US FDA accepts supplemental New Drug Application and grants Priority Review for Jardiance® for adults with heart failure independent of left ventricular ejection fraction

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If approved, Jardiance would be the first clinically proven treatment for adults across the full spectrum of heart failure regardless of ejection fraction

RIDGEFIELD, Conn. and INDIANAPOLIS, Nov. 11, 2021 /PRNewswire/ -- The U.S. Food and Drug Administration (FDA) has accepted a supplemental New Drug Application (sNDA) and granted Priority Review for Jardiance® (empagliflozin) 10 mg, which is being investigated as a potential new treatment to reduce the risk of cardiovascular death plus hospitalization for heart failure in adults with heart failure independent of left ventricular ejection fraction (LVEF), Boehringer Ingelheim and Eli Lilly and Company (NYSE: LLY) announced.

"If approved, Jardiance would be the first and only therapy clinically proven to significantly improve outcomes in a heart failure population that included a majority of people with preserved ejection fraction," said Mohamed Eid, M.D., M.P.H., M.H.A., vice president, Clinical Development & Medical Affairs, Cardio-Metabolism & Respiratory Medicine, Boehringer Ingelheim Pharmaceuticals, Inc. "Building on the recent FDA approval of Jardiance for heart failure with reduced ejection fraction, this supplemental New Drug Application acceptance is a step toward the potential to make Jardiance the sole treatment to demonstrate a statistically significant benefit for adults across the full spectrum of heart failure regardless of ejection fraction. The FDA's Priority Review designation further reinforces the urgent need for additional treatments for heart failure."

The sNDA is based on results from the EMPEROR-Preserved® phase III trial, in which Jardiance was associated with a 21% relative risk reduction (3.3% absolute risk reduction) for the composite primary endpoint of cardiovascular death or hospitalization for heart failure in adults with heart failure with LVEF over 40% compared with placebo. Results were independent of ejection fraction or diabetes status. Results from EMPEROR-Preserved were presented at the European Society of Cardiology Congress 2021 and published in *The New England Journal of Medicine*.

According to the FDA, a Priority Review designation is intended to direct overall attention and resources to the evaluation of applications for a treatment that, if approved, would be a significant improvement in the safety or effectiveness of treatments for serious conditions. In September, the FDA also granted Breakthrough Therapy designation to Jardiance as an investigational treatment for adults with heart failure with preserved ejection fraction (HFpEF).

Jardiance is currently indicated to reduce the risk of cardiovascular death plus hospitalization for heart failure in adults with heart failure and reduced ejection fraction. Jardiance is not for type 1 diabetes, or to improve glycemic control in adults with type 2 diabetes with an eGFR <30 mL/min/1.73m^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.**

HFpEF accounts for approximately half of the more than 6 million heart failure cases in the U.S. No currently approved treatments have been clinically proven to significantly improve outcomes specifically for people with HFpEF.

"This milestone offers renewed hope to adults with heart failure with preserved ejection fraction, for whom treatment options are especially lacking," said Jeff Emmick, M.D., Ph.D., vice president, Product Development, Lilly. "We believe Jardiance has the potential to be a transformative treatment in heart failure and look forward to working with the FDA during the review process toward a decision next year."

The FDA previously granted Fast Track designation for the development of Jardiance to reduce the risk of cardiovascular death and hospitalization for heart failure. The Fast Track designation is for the EMPEROR program, which consists of the EMPEROR-Reduced® and EMPEROR-Preserved trials. The EMPEROR-Reduced results formed the basis of the recent FDA approval for heart failure with reduced ejection fraction. Jardiance is not indicated for the treatment of HFpEF.

About EMPEROR-Preserved
EMPEROR-Preserved (NCT03057951) was a phase III international, randomized, double-blind trial that enrolled 5,988 adults with and without type 2 diabetes. All participants had heart failure (New York Heart Association [NYHA] functional class II, III or IV) and LVEF over 40%; 4,005 (67%) had HFpEF (LVEF of at least 50%), and 1,983 (33%) had mildly reduced LVEF (greater than 40% but less than 50%).

