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US FDA Approves Expanded FARXIGA and XIGDUO XR Labels for Use in Patients with Type 2 Diabetes and Moderate Renal Impairment

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Updated label confirms the well-established efficacy and safety profile for FARXIGA and XIGDUO XR

AstraZeneca today announced that the US Food and Drug Administration (FDA) has approved a label update for FARXIGA® (dapagliflozin) and XIGDUO® XR (dapagliflozin and metformin HCl extended-release) expanding use in patients with type 2 diabetes (T2D) and moderate renal impairment (chronic kidney disease with an estimated glomerular filtration rate [eGFR] of 45-59 mL/min/1.73 m^2). FARXIGA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. XIGDUO XR is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate.

The updated labels lower the eGFR threshold to 45 mL/min/1.73 m^2 from 60 mL/min/1.73 m^2, expanding the potential population of patients with T2D and impaired renal function who may benefit from the medicine. FARXIGA and XIGDUO XR are not recommended when the eGFR is less than 45 mL/min/1.73 m^2 and remains contraindicated in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2), end-stage renal disease, or in patients on dialysis.

The updates were based on the results of DERIVE, a Phase 3 study of patients with inadequately controlled T2D (HbA1c 7.0%-11.0%) and an eGFR of 45 to 59 mL/min/1.73 m^2 who received either FARXIGA (dapagliflozin 10 mg) or placebo over 24 weeks. At Week 24, FARXIGA (dapagliflozin 10 mg) provided statistically significant reductions in HbA1c compared with placebo. The safety profile following a treatment duration of 24 weeks was similar to that seen in the overall FARXIGA (dapagliflozin) clinical trial program.

Jim McDermott, PhD., Vice President, US Medical Affairs, Diabetes at AstraZeneca, said: “The DERIVE study, which further confirmed the well-established efficacy and safety profile for FARXIGA and XIGDUO XR, has resulted in important label changes for patients with type 2 diabetes that enable a broader population with impaired renal function to potentially benefit from these important treatment options.”

According to the Centers for Disease Control and Prevention, 30.3 million people in the US have diabetes, and T2D accounts for 90% to 95% of all diabetes cases. Diabetes is the leading cause of kidney disease, and approximately 1 in 4 adults with diabetes has kidney disease.

Indication and Limitations of Use for FARXIGA® (dapagliflozin)

FARXIGA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

FARXIGA is not recommended for patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Important Safety Information for FARXIGA® (dapagliflozin)

Contraindications

- Prior serious hypersensitivity reaction to FARXIGA
- Severe renal impairment (eGFR <30 mL/min/1.73 m^2), end-stage renal disease, or patients on dialysis

Warnings and Precautions

- **Hypotension:** FARXIGA causes intravascular volume contraction, and symptomatic hypotension can occur. Assess and correct volume status before initiating FARXIGA in patients with impaired renal function, elderly patients, or patients on loop diuretics. Monitor for hypotension
- **Ketoacidosis** has been reported in patients with type 1 and type 2 diabetes receiving FARXIGA. Some cases were fatal. Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue FARXIGA, evaluate and treat promptly. Before initiating FARXIGA, consider risk factors for ketoacidosis. Patients on FARXIGA may require monitoring and temporary discontinuation in situations known to predispose to ketoacidosis
- **Acute Kidney Injury and Impairment in Renal Function:** FARXIGA causes intravascular volume contraction and renal impairment, with reports of acute kidney injury requiring hospitalization and dialysis. Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and promptly treat.

