Interim analysis from EMPRISE real-world study shows Jardiance® decreased risk of hospitalization for heart failure compared with DPP-4 inhibitors and GLP-1 receptor agonists

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- This analysis on effectiveness also shows Jardiance® (empagliflozin) was associated with a similar risk of non-fatal atherosclerotic cardiovascular events compared with DPP-4 inhibitors or GLP-1 receptor agonists

- A second analysis on healthcare resource utilization shows Jardiance was associated with a reduced risk in all-cause hospitalizations compared with DPP-4 inhibitors

RIDGEFIELD, Conn. and INDIANAPOLIS, Nov. 17, 2019 /PRNewswire/ -- A new interim analysis of three-year data from the EMPagliflozin compaRative effectIveness and SafEty (EMPRISE) real-world study on effectiveness shows that Jardiance® (empagliflozin) was associated with a decreased risk of hospitalization for heart failure and a similar risk of non-fatal atherosclerotic cardiovascular events compared with DPP-4 inhibitors and GLP-1 receptor agonists. The interim analysis included 190,000 adults in the U.S. with type 2 diabetes with and without cardiovascular disease. The results were shared today on behalf of Boehringer Ingelheim and Eli Lilly and Company (NYSE: LLY) at the American Heart Association® Scientific Sessions 2019 in Philadelphia.

"Heart failure is a leading cause of hospitalizations in the U.S., with about one million admissions annually, yet treatment options that are available for people living with this debilitating disease are not adequate to improve the problem," 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. "Data showed that Jardiance reduced the risk of hospitalization for heart failure in adults with type 2 diabetes with and without cardiovascular disease in both routine clinical practice and in a clinical trial setting."

In this new interim analysis, Jardiance was associated with a reduction in risk of hospitalization for heart failure of 41% compared with DPP-4 inhibitors and of 17% compared with GLP-1 receptor agonists. Risk for non-fatal atherosclerotic cardiovascular events—defined as non-fatal heart attack or stroke, hospitalization for unstable angina or coronary revascularization—was similar for those treated with Jardiance (14.6 events per 1,000 patient-years) compared with DPP-4 inhibitors (17.6 events per 1,000 patient-years). The risk was also similar for those treated with Jardiance (14.2 events per 1,000 patient-years) compared with GLP-1 receptor agonists (14.8 events per 1,000 patient-years).

In a second interim analysis of EMPRISE, which included more than 45,000 patients, Jardiance was associated with a significant reduction in all-cause hospitalizations, emergency department visits and physician's office visits compared with DPP-4 inhibitors.

Results from the EMPRISE real-world study in routine clinical care complement data from the landmark EMPA-REG OUTCOME® trial, in which Jardiance showed a 35% relative risk reduction in hospitalization for heart failure compared with placebo in adults with type 2 diabetes and established cardiovascular disease. The EMPA-REG OUTCOME trial also showed a 38% relative risk reduction in cardiovascular death in those taking Jardiance versus placebo in the same population.

"We are pleased to see the three-year data for EMPRISE continues to complement findings from the EMPA-REG OUTCOME trial," said Sherry Martin, M.D., vice president, Global Medical Affairs, Lilly. "These new real-world findings are just one part of a broad and comprehensive clinical development program, including a large heart failure program, that explores how Jardiance can improve patient health outcomes and potentially fill treatment gaps for people with cardiorenal metabolic conditions."

The effects of empagliflozin on heart failure-related outcomes and functional capacity in people with heart failure are being evaluated in the empagliflozin heart failure program. The program, which includes more than 9,500 adults with heart failure, including those with and without diabetes, consists of the EMPEROR-Reduced, EMPEROR-Preserved, EMPERIAL-Reduced, EMPERIAL-Preserved, EMPULSE and EMPA-VISION studies.

About EMPRISE (NCT03363464, EUPAS20677)[5]

EMPRISE was initiated in 2016 to complement the EMPA-REG OUTCOME trial results by providing data on the comparative effectiveness, safety, healthcare resource utilization and costs in routine clinical care compared with DPP-4 inhibitors in people with type 2 diabetes with and without cardiovascular disease. In addition, a sub-group analysis has provided data on the effectiveness of empagliflozin compared with GLP-1 receptor agonists.

