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HEALTH TECHNOLOGY BRIEFING
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Empagliflozin for Chronic Heart Failure with Preserved Ejection Fraction

NIHRIO ID	23817	**NICE ID**	10198
Developer/Company	Boehringer Ingelheim Ltd	**UKPS ID**	656609

Licensing and market availability plans	Currently in phase III trials.

SUMMARY

Empagliflozin is in clinical development for chronic heart failure and preserved ejection fraction (HFpEF). Heart failure (HF) is a clinical syndrome caused by the impaired ability of the heart to cope with the metabolic needs of the body. This results in breathlessness, fatigue, and fluid retention. 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. HFpEF is a growing problem affecting more than half of the patients with HF. HFpEF has a significant morbidity and mortality rate and so far, no treatment has been demonstrated to improve the outcomes in HFpEF.

Empagliflozin is administered orally and usually taken once daily in the morning. Empagliflozin inhibits a protein found in the kidney called sodium-glucose co-transporter-2 (SGLT-2). It blocks glucose absorption in the kidney and increases the amount of glucose excreted in the urine. Empagliflozin significantly reduces the risk of cardiovascular events and heart failure hospitalisation. If licensed, empagliflozin may offer an additional treatment option for patients with HFpEF who currently have no effective treatments available.

PROPOSED INDICATION

Treatment of patients with chronic heart failure with preserved ejection fraction (HFpEF).[1]

TECHNOLOGY

DESCRIPTION

Empagliflozin (JARDIANCE, JARDIANZ, GIBTULIO).[1] Empagliflozin reversibly inhibits sodium-glucose co-transporter 2 (SGLT2) in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion.[2] Empagliflozin improves glycaemic control in patients with type 2 diabetes by reducing renal glucose reabsorption. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent on blood glucose concentration and GFR. Inhibition of SGLT2 in patients with type 2 diabetes and hyperglycaemia leads to excess glucose excretion in the urine. Also, the initiation of empagliflozin increases excretion of sodium resulting in osmotic diuresis and reduced intravascular volume.[3]

Empagliflozin is currently in phase III clinical development for patients with HFpEF. In the phase III clinical trial (EMPEROR-Preserved, NCT03057951), participants will receive 10 milligrams (mg) empagliflozin once daily.[1]

INNOVATION AND/OR ADVANTAGES

HFpEF is a growing epidemiologic problem affecting more than half of the patients with HF. HFpEF has a significant morbidity and mortality rate and so far, no treatment has been demonstrated to improve the outcomes in HFpEF.[4]

Diuretics are recommended by the European Society of Cardiology (ESC) in congested patients with HFpEF in order to alleviate symptoms and signs.[5] It is hypothesised that osmotic diuresis induced by SGLT2 inhibition, results in greater electrolyte-free water clearance and, ultimately, in greater fluid clearance from the interstitial fluid (IF) space than from the circulation, potentially resulting in congestion relief with minimal impact on blood volume, arterial filling and organ perfusion.[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Empagliflozin is licensed in the EU/UK for the treatment of adults with insufficiently controlled type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise to improve glycaemic control.[3] The most frequently reported adverse reaction (≥10%) was hypoglycaemia when used with sulphonylurea or insulin [3]

Empagliflozin is currently in phase III clinical development for HFpEF, refractory diabetes mellitus, diabetes mellitus (type 1 and 2), HF, acute HF, and dyslipidemia.[7]

PATIENT GROUP

DISEASE BACKGROUND

HF is a clinical syndrome characterised by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.[8] HF is defined based on the left ventricular ejection fraction (LVEF).[5] LVEF is a measurement, expressed as a percentage, of how much blood the left ventricle pumps out with each contraction. A normal LVEF may be between 50 and 70 per cent.[9]

The 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.[5]

HF is often the result of several problems affecting the heart at the same time. Conditions that can lead to HF include coronary heart disease; high blood pressure; cardiomyopathy; heart rhythm problems (arrhythmias); damage or other problems with the heart valves; congenital heart disease. Sometimes anaemia, drinking too much alcohol, an overactive thyroid or pulmonary hypertension can lead to HF.[10] The risk of HF is greater in men, smokers, and diabetic patients. Risk also increases with age.[11]

