

## HEALTH TECHNOLOGY BRIEFING MAY 2019

### Dapagliflozin for chronic heart failure with reduced ejection fraction

<b>NIHRIO ID</b>	26895	<b>NICE ID</b>	10149
<b>Developer/Company</b>	AstraZeneca UK Ltd	<b>UKPS ID</b>	Not available

<b>Licensing and market availability plans</b>	Currently in phase III clinical trials.
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#### SUMMARY

Dapagliflozin as a tablet is in clinical development for the treatment of heart failure (HF) with reduced 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. More than half of people with HF have a reduced ejection fraction (HFrEF), also referred to as systolic heart failure, where the heart muscle does not contract effectively, and therefore less oxygen-rich blood is pumped out to the body.

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 HFrEF who currently have limited therapies available.

## PROPOSED INDICATION

Chronic heart failure with reduced ejection fraction (HFrEF)<sup>1</sup>

## 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.<sup>2-5</sup>

Dapagliflozin is in development for the treatment of chronic heart failure with reduced ejection fraction (HFrEF). In the phase III clinical trial (NCT03036124; DAPA-HF), patients receive 10mg or 5mg dapagliflozin tablets once daily, per oral use. Duration of treatment is not reported on the trial registry.<sup>1,6</sup>

### INNOVATION AND/OR ADVANTAGES

Heart failure remains one of the leading causes of mortality and morbidity in developed countries and contributes significantly to the economic burden of modern health care systems.<sup>7</sup> There remains a large unmet need for new therapies in the treatment of HFrEF.<sup>8</sup> It is hypothesized that the use of SGLT2i in reducing heart failure hospitalization 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.<sup>9</sup>

### 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 ( $\geq 1/10$ ) and common ( $\geq 1/100$  to  $< 1/10$ ) adverse reactions may include: hypoglycaemia, genital infections, urinary tract infection, dizziness, rash, back pain, dysuria, and polyuria (among potential others).<sup>10</sup>

Dapagliflozin is currently in phase III clinical development for chronic kidney disease, heart failure with preserved ejection fraction (HFpEF), pre-diabetes, non-alcoholic steatohepatitis, diabetes mellitus (type 1 and 2), polycystic ovary syndrome and obesity.<sup>11</sup>

## 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).<sup>12</sup> 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%.<sup>13</sup>

The European Society of Cardiology (ESC) defines HFrEF as the presence of signs and symptoms of HF and LVEF <40%. Differentiation of patients with HF based on LVEF is important due to different underlying aetiologies, demographics, co-morbidities and response to therapies. It is only in patients with HFrEF that therapies have been shown to reduce both morbidity and mortality.<sup>14</sup>

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.<sup>15</sup>

## 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%).<sup>16</sup> In 2017, it was reported that 66.8% of patients are reported to have HFrEF; if applied to the 2017-18 GP figures this equates to approximately 324,355 people in England.<sup>17</sup>

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.<sup>15</sup>

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.<sup>15</sup>

## 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.<sup>18</sup>

Implantable cardioverter defibrillators (ICDs), cardiac resynchronisation therapy (CRT) with defibrillator (CRT-D) or CRT with pacing (CRT-P) are recommended as treatment options for people with heart failure who have left ventricular dysfunction with a left ventricular ejection fraction of 35% or less.<sup>19</sup>

### CURRENT TREATMENT OPTIONS

NICE recommends the following treatment options for patients with HFrEF:<sup>19</sup>

First line:

- Offer an angiotensin-converting-enzyme (ACE) inhibitor and a beta-blocker licensed for heart failure to people who have HFrEF.

- Consider an angiotensin II receptor blocker (ARB) licensed for heart failure as an alternative to an ACE inhibitor for people who have HFrEF and intolerable side effects with ACE inhibitors.
- If neither ACE inhibitors nor ARBs are tolerated, seek specialist advice and consider hydralazine in combination with nitrate for people who have HFrEF.
- Offer a mineralocorticoid receptor antagonist (MRA), in addition to an ACE inhibitor (or ARB) and beta-blocker, to people who have HFrEF if they continue to have symptoms of heart failure.

Specialist treatment:

- Specialist treatment options include ivabradine, sacubitril valsartan, hydralazine with nitrate, and digoxin.

## PLACE OF TECHNOLOGY

If licensed, dapagliflozin may offer an additional treatment option for patients with HFrEF who currently have few effective treatments available.

## CLINICAL TRIAL INFORMATION

<b>Trial</b>	DAPA-HF, <a href="#">NCT03036124</a> , <a href="#">2016-003897-41</a> ; ≥ 18 yrs; dapagliflozin vs placebo; phase III
<b>Sponsor</b>	AstraZeneca
<b>Status</b>	Ongoing
<b>Source of Information</b>	Trial registry <sup>1,6</sup>
<b>Location</b>	EU (incl UK), USA, Canada and other countries
<b>Design</b>	Randomised, placebo-controlled, parallel assignment
<b>Participants</b>	n=4744; ≥ 18 yrs; documented diagnosis of symptomatic HFrEF (NYHA functional class II-IV); LVEF ≤ 40%; elevated NT-pro BNP levels; pts should receive background standard of care for HFrEF and be treated according to locally recognized guidelines; eGFR ≥30 mL/min/1.73 m <sup>2</sup> (CKD-EPI formula) at enrolment
<b>Schedule</b>	Randomised 1:1 to either 10mg or 5mg dapagliflozin or matching placebo once daily; duration of treatment was not reported on the trial registry.
<b>Follow-up</b>	Up to approximately 3 yrs
<b>Primary Outcomes</b>	<ul style="list-style-type: none"> <li>• Time to the first occurrence of any of the components of the composite: CV death or hospitalization for HF or an urgent HF visit. [Time frame: From randomisation visit (day 0) up to approximately 3 yrs]</li> </ul>
<b>Secondary Outcomes</b>	<p>Time frame: From randomisation visit (day 0) up to approximately 3 yrs:</p> <ul style="list-style-type: none"> <li>• Time to the first occurrence of either of the components of the composite: CV death or hospitalization for HF</li> <li>• Total number of (first and recurrent) HF hospitalizations and CV death</li> <li>• Change from baseline measured at 8mos in the total symptom score of the Kansas City Cardiomyopathy Questionnaire (KCCQ), a specific HF patient reported outcome questionnaire</li> <li>• Time to the first occurrence of any of the components of the composite: ≥50% sustained decline in eGFR or reaching End Stage Renal Disease (ESRD) or renal death</li> </ul>

<b>Key Results</b>	-
<b>Adverse effects (AEs)</b>	-
<b>Expected reporting date</b>	Study and primary completion date reported as July 2019.

## 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.<sup>5</sup>

## RELEVANT GUIDANCE

### NICE GUIDANCE

- NICE technology appraisal guidance. Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction (TA388). April 2016.
- NICE technology appraisal guidance. Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure (TA314). June 2014.
- NICE technology appraisal guidance. Ivabradine for treating chronic heart failure (TA267). November 2012.
- 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

- NICE medical technologies guidance. ENDURALIFE powered CRT-D devices for treating heart failure (MTG33). 2017.<sup>20</sup>
- European Society of Cardiology (ESC). European Society of Cardiology Guidelines. 2016.<sup>14</sup>
- Scottish Intercollegiate Guidelines Network (SIGN). SIGN 147: Management of chronic heart failure. March 2016.<sup>12</sup>

## 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.

## REFERENCES

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