Q filings with the United States Securities and Exchange Commission. Except as required by law, Lilly undertakes no duty to update forward-looking statements to reflect events after the date of this release.

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SOURCE Eli Lilly and Company