For people with chronic 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 chronic HF often experience poor quality of life; symptoms include breathlessness, fatigue and ankle swelling, and over one-third of people experience severe and prolonged depressive illness.[12]

CLINICAL NEED AND BURDEN OF DISEASE

Both the incidence and the prevalence of HF increase with age, with an average age at first diagnosis of 76 years. The prevalence of HF 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 heart failure.[12]

HF has a poor prognosis: 30–40% of people diagnosed with HF die within 1 year, but thereafter the mortality is less than 10% per year. Patients on GP heart failure registers, representing prevalent cases of HF, have a 5-year survival rate of 58%, compared with 93% in the general population.[12] In England in 2018-19, 553,971 people were recorded by GPs as having HF (prevalence rate of 0.93%).[13] It is estimated that HFpEF accounts for approximately 50% of patients that have HF, which equates to approximately 276,986 people in England.[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.[15]

No therapies have been conclusively shown to alter morbidity or mortality in patients with HFpEF.[16] Instead, treatment aims to reduce mortality, relieve symptoms, improve exercise tolerance, and reduce the incidence of acute exacerbations.[11]

Lifestyle changes are also advised, for example, controlling salt and fluid intake; reducing smoking and alcohol consumption.[15]

CURRENT TREATMENT OPTIONS

NICE guidelines recommend that patients who suffer from HFpEF should usually be offered a low to medium dose of loop diuretics (for example, less than 80 mg furosemide per day). People whose heart failure does not respond to this treatment will need further specialist advice.[15] Existing treatment recommendations focus on judicious use of diuretics to relieve congestion (when present), and optimal management of comorbidities.[17]

Treatment options offered to patients with HF may include:[15]

- Diuretics
- Calcium channel blockers
- Amiodarone
- Anticoagulants

PLACE OF TECHNOLOGY

If licenced, empagliflozin will offer an additional treatment option for patients with HFpEF who currently have no effective treatments available.

CLINICAL TRIAL INFORMATION

Trial	**EMPEROR-Preserved, NCT03057951, 2016-002278-11;** A Phase III Randomised, Double-blind Trial to Evaluate Efficacy and Safety of Once Daily Empagliflozin 10 mg Compared to Placebo, in Patients With Chronic Heart Failure With Preserved Ejection Fraction (HFpEF) **Phase III** – Active, not recruiting **Location(s):** EU (including the UK), Canada, the United States, and other countries **Estimated primary completion date:** May/June 2021
Trial design	Randomised, placebo-controlled, double-blind

Population	N = 5988; adults ≥ 18yrs; patients with chronic heart failure (CHF) and with HFpEF
Intervention(s)	Once daily empagliflozin 10 mg
Comparator(s)	Matched placebo
Outcome(s)	Composite primary endpoint - Time to first event of adjudicated CV (Cardiovascular) death or adjudicated HHF (Hospitalisation for Heart Failure) in patients with Heart Failure with preserved Ejection Fraction (HFpEF) [Time Frame: up to 38 months] See trial record for the full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**EMPA-VISION, NCT03332212**, 2017-000376-28; A Randomised, Double-blind, Placebo-controlled, Mechanistic Cardiac Magnetic Resonance Study to Investigate the Effects of Empagliflozin Treatment on Cardiac Physiology and Metabolism in Patients With Heart Failure **Phase III** – Completed **Location(s):** UK **Actual study completion date:** May 2020
Trial design	Randomised, double-blind, placebo-controlled
Population	N = 72; adults ≥ 18yrs; patients with Heart Failure with Reduced Ejection Fraction (HFrEF); patients with HFpEF
Intervention(s)	Empagliflozin taken for 12 weeks
Comparator(s)	Matched placebo
Outcome(s)	Change from baseline to week 12 in PCr/ATP ratio in the resting state measured by 31P MRS. [Time Frame: Baseline and Week 12] See trial record for the full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**EMPERIAL, NCT03448406**, 2017-004072-59; A Phase III Randomised, Double-blind Trial to Evaluate the Effect of 12 Weeks Treatment of Once Daily EMPagliflozin 10 mg Compared With Placebo on ExeRcise Ability and Heart Failure Symptoms, In Patients With Chronic HeArt FaiLure With Preserved Ejection Fraction (HFpEF) **Phase III** – Completed **Location(s):** EU (including the UK), Canada, the United States, and other countries **Actual study completion date:** October 2019