  FARXIGA increases serum creatinine and decreases eGFR. Elderly patients and patients with impaired renal function may be more susceptible to these changes. Before initiating FARXIGA, evaluate renal function and monitor periodically. FARXIGA is not recommended when the eGFR is <45 mL/min/1.73 m^2

- **Urosepsis and Pyelonephritis:** SGLT2 inhibitors increase the risk for urinary tract infections [UTIs] and serious UTIs have been reported with FARXIGA. Evaluate for signs and symptoms of UTIs and treat promptly
- **Hypoglycemia:** FARXIGA can increase the risk of hypoglycemia when coadministered with insulin and insulin secretagogues. Consider lowering the dose of these agents when coadministered with FARXIGA
- **Necrotizing Fasciitis of the Perineum (Fournier's Gangrene):** Rare but serious, life-threatening cases have been reported in patients receiving SGLT2 inhibitors including FARXIGA. Cases have been reported in females and males. Serious outcomes have included hospitalization, surgeries, and death. Assess patients presenting with pain or tenderness, erythema, swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment and discontinue FARXIGA.
- **Genital Mycotic Infections:** FARXIGA increases the risk of genital mycotic infections, particularly in patients with prior genital mycotic infections. Monitor and treat appropriately
- **Increases in Low-Density Lipoprotein Cholesterol (LDL-C)** occur with FARXIGA. Monitor LDL-C and treat per standard of care

- **Bladder cancer**: An imbalance in bladder cancers was observed in clinical trials. There were too few cases to determine whether the emergence of these events is related to FARXIGA, and insufficient data to determine whether FARXIGA has an effect on pre-existing bladder tumors. FARXIGA should not be used in patients with active bladder cancer. Use with caution in patients with a history of bladder cancer
- **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with FARXIGA

Adverse Reactions
In a pool of 12 placebo-controlled studies, the most common adverse reactions (≥5%) associated with FARXIGA 5 mg, 10 mg, and placebo respectively were female genital mycotic infections (8.4% vs 6.9% vs 1.5%), nasopharyngitis (6.6% vs 6.3% vs 6.2%), and urinary tract infections (5.7% vs 4.3% vs 3.7%).

Use in Specific Populations

- **Pregnancy:** Advise females of potential risk to a fetus especially during the second and third trimesters.
- **Lactation:** FARXIGA is not recommended when breastfeeding.

Please see accompanying US Full Prescribing Information and Medication Guide for FARXIGA.

Indication and Limitations of Use for XIGDUO® XR (dapagliflozin and metformin HCl extended-release)

XIGDUO XR is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate.

XIGDUO XR is not recommended for patients with type 1 diabetes mellitus or diabetic ketoacidosis.

Important Safety Information for XIGDUO® XR (dapagliflozin and metformin HCl extended-release)

WARNING: LACTIC ACIDOSIS

Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio, and metformin plasma levels generally >5 mcg/mL.

Risk factors include renal impairment, concomitant use of certain drugs, age >65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the Full Prescribing Information.

If lactic acidosis is suspected, discontinue XIGDUO XR and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

Contraindications

- Severe renal impairment (eGFR <30 mL/min/1.73 m^2), end-stage renal disease, or patients on dialysis
- Prior serious hypersensitivity reaction to dapagliflozin or hypersensitivity to metformin hydrochloride
- Metabolic acidosis, including diabetic ketoacidosis

Warnings and Precautions
Hypotension: Dapagliflozin causes intravascular volume contraction, and symptomatic hypotension can occur. Assess and correct volume status before initiating XIGDUO XR in patients with impaired renal function, elderly patients, or patients on loop diuretics. Monitor for hypotension.

Ketoacidosis has been reported in patients with type 1 and type 2 diabetes receiving dapagliflozin. Some cases were fatal. Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue XIGDUO XR, evaluate and treat promptly. Before initiating XIGDUO XR, consider risk factors for ketoacidosis. Patients on XIGDUO XR may require monitoring and temporary discontinuation in situations known to predispose to ketoacidosis.

Acute Kidney Injury and Impairment in Renal Function: Dapagliflozin causes intravascular volume contraction and renal impairment, with reports of acute kidney injury requiring hospitalization and dialysis. Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and promptly treat.

Dapagliflozin increases serum creatinine and decreases eGFR. Elderly patients and patients with impaired renal function may be more susceptible to these changes. Before initiating XIGDUO XR, evaluate renal function and monitor periodically. XIGDUO XR is not recommended when the eGFR is <45 mL/min/1.73 m^2.