Participants were randomized to once-daily Jardiance 10 mg (n=2997) or placebo (n=2991), on top of treatment with guideline-directed heart failure therapy. Median follow-up time was 26.2 months. The composite primary endpoint was defined as time to first event of cardiovascular death or hospitalization for heart failure.

What is JARDIANCE? (www.jardiance.com)

JARDIANCE is a prescription medicine used to:

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

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 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 your JARDIANCE before you have surgery. Talk to your healthcare provider if you are having surgery about when to stop taking JARDIANCE 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. **Especially tell your healthcare provider if you take** water pills (diuretics) or medicines that can lower your blood sugar, such as insulin.

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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Prioritizing Cardio-Renal-Metabolic Care
Through research and educational initiatives, Boehringer Ingelheim and Lilly are driven to redefine care for people with cardio-renal-metabolic conditions, a group of interconnected disorders that affect more than one billion people worldwide and are a leading cause of death.

The cardiovascular, renal (kidney) and metabolic systems are closely intertwined and share many of the same disease-related pathways. Dysfunction in one system may accelerate the onset of dysfunction in others, resulting in the progression of comorbid diseases such as type 2 diabetes, heart failure and chronic kidney disease. Conversely, improving the health of one system can lead to positive effects across the others and can help reduce the risk for further complications.

Understanding their interconnected nature, we are working to advance treatments for people with cardio-renal-metabolic conditions. It is only through a holistic approach to care that we can truly transform outcomes and restore the harmony among these critical systems.

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
Making new and better medicines for humans and animals is at the heart of what we do. Our mission is to create breakthrough therapies that change lives. Since its founding in 1885, Boehringer Ingelheim is independent and family-owned. We have the freedom to pursue our long-term vision, looking

ahead to identify the health challenges of the future and targeting those areas of need where we can do the most good.

As a world-leading, research-driven pharmaceutical company, with around 52,000 employees, we create value through innovation daily for our three business areas: Human Pharma, Animal Health, and Biopharmaceutical Contract Manufacturing. In 2020, Boehringer Ingelheim achieved net sales of around 22.33 billion USD (19.57 billion EUR). Our significant investment of over 4.2 billion USD (3.7 billion EUR) in 2020 (18.9% of net sales) in R&D drives innovation, enabling the next generation of medicines that save lives and improve quality of life.

We realize more scientific opportunities by embracing the power of partnership and diversity of experts across the life-science community. By working together, we accelerate the delivery of the next medical breakthrough that will transform the lives of patients now, and in generations to come.

Boehringer Ingelheim Pharmaceuticals, Inc., based in Ridgefield, CT, is the largest U.S. subsidiary of Boehringer Ingelheim Corporation and is part of the Boehringer Ingelheim group of companies. In addition, there are Boehringer Ingelheim Animal Health in Duluth, GA and Boehringer Ingelheim Fremont, Inc. in Fremont, CA.

Boehringer Ingelheim is committed to improving lives and strengthening our communities. Please visit www.boehringer-ingelheim.us/csr to learn more about Corporate Social Responsibility initiatives.

For more information, please visit www.boehringer-ingelheim.us, or follow us on Twitter @BoehringerUS.

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, collaboration and quality manufacturing we strive to make life better for people affected by diabetes and related conditions. We work to deliver breakthrough outcomes through innovative solutions—from medicines and technologies to support programs and more. For the latest updates, visithttp://www.lillydiabetes.com/ or follow us on Twitter: @LillyDiabetes and Facebook: LillyDiabetesUS.

About Eli Lilly and Company
Lilly is a global health care leader that unites caring with discovery to create medicines that 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 lilly.com and lilly.com/newsroom.

This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about Jardiance and reflects Lilly's current belief. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of drug development and commercialization. Among other things, there can be no guarantee that future study results will be consistent with the results to date or that Jardiance will receive additional regulatory approvals. For a further discussion of these and other risks and uncertainties that could cause actual results to differ from Lilly's expectations, please see Lilly's most recent Forms 10-K and 10-Q filed with the U.S. Securities and Exchange Commission. Lilly undertakes no duty to update forward-looking statements.

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