US FDA accepts supplemental New Drug Application for Jardiance® (empagliflozin) for adults with heart failure with reduced ejection fraction

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RIDGEFIELD, Conn. and INDIANAPOLIS, Jan. 11, 2021 /PRNewswire/ -- The U.S. Food and Drug Administration (FDA) has accepted a supplemental New Drug Application (sNDA) for Jardiance® (empagliflozin) which is being investigated as a potential new treatment to reduce the risk of cardiovascular death and hospitalization for heart failure and to slow kidney function decline in adults with chronic heart failure with reduced ejection fraction, including those with and without type 2 diabetes, Boehringer Ingelheim and Eli Lilly and Company (NYSE: LLY) announced.

A high unmet need remains in the treatment of heart failure, as approximately half of all those diagnosed are expected to die within five years. Heart failure is also the leading cause of hospitalization in the U.S., with an estimated one million people being hospitalized due to the condition each year. The risk of death in people with heart failure rises with each hospital admission. Heart failure with reduced ejection fraction occurs when the heart muscle does not contract effectively, and less blood is pumped out to the body compared to a normally functioning heart.

"New treatments for heart failure are needed to help reduce the risk of death in those affected by this chronic, debilitating illness," 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. "We look forward to working with the FDA to potentially expand the number of adults who may benefit from Jardiance to include those affected by heart failure with reduced ejection fraction."

The sNDA is based on results from the EMPEROR-Reduced phase III trial, in which Jardiance was associated with a significant 25% relative risk reduction in the primary composite endpoint of time to cardiovascular death or hospitalization due to heart failure. Additionally, the rate of decline in eGFR, a measure of kidney function decline, was slower with Jardiance than with placebo, when both were given on top of standard of care treatment. Results were published in *The New England Journal of Medicine* in August 2020.

"With this filing acceptance, we move closer to starting yet another important chapter with Jardiance," said Jeff Emmick, M.D., Ph.D., vice president, Product Development, Lilly. "In addition, results are anticipated this year from the EMPEROR-Preserved trial in adults with heart failure with preserved ejection fraction, an area that currently has no approved treatment options."

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 not for people with type 1 diabetes or for people with diabetic ketoacidosis (increased ketones in the blood or urine). Jardiance is contraindicated in people with a history of serious hypersensitivity reaction to empagliflozin or any of the excipients of Jardiance, and in people with severe renal impairment, end-stage renal disease, or dialysis. Please see Important Safety Information below.

The FDA previously granted Fast Track designation to Jardiance for the reduction of the risk of cardiovascular death and hospitalization for heart failure in people with heart failure. This designation is for the EMPEROR program, which consists of the EMPEROR-Reduced and EMPEROR-Preserved trials. EMPEROR-Preserved is exploring the effect of Jardiance on cardiovascular death or hospitalization for heart failure in adults with heart failure with preserved ejection fraction. EMPEROR-Preserved results are expected in 2021. Jardiance is not indicated for the treatment of heart failure with reduced or preserved ejection fraction, to reduce hospitalization for heart failure, or to slow kidney function decline.

In March 2020, the FDA has also granted Fast Track designation to Jardiance for the treatment of chronic kidney disease. This designation covers the ongoing EMPA-KIDNEY trial, the results of which are expected in 2022. Jardiance is not indicated for the treatment of chronic kidney disease.

About the EMPEROR Heart Failure Studies
The EMPEROR (EMPagliflozin outcomE tRial in patients with chrOnic heaRt failure) heart failure studies are two phase III, randomized, double-blind trials investigating once-daily Jardiance compared with placebo in adults with heart failure with preserved or reduced ejection fraction*, both with and without diabetes, who are receiving current standard of care:

- **EMPEROR-Reduced** [NCT03057977] investigated the safety and efficacy of Jardiance in patients with chronic heart failure with **reduced ejection fraction** (HFrEF).
    - Primary composite endpoint: time to first event of adjudicated cardiovascular death or adjudicated hospitalization for heart failure
    - Number of patients: 3,730
    - Completion: 2020
- **EMPEROR-Preserved** [NCT03057951] investigates the safety and efficacy of Jardiance in patients with chronic heart failure with **preserved ejection fraction** (HFpEF).
    - Primary composite endpoint: time to first event of adjudicated cardiovascular death or adjudicated hospitalization for heart failure [Time Frame: up to 38 months]
    - Anticipated number of patients: approx. 5,990
    - Estimated completion: 2021

***Ejection fraction** is a measurement of the percentage of blood the left ventricle pumps out with each contraction. When the heart relaxes, the ventricle refills with blood.

- **HFrEF** occurs when the heart muscle does not contract effectively, and less blood is pumped out to the body compared with a normally functioning heart.
- **HFpEF** occurs when the heart muscle contracts normally but the ventricle does not fill with enough blood, so less blood can enter the heart compared with a normally functioning heart.

