November 30, 2020

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

Forxiga approved in Japan for the treatment of chronic heart failure

Forxiga is the first SGLT2 inhibitor approved in Japan for the treatment of chronic heart failure with or without type-2 diabetes

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 treatment of patients with chronic heart failure ("HF")* who are receiving standard of care, from the Ministry of Health, Labour and Welfare (MHLW) in Japan on November 27, 2020.

HF is a life-threatening disease that prevents the heart from pumping sufficient levels of blood around the body. It affects approximately 64 million people worldwide, at least half of whom have a reduced ejection fraction.[1-3]

The approval by the MHLW was based on the positive results from the landmark DAPA-HF Phase III trial in patients with a reduced ejection fraction, with or without type-2 diabetes. The result was published in November 2019 in The New England Journal of Medicine.[4]

Masafumi Kitakaze**,** Director of Hanwa Daini Senboku Hospital / Guest Professor of Graduate School of Medicine, University of Osaka and Investigator of the DAPA-HF Phase III trial in Japan, said: "Heart failure is a condition, affecting about 1.3 million people in Japan. Many patients have considerably reduced heart function, such as left ventricular reduced ejection fraction. Approximately half of patients will die within five years of diagnosis, which is worse than some cancers. Heart failure is treated with various drugs, but if they do not respond, there is no cure other than heart transplant. A new effective treatment option on top of the current standard of care may offer hope for people struggling with this disease. With this approval, Forxiga will be a new significant tool for the treatment of heart failure for cardiologists."

Mene Pangalos, Executive Vice President, BioPharmaceuticals R&D, said: "Forxiga's efficacy in reducing the risk of cardiovascular death or worsening of heart failure events could result in life-saving benefits for many heart failure patients in Japan. Today's approval will shift the way we manage the disease by providing a treatment option that is urgently needed to improve patient outcomes and symptoms for these patients."

Forxiga is the first SGLT2 inhibitor to have shown a statistically significant reduction in the risk of the composite cardiovascular (CV) death or worsening of HF events, including hospitalisation for HF (hHF). The DAPA-HF Phase III trial demonstrated that Forxiga, in addition to standard of care, reduced the risk of the composite outcome versus placebo by 26% and both components of the primary composite endpoint contributed benefit to the overall effect. During the trial, one CV death or hHF or an urgent visit resulting in intravenous therapy associated with HF could be avoided for every 21 patients treated. In the DAPA-HF Phase III trial, the safety profile of Forxiga was consistent with the well-established safety profile of the medicine.

Forxiga (known as Farxiga in the US) is approved in the US, Europe, and several other countries around the world for the treatment of patients with HF with reduced ejection fraction (HFrEF).

Forxiga is advancing cardiorenal prevention as science continues to identify the underlying links between the heart, kidneys and pancreas. The DAPA-HF trial is part of DapaCare, a robust clinical trial programme to assess the potential CV and renal benefits of Forxiga. The programme has also explored the treatment of patients with chronic kidney disease (CKD) in the ground-breaking DAPA-CKD Phase III trial. Additionally, Forxiga is currently being tested for HF patients with preserved ejection fraction (HFpEF) in the DELIVER Phase III trial with data readout anticipated in the second half of 2021.

In 2013, AstraZeneca K.K. (AZKK), a subsidiary in Japan of AstraZeneca, entered into an agreement with Ono Pharmaceutical Co., Ltd. for Forxiga. Based on this agreement, Ono is responsible for distribution and marketing of Forxiga tablets in Japan and has been co-promoting it with AZKK for the treatment of type-2 and type-1 diabetes. Both companies will co-promote for the treatment of chronic heart failure.

***INDICATIONS**
Chronic heart failure
Administration of Forxiga should be limited to the patients who receive standard of care for chronic heart failure.

PRECAUTION FOR INDICATIONS
Because the safety and efficacy of Forxiga in the treatment of chronic heart failure with preserved left ventricular ejection fraction have not been established, Forxiga should be administered to patients with chronic heart failure with reduced left ventricular ejection fraction.

Prescribers should have enough knowledge about the contents in the “Clinical Studies” section and fully understand background of the clinical study subjects (such as prior treatment, left ventricular ejection fraction) to select patients who are suitable for this drug

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Heart failure
HF affects approximately 64 million people worldwide (at least half of whom have a reduced ejection fraction), including 1.3 million in Japan, 15 million in the EU and six million in the US.[2,3,7,8] It is a chronic disease where half of patients will die within five years of diagnosis.[9] HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) are the two main categories of HF related to ejection fraction, a measurement of the percentage of blood leaving the heart each time it contracts.[4] HFrEF occurs when the left ventricle muscle is not able to contract adequately and therefore, expels less oxygen-rich blood in to the body. [5,6] It is the leading cause of hospitalisation for those over the age of 65 and represents a significant clinical and economic burden. [10]

DAPA-HF
DAPA-HF (Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure) is an international, multi-centre, parallel-group, randomised, double-blinded trial in 4,744 patients with HFrEF (LVEF ≤ 40%), with and without T2D, designed to evaluate the effect of Forxiga 10mg, compared with placebo, given once daily in addition to standard of care. The primary composite endpoint was time to the first occurrence of a worsening heart failure event (hospitalisation or equivalent event; i.e. an urgent heart failure visit), or CV death. The median duration of follow-up was 18.2 months.

Forxiga
Forxiga (dapagliflozin) is a first-in-class, oral, once-daily SGLT2 inhibitor indicated in adults for the treatment of insufficiently controlled T2D as both monotherapy and as part of combination therapy as an adjunct to diet and exercise to improve glycaemic control, with the additional benefits of weight loss and blood-pressure reduction.

Forxiga has been evaluated in patients with CKD in the Phase III DAPA-CKD trial, with the full results announced in August 2020 demonstrating that Forxiga met all primary and secondary endpoints, providing overwhelming efficacy. Forxiga is currently being tested for patients with HF in the DELIVER (HF with preserved ejection fraction, HFpEF) and DETERMINE (HFrEF and HFpEF) Phase III trials. Forxiga will also be tested in patients without T2D following an acute myocardial infarction (MI) or heart attack in the DAPA-MI trial - a first of its kind, indication-seeking registry-based randomised controlled trial. Forxiga has a robust programme of clinical trials that 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.

AstraZeneca in CVRM
Cardiovascular, Renal and Metabolism (CVRM) together forms one of AstraZeneca's three therapy 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 to protect organs and improve outcomes by slowing disease progression, reducing risks and tackling comorbidities. 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 cardiovascular 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, primarily for the treatment of diseases in three therapy areas - Oncology, CVRM, 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.

About 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 www.ono.co.jp/eng/index.html.

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