Trial design	Randomised, parallel assignment, double-blind, primary treatment
Population	N = 315; adults ⩾ 18 years; patients with CHF; patients with HFpEF
Intervention(s)	12 weeks treatment of once-daily empagliflozin 10 mg
Comparator(s)	Matched placebo
Outcome(s)	The change from baseline to week 12 in exercise capacity as measured by the distance walked in 6 minutes in standardised conditions [Time Frame: Week 0 and Week 12] See trial record for the full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**ELSI, NCT03128528;** Randomized, Double-blind, Placebo Controlled, Parallel-group, Prospective Clinical Study to Analyse the Effect of Empagliflozin on Reduction of Tissue Sodium Content in Patients with Chronic Heart Failure **Phase II** – Completed **Location(s):** Germany **Actual study completion date:** April 2020
Trial design	Randomised, double-blind, placebo-controlled, parallel-group
Population	N = 84, adults aged 18-85 years, CHF (symptoms and/or sign of CHF)
Intervention(s)	Empagliflozin 10 mg orally once daily
Comparator(s)	Matched placebo
Outcome(s)	Skin sodium content [Time Frame: 14 weeks] Skin sodium content (23Na-MRI) assessed at the lower leg For the full list of outcomes, see the trial registry
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Empagliflozin is already marketed in the UK for the treatment of T2DM. The NHS indicative price is:[18]

- A packet of 28 x 10mg tablets costs £36.59
- A packet of 28 x 25mg tablets costs £36.59

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Rivaroxaban for treating chronic heart failure. (TA607). October 2019.
- 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 quality standard. Chronic heart failure in adults. (QS9). September 2018.
- NICE interventional procedures guidance. Permanent His-bundle pacemaker implantation for heart failure. (GID-IPG10145). Expected publication date: April 2021.
- NICE interventional procedures guidance. Electrical stimulation to improve muscle strength in chronic respiratory conditions, chronic heart failure and chronic kidney disease. (IPG677). August 2020.
- NICE interventional procedures guidance. Cardiac contractility modulation device implantation for heart failure. (IPG655). June 2019.
- NICE interventional procedures guidance. Insertion and use of implantable pulmonary artery pressure monitor in chronic heart failure. (IPG463). August 2013.
- NICE medical technologies guidance. ENDURALIFE powered CRT-D devices for treating heart failure. (MTG33). March 2017.
- NICE guideline. Chronic heart failure in adults: diagnosis and management. (NG106). September 2018.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No relevant guidance identified

OTHER GUIDANCE

- European Society of Cardiology (ESC). European Society of Cardiology Guidelines. (2016)[5]
- Scottish Intercollegiate Guidelines Network (SIGN). SIGN 147: Management of chronic heart failure. (March 2016)[16]

ADDITIONAL INFORMATION

REFERENCES

1 ClinicalTrials.gov. *EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction (EMPEROR-Preserved)*. 2017. Available from: https://clinicaltrials.gov/ct2/show/record/NCT03057951 [Accessed 03 Nov 2020]

2 National Institute for Health and Care Excellence (NICE). *EMPAGLIFLOZIN*. Available from: https://bnf.nice.org.uk/drug/empagliflozin.html [Accessed 18 Feb 2021]

3 electronic medicines compendium (emc). *Jardiance 10 mg film-coated tablets*. Available from: https://www.medicines.org.uk/emc/product/5441/smpc [Accessed 04 Nov 2020]

