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HEALTH TECHNOLOGY BRIEFING
MAY 2019

Dapagliflozin for heart failure with preserved ejection fraction

NIHRIO ID	25362	**NICE ID**	10147
Developer/Company	AstraZeneca UK Ltd	**UKPS ID**	Not available

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Dapagliflozin as a tablet is in clinical development for the treatment of heart failure (HF) with preserved ejection fraction. HF is a complex clinical syndrome of symptoms and signs that suggest the efficiency of the heart as a pump is impaired. Symptoms include breathlessness and fatigue, and signs of the condition include swollen ankles and crackling sounds in the lungs. People with HF often have a poor quality of life, and about a third of people experience severe and prolonged depressive illness. About half of people with HF have a preserved ejection fraction (HFpEF), also referred to as diastolic heart failure, where the heart muscle contracts normally but the ventricles do not relax as they should during ventricular filling (or when the ventricles relax).

Dapagliflozin blocks the action of a protein in the kidneys called sodium-glucose co-transporter 2 (SGLT2). As blood is filtered by the kidneys, SGLT2 stops glucose in the bloodstream from being passed out into the urine. By blocking the action of SGLT2, dapagliflozin causes the kidney to pass out more glucose in the urine, thereby reducing the levels of glucose in the blood. Blood vessels can be damaged by the effects of high blood glucose levels and this can in turn cause damage to organs, such as the heart. Dapagliflozin may also increase the removal of fluid between tissue cells, contributing to reduced congestion with minimal impact on blood volume. If licensed, dapagliflozin may provide a treatment option for people with HFpEF who currently have no effective therapies available.

PROPOSED INDICATION

Heart failure with preserved ejection fraction (HFpEF)[1]

TECHNOLOGY

DESCRIPTION

Dapagliflozin (Forxiga) is a sodium-glucose cotransporter 2 inhibitor (SGLT2i). Dapagliflozin reversibly inhibits SGLT2 in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion. SGLT2i have a mechanism of action that involves blocking a protein that normally allows the body to reabsorb glucose; instead, the body discharges excess glucose through the urine, offering people with type 2 diabetes glycaemic control, as well as reduced blood pressure and modest weight loss. SGLT2i offer a distinctly different diuretic mechanism than that of other diuretic classes.[2-5]

Dapagliflozin is in development for the treatment of heart failure with preserved ejection fraction (HFpEF). In the phase III clinical trial (NCT03619213; DELIVER), patients receive 10mg dapagliflozin tablets once daily, per oral use. Duration of treatment is not reported on the trial registry.[1,6]

INNOVATION AND/OR ADVANTAGES

HFpEF has a significant morbidity and mortality and so far no treatment has been clearly demonstrated to improve outcomes.[7] It is hypothesised that the use of SGLT2i in reducing heart failure hospitalisation is due to the osmotic diuresis induced by SGLT2 inhibition that results in greater electrolyte-free water clearance and, ultimately, in greater fluid clearance from the interstitial fluid space than from the circulation, potentially resulting in congestion relief with minimal impact on blood volume, arterial filling and organ perfusion.[8]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Dapagliflozin is indicated in the EU/UK in adults for the treatment of insufficiently controlled type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise to improve glycaemic control; as monotherapy when metformin is considered inappropriate due to intolerance; and in addition to other medicinal products for the treatment of T2DM. Very common (≥ 1/10) and common (≥ 1/100 to < 1/10) adverse reactions may include: hypoglycaemia, genital infections, urinary tract infection, dizziness, rash, back pain, dysuria, and polyuria (among potential others).[9]

Dapagliflozin is currently in phase III clinical development for chronic kidney disease, heart failure with reduced ejection fraction (HFrEF), pre-diabetes, non-alcoholic steatohepatitis, diabetes mellitus (type 1 and 2), polycystic ovary syndrome and obesity.[10]

PATIENT GROUP

DISEASE BACKGROUND

HF is a clinical syndrome of symptoms (e.g. breathlessness, fatigue) and signs (e.g. oedema, crepitations) resulting from structural and/or functional abnormalities of cardiac function which lead to reduced cardiac output or high filling pressures at rest or with stress. HF may arise as a consequence of a myocardial, valvular, endocardial or arrhythmic problem (or a combination of

these). HF is defined on the basis of left ventricular ejection fraction (LVEF).[11] This is calculated as the percentage of how much blood in the left ventricle (LV) is pumped out with each contraction; a normal LVEF may be between 50% and 70%.[12]

