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Forxiga HF receives positive CHMP opinion

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Forxiga recommended for approval in the EU by CHMP for heart failure

If approved, Forxiga would become the first SGLT2 inhibitor indicated for heart failure with reduced ejection fraction in patients with and without type-2 diabetes

AstraZeneca's *Forxiga* (dapagliflozin) has been recommended for an indication extension of its marketing authorisation in the European Union (EU) for the treatment of symptomatic chronic heart failure with reduced ejection fraction (HFrEF) in adults with and without type-2 diabetes (T2D). Heart failure (HF) is a life-threatening chronic disease in which the heart cannot pump enough blood around the body,[1] affecting 15 million people in the EU, at least half of which have a reduced ejection fraction.[2,3]

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) based its positive opinion on results from the landmark DAPA-HF Phase III trial, published in *The New England Journal of Medicine*.[4]

Forxiga is the first SGLT2 inhibitor to have shown a statistically significant reduction in the risk of cardiovascular (CV) death or worsening of HF events (including hospitalisation for HF, hHF) versus placebo where both components of the primary composite endpoint contributed benefit to the overall effect. In the DAPA-HF Phase III trial, the safety profile of *Forxiga* was consistent with the well-established safety profile of the medicine.

John McMurray, MD, Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, UK, said: "I am delighted that we may soon have a new treatment that is effective, safe and simple to use for patients with heart failure with reduced ejection fraction. Dapagliflozin is a major and welcome breakthrough with the potential to improve not only the quality, but also importantly, the length of life for millions of people suffering from this terrible disease in Europe and throughout the world."

Mene Pangalos, Executive Vice President, BioPharmaceuticals R&D, said: "The unmet need for novel medicines in heart failure remains high, with more than half of patients expected to die within five years of diagnosis. Novel treatment options reducing cardiovascular death and hospitalisation, in addition to improving symptoms, are urgently needed. With the positive opinion for *Forxiga* we are one step closer to transforming the standard of care for millions of people in the EU living with heart failure."

The DAPA-HF Phase III trial demonstrated that *Forxiga*, in addition to standard of care, reduced the risk of the composite outcome of CV death or the worsening of HF versus placebo by 26% (hazard ratio [HR] = 0.74 [95% confidence interval {CI} 0.65-0.85]; p < 0.0001) (absolute risk reduction [ARR] = 4.9% [16.3% vs 21.2% patients with event, respectively]). During the trial, one CV death or hHF or an urgent visit associated with HF could be avoided for every 21 patients treated.

The CHMP recommendation states *Forxiga* is indicated in adults for the treatment of symptomatic chronic HFrEF.

Forxiga (known as *Farxiga* in the US) is approved by the US Food and Drug Administration (FDA), as well as in several other countries around the world, for the for the treatment of patients with HFrEF.

Forxiga is evolving cardiorenal prevention as science continues to identify the underlying links between the heart, kidneys and pancreas. DAPA-HF is part of DapaCare, a robust clinical trial programme to assess the potential CV and renal benefits of *Forxiga*, including the DECLARE-TIMI 58 trial which first evaluated *Forxiga* for the treatment of hHF and CV risk factors in patients with T2D. The programme has also explored the treatment of patients with chronic kidney disease (CKD) in the ground-breaking DAPA-CKD Phase III trial and is also currently being tested for HF patients with preserved ejection fraction (HFpEF) in the DELIVER Phase III trial with data anticipated in the second half of 2021.

Heart failure

HF is a life-threatening disease in which the heart cannot pump enough blood around the body.[1] It affects approximately 64 million people worldwide (at least half of which have a reduced ejection fraction), including 15 million in the EU and six million in the US.[2-3,5] It is a chronic disease where half of patients will die within five years of diagnosis.[6] There are two main categories of HF related to ejection fraction (EF), a measurement of the percentage of blood leaving the heart each time it contracts: HFrEF and HFpEF.[7] HFrEF occurs when the left ventricle (LV) muscle is not able to contract adequately and therefore, expels less oxygen-rich blood in to the body.[7,8] HF remains as fatal as some of the most common cancers in both men (prostate and bladder cancers) and women (breast cancer).[9] 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 Phase III 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 HF event (hospitalisation or equivalent event; i.e. an urgent HF 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 sodium-glucose co-transporter-2 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. In the DECLARE-TIMI 58 CV outcomes trial in adults with T2D, *Forxiga* reduced the risk of the composite endpoint of hHF or CV death versus placebo, when added to standard of care.

In May 2020, *Farxiga* was approved in the US to reduce the risk of CV death and hHF in adults with HF (NYHA class II-IV) with reduced ejection fraction with and without T2D. *Forxiga* has also been evaluated in patients with CKD in the DAPA-CKD Phase III trial, with the full results announced in August 2020 showing *Forxiga* met all primary and secondary endpoints, providing overwhelming efficacy. *Forxiga* is currently being tested for patients with HF in the DELIVER (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 Phase III 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.

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Contacts

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