August 26, 2021

AstraZeneca K.K.
Ono Pharmaceutical Co., Ltd.

Forxiga Approved in Japan for the Treatment of Chronic Kidney Disease in Patients with and without Type-2 Diabetes

Approval marks a significant progress in the treatment of patients suffering from chronic kidney disease in Japan

AstraZeneca K.K. (Osaka, Japan; President and Representative Director: Stefan Woxström) and Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President, Representative Director: Gyo Sagara) announced that Forxiga® (generic name: dapagliflozin propylene glycolate hydrate) Tablets 5mg, 10mg ("Forxiga"), an inhibitor of sodium-glucose co-transporter 2 (SGLT2), received an additional approval for the indication of "chronic kidney disease (excluding patients with end-stage renal disease or undergoing dialysis)" with and without type-2 diabetes on August 25, 2021.

The approval by the Ministry of Health, Labour and Welfare (MHLW) is based on positive results from the DAPA-CKD Phase III trial.[1] The approval was made under the Priority Review designated by the MHLW earlier this year.

CKD is a serious, progressive condition defined by decreased kidney function and is often associated with an increased risk of heart disease or stroke.[2-4] The condition affects 840 million people worldwide and approximately 13 million people in Japan.[5,6] However, diagnosis rates remain low and up to 90% of patients are unaware they have the disease.[4] Forxiga is the first ever approved medicine for the treatment of the disease in Japan.[7,8]

The national coordinator of the DAPA-CKD Phase III trial in Japan, Naoki Kashihara, President of Japanese Society of Nephrology, said: "DAPA-CKD is the landmark trial that demonstrated unprecedented risk reduction for chronic kidney disease patients with and without type-2 diabetes. This transformational milestone will bring great hope to many patients with chronic kidney disease in Japan."

Mene Pangalos, Executive Vice President, BioPharmaceuticals R&D, said: "This approval is an important step towards realising our ambition of improving outcomes for patients with chronic kidney disease. While new medicines like Forxiga advance the standard of care, we are also committed to the prevention and early detection of this often debilitating and life-threatening disease."

The DAPA-CKD Phase III trial demonstrated that Forxiga, on top of standard-of-care (SoC) treatment with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB), reduced the relative risk of worsening of renal function, onset of end-stage kidney disease (ESKD), or risk of cardiovascular (CV) or renal death by 39%, the primary composite endpoint, compared to

placebo (absolute risk reduction [ARR]=5.3%, p<0.0001) in patients with CKD Stages 2-4 and elevated urinary albumin excretion. Forxiga also significantly reduced the relative risk of death from any cause by 31% (ARR=2.1%, p=0.0035) compared to placebo.[9] The safety and tolerability of Forxiga were consistent with the well-established safety profile of the medicine.

Forxiga (known as Farxiga in the US) was recently approved in the US and the European Union for the treatment of CKD in adults with and without T2D and is currently under review in several other countries around the world. Forxiga is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with T2D and as an oral adjunct treatment to insulin for adults with type-1 diabetes (T1D). It is also approved for the treatment of symptomatic chronic heart failure (HF) with reduced ejection fraction (HFrEF) in adults with and without T2D.

In 2013, AstraZeneca K.K. (AZKK), a subsidiary in Japan of AstraZeneca, entered into an agreement with Ono Pharmaceutical Co., Ltd. (Ono) for Forxiga. Based on this agreement, Ono is responsible for distribution and marketing of Forxiga in Japan and has been co-promoting it with AZKK for the treatment of T2D, T1D and chronic HF. Both Companies will co-promote for the treatment of CKD.

* * * * *

Chronic Kidney Disease (CKD)

CKD is a serious, progressive condition defined by decreased kidney function (shown by reduced estimated glomerular filtration rate (eGFR) or markers of kidney damage, or both, for at least three months).[4] The most common causes of CKD are diabetes, hypertension and glomerulonephritis.[10] CKD is associated with significant patient morbidity and an increased risk of CV events, such as HF and premature death. In its most severe form, known as ESKD, kidney damage and deterioration of kidney function have progressed to the point where dialysis or kidney transplantation are required.[2] The majority of patients with CKD will die from CV causes before reaching ESKD.[11] Currently in Japan, more than 13 million people are living with CKD.[6]

DAPA-CKD

DAPA-CKD was an international, multi-centre, randomised, double-blinded Phase III trial in 4,304 patients designed to evaluate the efficacy of Forxiga 10mg, compared with placebo, in patients with CKD Stage 2-4 and elevated urinary albumin excretion, with and without T2D. Forxiga was given once daily in addition to SoC. The primary composite endpoint was worsening of renal function or risk of death (defined as a composite of an eGFR decline ≥50%, onset of ESKD or death from CV or renal cause). The secondary endpoints included the time to first occurrence of the renal composite (sustained ≥50% eGFR decline, ESKD or renal death), the composite of CV death or hospitalisation for HF (hHF), and death from any cause. The trial was conducted in 21 countries.[1] Detailed results from the trial were published in The New England Journal of Medicine.[1]

Forxiga

Forxiga (dapagliflozin) is a first-in-class, oral, once-daily SGLT2 inhibitor. Research has shown Forxiga's efficacy in preventing and delaying cardiorenal disease, while also protecting the organs – important findings given the underlying links between the heart, kidneys and pancreas.[1,12,13] Damage to one of these organs can cause the other organs to fail, contributing to leading causes of death worldwide, including T2D, HF and CKD.[14-16]

Forxiga is approved as an adjunct to diet and exercise to improve glycaemic control in adults with T2D and in T2D to reduce the risk of hHF or CV death when added to SoC based on the findings of the DECLARE-TIMI 58 Phase III CV outcomes trial.[12] Forxiga is also approved for the treatment of HFrEF and the treatment of CKD based on the findings of the DAPA-HF and DAPA-CKD Phase III trials.[1,13]

