January 10, 2023

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

**Revision of Electronic Package Insert of Forxiga, a Selective SGLT2 inhibitor, related to Indication of Chronic Heart Failure**

- Forxiga available as a therapeutic agent for chronic heart failure regardless of left ventricular ejection fraction -

AstraZeneca K.K. (Osaka, Japan; President and Representative Director: Takafumi Hori) and Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President and CEO: Gyo Sagara) announced that the electronic Japanese package insert of Forxiga® (generic name: dapagliflozin propylene glycolate hydrate) Tablets 5mg, 10mg (“Forxiga”), an inhibitor of sodium-glucose co-transporter 2 (SGLT2) has been revised for currently approved indication of chronic heart failure.

In this revision, the description related to "left ventricular ejection fraction" in the "Precautions related to Indications" for the approved chronic heart failure was deleted, and its concerned information was added.

The main revisions are as follows:

- The description “Safety and efficacy of Forxiga have not been established for the treatment of chronic heart failure with preserved left ventricular ejection fraction, and therefore, it should be administered to patients with reduced chronic heart failure” In the item of “"Precautions related to Indications" was deleted.
- The results of the global Phase III trial (DELIVER trial) in patients with chronic heart failure with preserved left ventricular ejection fraction were added to the “Clinical Studies” section.

These revisions have been made based on the results of the DELIVER trial described above. This revision of the electronic package insert allows Farxiga to be used as a treatment of patients with chronic heart failure regardless of left ventricular ejection fraction.

The currently approved indications of Forxiga in Japan are “type 2 diabetes mellitus”, “type 1 diabetes mellitus”, “chronic heart failure (limited to the patients who receive standard of care for chronic heart failure)” and “chronic kidney disease (excluding patients with end-stage renal disease or undergoing dialysis)”.

AstraZeneca and Ono Pharmaceutical Co., Ltd. entered into a co-promotion agreement for Forxiga in Japan. Under the agreement, Ono is responsible for the distribution and marketing of Forxiga, and has been co-promoting Forxiga with AstraZeneca in Japan.

**About Heart Failure**

Heart Failure (HF) is a chronic, long-term condition that worsens over time[1]. It affects nearly 64 million people globally[2] and is associated with substantial morbidity and mortality[3]. Chronic HF is the leading cause of hospitalisation for those over the age of 65 and represents a significant clinical and economic burden[4]. There are several types of HF often defined by left ventricular ejection fraction (LVEF), a measurement of the percentage of blood leaving the heart each time it contracts, including: HFrEF (LVEF less than or equal to 40%), HFmrEF (LVEF 41-49%) and HFpEF (LVEF greater than or equal to 50%)[5]. Approximately half of all HF patients have HFmrEF or HFpEF, with few therapeutic options available[5, 6].

**About DELIVER Trial[7, 8]**

DELIVER trial was an international, randomised, double-blind, parallel-group, placebo-controlled, event-driven Phase III trial designed to evaluate the efficacy of Forxiga, compared with placebo, in the treatment of heart failure (HF) patients with left ventricular ejection fraction (LVEF) greater than 40%, with or without type 2 diabetes mellitus. Forxiga was given once daily in addition to background therapy (regional standard of care for all comorbidities, including diabetes and hypertension, with the exception of concomitant use of a sodium-glucose cotransporter 2 (SGLT2) inhibitor)[7]. DELIVER trial is the largest clinical trial to date in HF patients with LVEF above 40%, with 6,263 randomized patients[7].

The primary composite endpoint was the time to first occurrence of CV death, hospitalization due to HF (hHF) or an urgent HF visit. Key secondary endpoints include the total number of HF events (hHF or urgent HF visit) and CV death, change from baseline in the total symptom score of the KCCQ at eight months, time to the occurrence of CV death and time to the occurrence of death from any cause[7].

**About 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. Damage to one of these organs can cause the other organs to fail, contributing to leading causes of death worldwide, including type 2 diabetes (T2D) mellitus, heart failure and chronic kidney disease (CKD).

Forxiga is approved in adults and children aged 10 years and above (adults only approved in Japan) for the improvement of glycaemic control in patients with T2D mellitus as an adjunct to diet and exercise. Forxiga is also approved for the treatment of CKD in adults based on the findings of the DAPA-CKD Phase III trial.

**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 improving 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.

**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 at https://www.ono-pharma.com/en.

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