The European Society of Cardiology (ESC) defines HFpEF as the presence of signs and symptoms of HF, LVEF ≥50%, elevated natriuretic peptides (NP) levels, and structural heart disease and/or diastolic dysfunction. Patients with HFpEF generally do not have a dilated LV, but instead often have an increase in LV wall thickness and/or increased left atrial size as a sign of increased filling pressures. Most have additional evidence of impaired LV filling or suction capacity, also classified as diastolic dysfunction, which is generally accepted as the likely cause of HF in these patients.[13]

For people with HF and their family members and carers, the condition can have adverse effects on their quality of life and be a financial burden. People with HF often experience poor quality of life because of breathlessness and fatigue, and over one-third of people experience severe and prolonged depressive illness.[14]

CLINICAL NEED AND BURDEN OF DISEASE

In England in 2017-18, 485,561 people were recorded by GPs as having heart failure (prevalence rate of 0.83%).[15] As it is estimated that HFpEF accounts for up to half of all HF, this would equate to approximately 242,780 people in England.[16]

Both the incidence and prevalence of HF increase with age, with an average age at first diagnosis of 76 years. The prevalence is expected to rise in the future as a result of an ageing population, improved survival of people with ischaemic heart disease and more effective treatments for HF.[14]

HF has a poor prognosis: 30-40% of people diagnosed with HF die within one year, but thereafter the mortality is less than 10% per year. Patients on GP HF registers, representing prevalent cases of HF, have a 5-year survival rate of 58%, compared with 93% in the general population.[14]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The core specialist HF multidisciplinary team should work in collaboration with the primary care team, and should include a lead physician with subspecialty training in HF, a specialist HF nurse, and a healthcare professional with expertise in specialist prescribing for HF.[17]

No therapies have been conclusively shown to alter morbidity or mortality in patients with HFpEF.[11] Existing recommendations focus on judicious use of diuretics to relieve congestion (when present), and optimal management of comorbidities.[18]

CURRENT TREATMENT OPTIONS

NICE guidelines recommend that patients with HFpEF should usually be offered a low to medium dose of loop diuretics (e.g. less than 80mg furosemide per day). People whose HF does not respond to this treatment will need further specialist advice.[17]

PLACE OF TECHNOLOGY

If licensed, dapagliflozin may offer an additional treatment option for patients with HFpEF who currently have no effective treatments available.

CLINICAL TRIAL INFORMATION

Trial	**DELIVER, NCT03619213, 2018-000802-46; adults ≥40 yrs; dapagliflozin vs placebo; phase III**
Sponsor	AstraZeneca
Status	Ongoing
Source of Information	Trial registry[1,6]
Location	EU (not UK), USA, Canada and other countries
Design	Randomised, placebo-controlled, parallel assignment, double-blind
Participants	n=4700 (planned); ≥40 yrs; documented diagnosis of symptomatic heart failure (NYHA class II-IV); LVEF >40% and evidence of structural heart disease; elevated NT-pro BNP levels; pts currently hospitalised for HF must be off intravenous HF medications for at least 24hrs before randomisation
Schedule	Randomised 1:1 to either 10mg dapagliflozin or matching placebo once daily; duration of treatment was not reported on the trial registry.
Follow-up	Up to approximately 33mos
Primary Outcomes	Time to the first occurrence of any of the components of this composite: 1) cardiovascular (CV) death; 2) hospitalisation for HF; 3) urgent HF visit (e.g., emergency department or outpatient visit) [Time frame: Up to approximately 33mos] • To determine whether dapagliflozin is superior to placebo, when added to standard of care, in reducing the composite of CV death and HF events (hospitalisation for HF or urgent HF visit) in patients with HF and preserved systolic function
Secondary Outcomes	• Total number of (first and recurrent) hospitalisations for HF and CV death [Time frame: Up to approximately 33mos] • Change from baseline in the total symptom score (TSS) of the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 8mos [Time frame: Evaluated at 8mos after randomisation] • Proportion of patients with worsened NYHA class from baseline to 8mos [Time frame: Evaluated at 8mos after randomization] • Time to the occurrence of death from any cause [Time frame: Up to approximately 33mos]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study and primary completion date reported as June 2021.

ESTIMATED COST

Dapagliflozin is already marketed in the UK for the treatment of T2DM; a pack of 28 x 5mg tablets or a pack of 28 x 10mg tablets costs £36.59.[5]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guideline. Chronic heart failure in adults: diagnosis and management (NG106). September 2018.
- NICE quality standard. Chronic heart failure in adults (QS9). September 2018.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No guidance identified.

OTHER GUIDANCE

- European Society of Cardiology (ESC). European Society of Cardiology Guidelines. 2016.[13]
- Scottish Intercollegiate Guidelines Network (SIGN). SIGN 147: Management of chronic heart failure. March 2016.[11]

ADDITIONAL INFORMATION

No information was received from AstraZeneca UK Ltd.

AstraZeneca UK Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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