* Indications of Forxiga approved in Japan:
- Type 2 diabetes mellitus
- Type 1 diabetes mellitus
- Chronic heart failure (limited to the patients who receive standard of care for chronic heart failure)
- Chronic kidney disease (excluding patients with end-stage renal disease or undergoing dialysis)

DapaCare is a robust programme of clinical trials to evaluate the potential CV, renal and organ protection benefits of Forxiga. It includes more than 35 completed and ongoing Phase IIb/III trials in more than 35,000 patients, as well as more than 2.5 million patient-years' experience. Forxiga is currently being tested in the DELIVER Phase III trial to evaluate its efficacy in the treatment of patients with HF with preserved ejection fraction with or without T2D and in the DAPA-MI Phase III trial - a first of its kind, indication-seeking registry-based randomised controlled trial in patients without T2D following an acute myocardial infarction (MI) or heart attack.

AstraZeneca in CVRM

Cardiovascular, Renal and Metabolism (CVRM), part of BioPharmaceuticals, forms one of AstraZeneca's main disease areas and is a key growth driver for the Company. By following the science to understand more clearly the underlying links between the heart, kidneys and pancreas, AstraZeneca is investing in a portfolio of medicines for organ protection and improve outcomes by slowing disease progression, reducing risks and tackling co-morbidities. The Company's ambition is to modify or halt the natural course of CVRM diseases and potentially regenerate organs and restore function, by continuing to deliver transformative science that improves treatment practices and CV health for millions of patients worldwide.

AstraZeneca

AstraZeneca (LSE/STO/Nasdaq: AZN) is a global, science-led biopharmaceutical company that focuses on the discovery, development, and commercialisation of prescription medicines in Oncology, Rare Diseases and BioPharmaceuticals, including Cardiovascular, Renal & Metabolism, and Respiratory & Immunology. Based in Cambridge, UK, AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide. Please visit astrazeneca.com and follow the Company on Twitter @AstraZeneca.

In Japan, AstraZeneca is actively working to further contribute to the health and medical development of patients with primary focus on Oncology, Cardiovascular, Renal and Metabolism, and Respiratory, Immunology fields. For more information, please visit https://www.astrazeneca.co.jp/

Ono Pharmaceutical Co., Ltd.

Ono Pharmaceutical Co., Ltd., headquartered in Osaka, is an R&D-oriented pharmaceutical company committed to creating innovative medicines in specific areas. Ono focuses its research on the oncology, immunology, neurology and specialty research with high medical needs, as priority areas for discovery and development of innovative medicines. For further information, please visit the company's website https://www.ono-pharma.com/.

References

1. Heerspink HJL, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383(15):1436-1446.
2. Centers for Disease Control and Prevention (CDC) [Internet]. Chronic kidney disease in the United States; 2019 [cited 2021 Jul 08]. Available from: URL: https://www.cdc.gov/kidneydisease/publications-resources/2019-national-facts.html.
3. Segall L, et al. Heart failure in patients with chronic kidney disease: a systematic integrative review. *Biomed Res Int*. 2014;2014:937398.
4. Bikbov B, et al. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2020;395(10225):709-733.
5. Jager KJ, et al. A single number for advocacy and communication-worldwide more than 850 million individuals have kidney diseases. *Nephrol Dial Transplant*. 2019;34(11):1803-1805.
6. Okada K, et al. Evidence-based clinical practice guidelines for chronic kidney disease 2018. Tokyo Medical Co., Ltd; 2018 Jun.
7. Fukui, A., Yokoo, T., Nangaku, M. et al. New measures against chronic kidney diseases in Japan since 2018. *Clinical and Experimental Nephrology*. 2019;23:1263–1271.
8. National Health Service [Internet]. Chronic kidney disease; Treatment; 2016 [cited 2021 Jul 09]. Available from: URL: https://www.nhs.uk/conditions/kidney-disease/treatment/.
9. Heerspink H. DAPA-CKD - Dapagliflozin in Patients with Chronic Kidney Disease. presented at: ESC Congress 2020 - The Digital Experience, 2020 August 29 - September 01.
10. National Kidney Foundation [Internet]. Kidney Disease: Causes; 2015 [cited 2021 Jul 08]. Available from: URL: https://www.kidney.org/atoz/content/kidneydiscauses.
11. Briasoulis A, Bakris GL. Chronic kidney disease as a coronary artery disease risk equivalent. *Curr Cardiol Rep*. 2013;15(3):340.
12. Wiviott SD et al., for the DECLARE-TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type-2 diabetes [article and supplementary appendix]. *N Engl J Med*. 2019;380:347-357.
13. McMurray J et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019; 381:1995-2008
14. Mayo Clinic [Internet]. Heart failure; 2020 [cited 2021 Jul 09]. Available from: https://www.mayoclinic.org/diseases-conditions/heart-failure/symptoms-causes/syc-20373142
15. Centers for Disease Control and Prevention (CDC) [Internet]. A snapshot: Diabetes in the United States; 2020 [cited 2021 Jul 09]. Available from: URL: https://www.cdc.gov/diabetes/library/socialmedia/infographics/diabetes.html.
16. National Institute of Diabetes and Digestive And Kidney Diseases (NIH) [Internet]. Heart disease & kidney disease; 2016 [cited 2021 Jul 09]. Available from: URL: https://www.niddk.nih.gov/health-information/kidney-disease/heart-disease.

Contact
Ono Pharmaceutical Co., Ltd.
Corporate Communications
public_relations@ono.co.jp