About the EMPOWER program
The Alliance has developed the EMPOWER program to explore the impact of Jardiance on major clinical cardiovascular and renal outcomes in a spectrum of cardio-renal-metabolic conditions. Cardio-renal-metabolic conditions are the leading cause of mortality worldwide and account for up to 20 million deaths annually. Through the EMPOWER program, Boehringer Ingelheim and Lilly are working to advance knowledge of these interconnected systems and create care which offers integrated, multi-organ benefits. Comprised of nine clinical trials and two real-world evidence studies, EMPOWER reinforces the long-term commitment of the Alliance to improve outcomes for people living with cardio-renal-metabolic conditions. With 377,000 adults estimated to have enrolled worldwide upon completion of the studies, it is one of the broadest and most comprehensive clinical programs for an SGLT2 inhibitor to date.

The development program encompasses:

- EMPEROR-Reduced, in adults with chronic heart failure with reduced ejection fraction to reduce the risk of cardiovascular death or hospitalization due to heart failure
- EMPEROR-Preserved, in adults with chronic heart failure with preserved ejection fraction to reduce the risk of cardiovascular death or hospitalization due to heart failure
- EMPULSE, in adults hospitalized for acute heart failure and stabilized to improve clinical and patient reported outcomes
- EMPACT-MI, to evaluate all-cause mortality and hospitalization for heart failure in adults with and without type 2 diabetes who have had an acute myocardial infarction, with the aim to prevent heart failure and improve outcomes
- EMPA-KIDNEY, in adults with established chronic kidney disease to reduce the progression of kidney disease and the occurrence of cardiovascular death
- EMPERIAL-Reduced, in adults with chronic heart failure with reduced ejection fraction to evaluate functional ability and patient-reported outcomes
- EMPERIAL-Preserved, in adults with chronic heart failure with preserved ejection fraction to evaluate functional ability and patient-reported outcomes
- EMPA-REG OUTCOME®, in adults with type 2 diabetes and established cardiovascular disease to reduce the risk of major adverse cardiovascular events, including cardiovascular death
- EMPRISE, two non-interventional studies (U.S. and EU-Asia) of the effectiveness, safety, healthcare utilization and cost of care of empagliflozin in routine clinical practice in adults with type 2 diabetes across the cardiovascular risk continuum

About Cardio-Renal-Metabolic Conditions
Boehringer Ingelheim and Lilly are driven to transform 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 and metabolic systems are interconnected, and share many of the same risk factors and pathological pathways along the disease continuum. Dysfunction in one system may accelerate the onset of others, resulting in progression of interconnected diseases such as type 2 diabetes, cardiovascular disease, heart failure, and kidney disease, which in turn leads to an increased risk of cardiovascular death. Conversely, improving the health of one system can lead to positive effects throughout the others.

Through our research and treatments, our goal is to support people's health, restoring the harmony between the interconnected cardio-renal-metabolic systems and reducing their risk of serious complications. As part of our commitment to those whose health is jeopardized by cardio-renal-metabolic conditions, we will continue embracing a multidisciplinary approach towards care and focusing our resources on filling treatment gaps.

What is JARDIANCE? (www.jardiance.com)
JARDIANCE is a prescription medicine used along with diet and exercise to lower blood sugar in adults with type 2 diabetes.

JARDIANCE is also used to reduce the risk of cardiovascular death in adults with type 2 diabetes who have known cardiovascular disease.

JARDIANCE is not for people with type 1 diabetes or for people with diabetic ketoacidosis (increased ketones in the blood or urine).

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 have severe kidney problems or are on dialysis.

JARDIANCE can cause serious side effects, including:

- **Dehydration. JARDIANCE** 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 a 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
- are 65 years of age or older.

- **Vaginal yeast infection.** Women who take JARDIANCE 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 JARDIANCE 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.

- **Ketoacidosis (increased ketones in your blood or urine).** Ketoacidosis is a serious condition and may need 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 doctor right away 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
  - **Kidney problems.** Sudden kidney injury has happened in people taking JARDIANCE. Talk to your doctor right away if you reduce the amount you eat or drink, or if you lose liquids; for example, 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 doctor 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).**

  - **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 doctor or go to the nearest emergency room right away.

- **Increased fats in your blood (cholesterol).**

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 doctor or pharmacist.

Before taking JARDIANCE, tell your doctor if you:

- have kidney problems. Your doctor may do blood tests to check your kidneys before and during your treatment with JARDIANCE
- have liver problems
- have a history of urinary tract infections or problems with urination
- are going to have surgery. Your doctor may stop your JARDIANCE before you have surgery. Talk to your doctor 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 any other medical conditions
- are pregnant or plan to become pregnant. JARDIANCE may harm your unborn baby. Tell your doctor 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 doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Especially tell your doctor 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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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. Clinical trials have been initiated to evaluate the impact of Jardiance on people living with heart failure or chronic kidney disease.

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, more than 51,000 employees create value through innovation daily for our three business areas: Human Pharma, Animal Health, and Biopharmaceutical Contract Manufacturing. In 2019, Boehringer Ingelheim achieved net sales of around $21.3 billion (19 billion euros). Our significant investment of over $3.9 billion (3.5 billion euros) 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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CONTACT:
Jennifer Forsyth
Director, Public Relations
Boehringer Ingelheim Pharmaceuticals, Inc.
Email: jennifer.forsyth@boehringer-ingelheim.com
Phone: (203) 791-5889

Stephan Thalen
Global Business Communications
Lilly Diabetes and Lilly USA
Email: stephan.thalen@lilly.com
Phone: (317) 903-5640

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