Urosepsis and Pyelonephritis: SGLT2 inhibitors increase the risk for urinary tract infections (UTIs) and serious UTIs have been reported with dapagliflozin. Evaluate for signs and symptoms of UTIs and treat promptly.

Use with Medications Known to Cause Hypoglycemia: Consider a lower dose of insulin and insulin secretagogues to reduce risk of hypoglycemia when coadministered with XIGDUO XR.

Hypoglycemia could occur when caloric intake is deficient, strenuous exercise is not compensated by caloric supplementation, or when XIGDUO XR is used with other glucose-lowering agents or ethanol.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene): Rare but serious, life-threatening cases have been reported in patients receiving SGLT2 inhibitors including dapagliflozin. Cases have been reported in females and males. Serious outcomes have included hospitalization, surgeries, and death. Assess patients presenting with pain or tenderness, erythema, swelling in the genital or perineal area,

along with fever or malaise. If suspected, institute prompt treatment and discontinue XIGDUO XR.

Vitamin B_{12} Deficiency: Metformin may lower vitamin B_{12} levels. Measure hematological parameters annually.

Genital Mycotic Infections: Dapagliflozin increases the risk of genital mycotic infections, particularly in patients with prior genital mycotic infections. Monitor and treat appropriately.

Increases in Low-Density Lipoprotein Cholesterol (LDL-C) occur with dapagliflozin. Monitor LDL-C and treat per standard of care.

Bladder Cancer: An imbalance in bladder cancers was observed in clinical trials. There were too few cases to determine whether the emergence of these events is related to dapagliflozin, and insufficient data to determine whether dapagliflozin has an effect on pre-existing bladder tumors. XIGDUO XR should not be used in patients with active bladder cancer. Use with caution in patients with a history of bladder cancer.

Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with XIGDUO XR.

Adverse Reactions
Most common adverse reactions (≥5%) with dapagliflozin (5 mg or 10 mg) plus metformin vs placebo plus metformin were female genital mycotic infection (9.4%, 9.3%, 1.5%), nasopharyngitis (6.3%, 5.2%, 5.9%), urinary tract infection (6.1%, 5.5%, 3.6%), diarrhea (5.9%, 4.2%, 5.6%), and headache (5.4%, 3.3%, 2.8%), respectively.

Adverse reactions reported in >5% of patients treated with metformin XR and more commonly than in patients treated with placebo are diarrhea (9.6% vs 2.6%) and nausea/vomiting (6.5% vs 1.5%).

Use in Specific Populations
Pregnancy: Advise females of the potential risk to a fetus especially during the second and third trimesters. Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women.

Lactation: XIGDUO XR is not recommended when breastfeeding.

Please see accompanying US Full Prescribing Information, including Boxed WARNING about lactic acidosis, and Medication Guide for XIGDUO XR.

NOTES TO EDITORS

About AstraZeneca in Cardiovascular, Renal & Metabolism (CVMD)
Cardiovascular, renal and metabolic diseases together form one of AstraZeneca's main therapy areas and platforms for future growth. By following the science to understand more clearly the underlying links between the heart, kidney and pancreas, AstraZeneca is investing in the development of a portfolio of medicines to protect organs and improve outcomes by slowing disease progression, reducing risks and tackling co-morbidities. Our ambition is to modify or halt the natural course of CVMDs and even regenerate organs and restore function, by continuing to deliver

transformative science that improves treatment practices and CVMD health for millions of patients worldwide.

About AstraZeneca
AstraZeneca is a global, science-led biopharmaceutical company that focuses on the discovery, development and commercialization of prescription medicines, primarily for the treatment of diseases in three main therapy areas - Oncology, Cardiovascular, Renal & Metabolism and Respiratory. The Company also is selectively active in the areas of autoimmunity, neuroscience and infection. AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide. For more information, please visit www.astrazeneca-us.com and follow us on Twitter @AstraZenecaUS.

CONTACTS

Media Inquiries

Michele Meixell +1 302 885 2677

Abigail Bozarth +1 302 885 2677

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