4 Iliești AM, Hodorogea AS. Treatment of Heart Failure with Preserved Ejection Fraction. *Research to Clinical Practice Advances in Experimental Medicine and Biology*. 2018;1067:67-87. Available from: https://link.springer.com/chapter/10.1007/5584_2018_149#citeas [Accessed 04 Nov 2020]

5 Ponikowski P, Voors AA, Anker SD, Bueno G, Cleland JF. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *European Heart Journal*. 2016;37(27):2129-200. Available from: https://academic.oup.com/eurheartj/article/37/27/2129/1748921 [Accessed 04 Nov 2020]

6 Hallow KM, Helmlinger G, Greasley PJ, McMurray JJV, Boulton DW. Why do SGLT2 inhibitors reduce heart failure hospitalization? A differential volume regulation hypothesis. *Diabetes, Obesity and Metabolism*. 2017;20(3). Available from: https://dom-pubs.onlinelibrary.wiley.com/doi/full/10.1111/dom.13126 [Accessed 04 Nov 2020]

7 ClinicalTrials.gov. *empagliflozin | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Phase 3*. Available from: https://clinicaltrials.gov/ct2/results?term=empagliflozin&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=&phase=2&Search=Apply [Accessed 04 Nov 2020]

8 Nussbaumerová B, Rosolová H. Diagnosis of heart failure: the new classification of heart failure. *Vnitr Lek*. 2018;64(9):847-51. Available from: https://pubmed.ncbi.nlm.nih.gov/30441997/#:~:text=Heart%20failure%20(HF)%20is%20a,cardiac%20abnormality%2C%20resulting%20in%20a [Accessed 12 Nov 2020]

9 The American Heart Association (AHA). *Ejection Fraction Heart Failure Measurement.* Available from: https://www.heart.org/en/health-topics/heart-failure/diagnosing-heart-failure/ejection-fraction-heart-failure-measurement [Accessed 05 Nov 2020]

10 NHS Digital. *Overview - Heart failure.* Available from: https://www.nhs.uk/conditions/heart-failure/ [Accessed 05 Nov 2020]

11 National Institute for Health and Care Excellence (NICE). *Chronic heart failure.* Available from: https://bnf.nice.org.uk/treatment-summary/chronic-heart-failure.html [Accessed 12 Nov 2020]

12 National Institute for Health and Care Excellence (NICE). *Chronic heart failure in adults* 2011. Available from: https://www.nice.org.uk/guidance/qs9/resources/chronic-heart-failure-in-adults-pdf-58304464837 [Accessed 05 Nov 2020]

13 NHS Digital. *Quality and Outcomes Framework, Achievement, prevalence and exceptions data 2018-19 [PAS].* 2019. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/quality-and-outcomes-framework-achievement-prevalence-and-exceptions-data/2018-19-pas [Accessed 05 Nov 2020]

14 Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. *Nature Reviews Cardiology*. 2017;14:591-602. Available from: https://www.nature.com/articles/nrcardio.2017.65 [Accessed 05 Nov 2020]

15 National Institute for Health and Care Excellence (NICE). *Chronic heart failure in adults: diagnosis and management* 2018. Available from: https://www.nice.org.uk/guidance/ng106/resources/chronic-heart-failure-in-adultsdiagnosis-and-management-pdf-66141541311685 [Accessed 05 Nov 2020]

16 Scottish Intercollegiate Guidelines Network (SIGN). SIGN 147 • Management of chronic heart failure. 2016. Available from: https://www.sign.ac.uk/assets/sign147.pdf [Accessed 05 Nov 2020]

17 Zakeri R, Cowie MR. Heart failure with preserved ejection fraction: controversies, challenges and future directions. *Heart*. 2018;104:337-84. Available from: https://heart.bmj.com/content/104/5/377.abstract [Accessed 05 Nov 2020]

18 National Institute for Health and Care Excellence (NICE). *EMPAGLIFLOZIN - Medicinal Forms.* Available from: https://bnf.nice.org.uk/medicinal-forms/empagliflozin.html [Accessed 18 Feb 2021]

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