March 27, 2019

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

A selective sodium-glucose co-transporter 2 (SGLT2) inhibitor Forxiga receives additional regulatory approval on indication and dosage and administration in type-1 diabetes in Japan

AstraZeneca K.K. (Osaka, President and Representative Director: Stefan Woxström) and Ono Pharmaceutical Co., Ltd. (Osaka, Japan, President, Representative Director, and CEO: Gyo Sagara) announced that Forxiga® Tablets 5mg, 10mg (generic name: dapagliflozin propylene glycolate hydrate, hereinafter Forxiga), an inhibitor of sodium-glucose co-transporter 2 (SGLT2), received an additional approval on indication as well as dosage and administration for type-1 diabetes.

Forxiga is a highly selective and reversible inhibitor of SGLT2 which inhibits glucose reabsorption from renal uriniferous tubule. It is a drug that reduces blood glucose by releasing excess glucose in blood to urine. It works independently of insulin to improve fasting blood glucose and postprandial hyperglycemia.

Type 1 diabetes is the disease with which the body does not produce insulin, and its main cause is an autoimmune reaction where the body's immune system attacks the insulin-producing beta cells in the islets of the pancreas gland. The causes of this destructive process are not fully understood but a combination of genetic susceptibility and environmental triggers have been implicated[1].

According to the survey by Ministry of Health, Labour and Welfare, the population of "the type-1 diabetes patients with no insulin secretion" in Japan is estimated to be about 100,000 to 140,000 people[2]. The disease occurs most frequently in children and adolescents, and 4.4 in 1000 people aged 0-19 years develop type-1 diabetes every year in Japan. However, the disease can develop at any age[1].

Daily insulin injections are essential for type-1 diabetes patients in order for them to maintain a glucose level in the proper range which fluctuates by daily activities. Less than 7% of haemoglobin A1c (HbA1c), an indication of long-term blood glucose control, is set as a goal for adult diabetes patients to prevent complications by diabetes, but the average HbA1c level in patients with type-1 diabetes tends to be as high as 7.8%[3]. Therefore, the development of the treatment which can be used with the insulin has been desired for better control of type-1 diabetes patients' blood glucose levels.

This approval is based on data from the Phase III DEPICT clinical programme, and a dedicated trial in Japanese patients (D1695C00001). Results showed that Forxiga, when given as an oral treatment in addition to adjustable insulin in patients with inadequately-controlled T1D, demonstrated significant and clinically-meaningful reductions from baseline in average blood glucose levels HbA1c (primary endpoint), weight and total daily insulin dose (secondary endpoints) at 24 weeks[4,5,6], at both 5mg and 10mg doses.

The safety profile of Forxiga in these T1D trials was consistent with its well-established profile in type-2 diabetes (T2D), with the exception of a higher number of diabetic ketoacidosis (DKA) events in Forxiga-treated patients versus placebo. DKA is a known complication for adults with T1D that affects those with T1D more frequently than with T2D.

Other than Japan, it is announced on March 25, 2019 that Forxiga was approved by the European Commission as an oral adjunct treatment to insulin in adults with type-1 diabetes. The medicine is under regulatory review in the US for the same indication, with a decision expected in the second half of 2019.

Product summary (Parts with underline were newly added upon this approval)

Product name	Forxiga® Tablets 5mg, Forxiga® Tablets 10mg
General name	Dapagliflozin propylene glycolate hydrate
Indication or usage	Type 2 diabetes mellitus**,** Type 1 diabetes mellitus
Dosage and Administration	**Type 2 diabetes mellitus** The usual adult dosage is 5mg of dapagliflozin given orally once daily. For patients who show inadequate response, the dosage may be increased to 10mg once daily while carefully monitoring the patient's condition. **Type 1 diabetes mellitus** In combination with insulin, the usual adult dosage is 5mg of dapagliflozin given orally once daily. For patients who show inadequate response, the dosage may be increased to 10 mg once daily while carefully monitoring the patient's condition
Approval date for change of approved indication	March 26, 2019
Manufactured and distributed by	AstraZeneca K.K.
Distributed by	Ono Pharmaceutical Co., Ltd.

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About the DEPICT Clinical Programme

The DEPICT (**D**apagliflozin **E**valuation in **P**atients with **I**nadequately **C**ontrolled **T**ype 1 Diabetes) clinical trial programme consists of two trials: DEPICT-1 and DEPICT-2 which are 24-week, randomised, double-blinded, parallel-controlled trials designed to assess the effects of *Forxiga* 5mg or 10mg on glycaemic control in patients with T1D inadequately controlled by insulin. All patients were evaluated at week 24 and after a 28-week extension (52 weeks in total).

About Forxiga (dapagliflozin)

Forxiga is a first-in-class, oral once-daily selective inhibitor of human sodium-glucose co-transporter 2 (SGLT2) indicated as both monotherapy and as part of combination therapy to improve glycaemic control as an adjunct to diet and exercise in adults with T2D. Forxiga has a robust clinical trial programme of more than 35 completed and ongoing Phase IIb/III trials in over 35,000 patients, as well as more than 1.8 million patient-years' experience. Forxiga received additional regulatory approval on indication and dosage and administration in type-1 diabetes in Japan in March 2019. Forxiga is also approved in T1D in the EU.

About AstraZeneca

AstraZeneca 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, Cardiovascular, Renal & Metabolism and Respiratory. AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide. For more information, please visit www.astrazeneca.com and follow us on Twitter @AstraZeneca.

In Japan, we focus on three therapy areas, Oncology, Cardiovascular and Metabolic/ Gastrointestinal Diseases, and Respiratory and Autoimmunity, to contribute to patients' health and healthcare advancements. For more information, please visit: www.astrazeneca.co.jp

About Ono Pharmaceutical Co., Ltd.

Ono Pharmaceutical Co., Ltd. is a R&D-oriented pharmaceutical company specialized in creating innovative medicines in specific areas and is headquartered in Osaka, Japan, putting focus in the area of diabetes and oncology. For more information about Ono, visit the company's website at http://www.ono.co.jp/eng/index.html

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