The study will assess the first five years of Jardiance use in the U.S. between 2014 and 2019. Data analyses includes planned interim analyses (based on 12-month data updates) and a final analysis. More than 200,000 people with type 2 diabetes are projected to participate in the EMPRISE trial by its completion. From 2019, additional EMPRISE studies including Asia and Europe will provide insights from different regions of the world with an international perspective on the use of empagliflozin in routine clinical care.

The EMPRISE study was initiated, and is being led, by academic partners from the Division of Pharmacoepidemiology at Brigham and Women's Hospital and Harvard Medical School, Boston, U.S. The study is part of an academic collaboration between Brigham and Women's Hospital and Boehringer Ingelheim.

About EMPA-REG OUTCOME® (NCT01131676)

EMPA-REG OUTCOME was a long-term, multicenter, randomized, double-blind, placebo-controlled trial of more than 7,000 patients from 42 countries with type 2 diabetes and established cardiovascular disease.

The study assessed the effect of Jardiance (10 mg or 25 mg once daily) added to standard of care compared with placebo added to standard of care. Standard of care was comprised of glucose-lowering agents and cardiovascular drugs (including medication for the treatment of hypertension and hypercholesterolemia). The primary endpoint was defined as time to first occurrence of cardiovascular death, non-fatal heart attack or non-fatal stroke.

The overall safety profile of Jardiance was consistent with that of previous trials.

About Heart Failure
Heart failure is a progressive, debilitating and potentially fatal condition that occurs when the heart cannot supply adequate circulation to meet the body's demands for oxygenated blood or, to do so, requires increased blood volume leading to fluid accumulation (congestion) in the lungs and peripheral tissues. It is a widespread condition affecting 60 million people worldwide and expected to increase as the population ages. Heart failure is highly prevalent in people with diabetes; however, approximately half of all people with heart failure do not have diabetes.

Symptoms of heart failure include difficulty breathing, swelling – most commonly in feet, legs and ankles – and fatigue, among others. People with heart failure experience a substantial reduction in quality of life, approximately 76% of whom find it difficult to carry out usual activities. This is, in part, due to the limitation of physical activity.

There is a high unmet need in the treatment of heart failure, as approximately 50% of people diagnosed with heart failure will die within five years. Additionally, heart failure represents the most common cause of hospitalization among individuals aged 65 years and over in the U.S. and Europe.

About Cardiorenal Metabolic Conditions
Cardiorenal metabolic conditions are a group of interconnected disorders affecting the heart, kidneys and endocrine system. In aggregate, these conditions are the leading cause of deaths worldwide, accounting for up to 20 million deaths annually. Conditions within this group include coronary artery disease, heart failure, chronic kidney disease and type 2 diabetes, among many others.

Emerging science on the link between the cardiorenal and metabolic systems supports taking a multidisciplinary approach toward diagnostic, preventive and therapeutic strategies for people living with these conditions. A team approach to optimize patient care by coordinating treatment of related comorbidities, including the use of emerging therapies with broad cardiorenal metabolic effects, may improve outcomes for people with serious chronic conditions such as these.

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. **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
- are eating less due to illness, surgery, or 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 to help those living with heart failure or chronic kidney disease.

Currently, no Boehringer Ingelheim and Lilly products are approved for the treatment of heart failure or chronic kidney disease.

About Boehringer Ingelheim Pharmaceuticals, Inc.
Boehringer Ingelheim Pharmaceuticals, Inc., based in Ridgefield, Conn., is the largest U.S. subsidiary of Boehringer Ingelheim Corporation.

Boehringer Ingelheim is one of the world's top 20 pharmaceutical companies. Headquartered in Ingelheim, Germany, the company operates globally with approximately 50,000 employees. Since its founding in 1885, the company has remained family-owned, and today our goal is to improve the lives of humans and animals through its three business areas: human pharmaceuticals, animal health and biopharmaceutical contract manufacturing.

Boehringer Ingelheim concentrates on developing innovative therapies that can improve and extend patients' lives. As a research-driven pharmaceutical company, it plans in generations for long-term success. Its research efforts are focused on diseases with high, unmet medical need. In animal health, the company stands for advanced prevention.

In 2018, Boehringer Ingelheim achieved net sales of around $20.7 billion (17.5 billion euros). R&D expenditure of almost $3.7 billion (3.2 billion euros) corresponded to 18.1 per cent of net sales.

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 and collaboration, a wide range of therapies 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 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 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 further discussion of these and other risks and uncertainties, see Lilly's most recent 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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