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FDA OKs Dapagliflozin to Reduce HF Hospitalization in Diabetes

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The type 2 diabetes drug dapagliflozin (*Farxiga*, AstraZeneca) has been approved in the United States for reducing hospitalization for heart failure (HF) in adults with type 2 diabetes and other cardiovascular (CV) risk factors, the company has announced.

The US Food and Drug Administration's (FDA's) approval for this additional indication is based on the results of the DECLARE-TIMI 58 CV outcomes trial, first reported at the American Heart Association Scientific Sessions in November last year and simultaneously published in the *New England Journal of Medicine* (NEJM). It follows a similar approval in the European Union in the summer, in which the label was updated to include CV outcomes data from DECLARE-TIMI 58.

However, the US approval is specific to hospitalization for HF and as such represents the first of the class of sodium-glucose cotransporter 2 (SGLT2) inhibitors to be approved for this particular indication, says AstraZeneca.

The labels for the other two SGLT2 inhibitors, empagliflozin (*Jardiance,* Boehringer Ingelheim/Lilly) and canagliflozin (*Invokana,* Janssen), were updated in the United States to include positive CV outcomes data from the EMPA-REG OUTCOME study in December 2016 and the CANVAS trial in September 2018, respectively.

The DECLARE-TIMI 58 results were similar to those of EMPA-REG OUTCOME and CANVAS and showed a significant reduction in HF hospitalization and renal events with the SGLT2 inhibitors compared with placebo.

However, the fall in HF was the main driver of the significant reduction in the composite endpoint of hospitalization for HF or CV death vs placebo, one of two primary efficacy endpoints in DECLARE-TIMI 58. There were fewer major adverse cardiac events with dapagliflozin, the other primary efficacy endpoint; however, this did not reach statistical significance.

However, one expert told *Medscape Medical News* that, effectively, all SGLT2 inhibitors are believed to work in the same way — these specific drugs simply received slightly differently worded additional approvals from the FDA that were based on how their respective CV outcomes trials were designed.

This latest approval for dapagliflozin effectively levels the playing field between it and empagliflozin and canagliflozin.

"Most consider the CV benefits are more similar than different across each member of the class, at least for the three medications with completed CV outcomes trials," said Darren McGuire, MD, MHSC, of the University of Texas Southwestern Medical Center, Dallas. He has participated in a clinical trial leadership capacity for AstraZeneca and has financial relationships with other pharmaceutical companies.

"The differences in the specifics of the product-labeled indications most likely reflect differences in trial designs and populations studied, with differential treatment effects for both atherosclerotic CVD outcomes and risk for HF hospitalization based on prevalence of atherosclerotic CVD and, importantly, based on underlying kidney function — with augmentation of benefits for the sicker of the patients, those with prevalent atherosclerotic CVD and those with worse kidney function," he added.

Dapagliflozin in Development for HF Without Diabetes, Fast-Tracked by FDA

Dapagliflozin is also the first of the SGLT2 inhibitors to demonstrate benefits in HF patients even if they do not have diabetes.

In the DAPA HF trial, reported at the European Society of Cardiology Congress 2019 and the annual meeting of the European Association for the Study of Diabetes in September and published in the NEJM, the drug was compared with placebo on top of contemporary therapy in patients with chronic HF with reduced ejection fraction (HFrEF) both with and without type 2 diabetes.

Dapagliflozin reduced the relative risk for the primary outcome — a composite of time to first CV death or HF hospitalization or urgent HF visit requiring intravenous therapy — by 26% when added to standard therapy, compared with placebo (hazard ratio [HR], 0.74; *P* = .00001). The number needed to treat was 21.

The treatment effect was consistent across all 14 prespecified subgroups, including, most importantly, patients with and those without baseline diabetes (HRs, 0.75 and 0.73, respectively).

The FDA has granted fast-track designation to dapagliflozin to reduce the risk for CV death or the worsening of HF in adults with HFrEF or those who have HF with preserved EF.

The DELIVER trial, which is ongoing, is randomizing patients who have HF with preserved EF to receive dapagliflozin 10 mg or placebo on top of standard therapy. Results are expected in 2021.

Trials with the other SGLT2 inhibitors in HF are ongoing.

SGLT-2 Inhibitor Success in Diabetic Kidney Disease Too

SGLT2 inhibitors are also proving beneficial for adults with type 2 diabetes and diabetic kidney disease (DKD), with the landmark CREDENCE study representing the first successful renal outcomes trial, in this instance with canagliflozin.

Canagliflozin was recently approved by the FDA for the additional indication of reducing the risk for end-stage kidney disease, worsening of kidney function, CV death, and HF hospitalization for adults with type 2 diabetes and DKD.

Renal outcomes trials are ongoing with the other two drugs in the class, Dapa-CKD with dapagliflozin and EMPA-KIDNEY with empagliflozin.

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