NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING
JUNE 2020

Empaglifozin for treatment of chronic heart failure with reduced ejection fraction.

NIHRIO ID	29154	**NICE ID**	10378
Developer/Company	Boehringer Ingelheim Ltd	**UKPS ID**	

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

SUMMARY

Empagliflozin is currently 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 to pump blood around the body is impaired. Symptoms of HF include breathlessness, fatigue and ankle swelling, and signs of the condition include crackling sounds in the lungs or excess fluid in the lungs. More than half of people with HF have reduced ejection fraction (HRrEF), also referred to as systolic HF. This means that the heart muscle does not contract effectively and therefore less oxygen-rich blood is pumped out to the body. There remains a large unmet need for new therapies in the treatment of HRrEF.

Empagliflozin is given by mouth in the form of a tablet and works by inhibiting the sodium transporter NHE1. This prevents salt from being re-absorbed so there is increased excretion of salt from the body and a reduced volume of fluid in the blood vessels. It's thought that these changes in sugar, salt and water metabolism in the body may contribute to the reductions in cardiovascular death. If licensed, empagliflozin may provide an additional treatment option for people with HFrEF who currently have limited therapies available.

PROPOSED INDICATION

To reduce the risk of cardiovascular death and hospitalization for heart failure (HF) in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction (HFrEF).[a]

TECHNOLOGY

DESCRIPTION

Empagliflozin (Jardiance) is given orally as a tablet and works as a selective inhibitor of sodium-glucose cotransporter-2 (SGLT2) that acts by decreasing renal glucose reabsorption and increasing urinary glucose excretion.[1] In addition, initiation of empagliflozin also prevents salt being re-absorbed, leading to increased excretion of salt from the body and reducing the fluid load of the body's vessel system. Empagliflozin induces changes to the sugar, salt and water metabolism in the body that may contribute to the reductions in cardiovascular death.[2] Empagliflozin interacts with the cardiac NHE1 directly to inhibit its activity and reduce cardiac cytosolic Na+ and cytosolic Ca2+. Inhibition of NHE1 attenuates cardiomyocyte injury, remodelling systolic dysfunction and ultimately HF.[3]

Empagliflozin is currently in clinical development for the treatment of adults with HFrEF. In the phase III clinical trial (NCT03057977; Eudra CT 2016-002280-34) patients are given 10mg of empagliflozin by enteral administration once daily.[4,5]

INNOVATION AND/OR ADVANTAGES

HF 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.[6] There remains a large unmet need for new therapies in the treatment of HFrEF.[7]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Empagliflozin is currently licenced in the EU for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:[8]

- as monotherapy when metformin is considered inappropriate due to intolerance
- in addition to other medicinal products for the treatment of diabetes

Hypoglycaemia (when used with sulphonylurea or insulin) was a very common adverse event occurring in more than 10% of patients with type 2 diabetes who received empagliflozin in placebo-controlled studies assessing the safety of this medicine.[8]

Empagliflozin is currently in phase II development for:[9]

- Nephropathy
- Glucose 6 phosphatase deficiency
- Glycogen storage disease type I
- Acute heart failure
- Non-alcoholic fatty liver disease

Empagliflozin is currently in phase III development for:[9]

[a] Information provided by Boehringer Ingelheim Ltd

- Diabetes mellitus type 1 and type 2
- Kidney disease
- Hypertension
- Obesity
- Polycystic ovary syndrome
- Syndrome of inappropriate anti-diuresis
- Hyponatremia

PATIENT GROUP

DISEASE BACKGROUND

HF is a progressive clinical syndrome caused by structural or functional abnormalities of the heart, resulting in reduced cardiac output. It is characterised by symptoms (shortness of breath, persistent coughing or wheezing, ankle swelling, reduced exercise tolerance fatigue) and signs (oedema, crepitations).[10,11] HF is often the result of a number of conditions affecting the heart at the same time such as coronary heart disease, high blood pressure or cardiomyopathy.[12] The risk of HF is greater in men, smokers and diabetic patients and increases with age.[10]

HF can be defined as HF with reduced ejection fraction (HFrEF) or HF with preserved ejection fraction on the basis of left ventricular ejection fraction (LVEF), how much blood in the left ventricle is pumped out with each contraction.[11,13] In HFrEF, the left ventricle loses its ability to contract normally and therefore presents with an ejection fraction of less than 40%.[10] 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 HRrEF that therapies have been shown to reduce both morbidity and mortality.[14]

For people with chronic HF and their family members and carers, the condition can have adverse effects on their quality of life and can be a financial burden. People with HF often experience poor quality of life because of breathlessness and fatigue symptoms, and over one-third of people experience severe and prolonged depressive illness.[15]

CLINICAL NEED AND BURDEN OF DISEASE

In England in 2017-18, 485,561 people were recorded by GPs as having HF (prevalence rate of 0.83%).[16] 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 324,366 people in England.[17] In England in 2018-19 there were 188,683 finished consultant episodes (FCE) for heart failure (ICD-10 code I50) resulting in 86,474 admissions and 825,089 FCE bed days.[18]

The prevalence of HF incidence in the UK is rising due to an ageing population and increasing rates of obesity. The prevalence and incidence of HF both increase with age, with the rise starting at age 65 and peaking between 75 and 85. The average age of diagnosis is 77.[19]

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.[15]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

For most people, heart failure is a long term condition that can't be cured. The goal of treatment is to keep symptoms under control through lifestyle changes (eating a balanced diet, not smoking, regular exercise), medication or surgery.[20] Implantable cardioverter defibrillators, cardiac, resynchronisation therapy with defibrillator (CRT) or CRT with pacing are recommended as treatment options for people with HF who have left ventricular dysfunction with a LVEF of 35% or less.[21]

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.[19]

CURRENT TREATMENT OPTIONS

NICE recommends the following treatment options for patients with HRrEF:[22]

First line:

- Offer an angiotensin-converting enzyme (ACE) inhibitor and a beta-blocker licensed for heart failure to people who have HFrEF. Use clinical judgement when deciding which drug to start first
- Consider an angiotensin II receptor blocker (ARB) licensed for HF as an alternative to an ACE inhibitor for people who have HFrEF and intolerable side effects with ACE inhibitors
- If neither ACE inhibitors not 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, empagliflozin may offer an additional treatment option for patients with HFrEF who currently have few effective treatments available.

CLINICAL TRIAL INFORMATION

Trial	**EMPEROR-reduced, NCT03057977, Eudra CT 2016-002280-34; A phase III Randomised, Double-blind Trial to Evaluate Efficacy and Safety of Once Daily Empagliflozin 10mg Compared to Placebo, in Patients With Chronic Heart Failure With Reduced Ejection fraction (HFrEF)** **Phase III – Ongoing**

	Locations: 8 EU countries (incl UK), USA and other countries
Trial design	Parallel assignment, Double blind, Randomised
Population	N=3730 (planned); adults aged 18 years and older; patients with chronic HF, New York Heart Association (NYHA) class II-IV; LVEF ⩽ 40%; elevated NT-proBNP (N-terminal of the prohormone brain natriuretic peptide)
Intervention(s)	Empagliflozin 10mg (oral tablet)
Comparator(s)	Placebo
Outcome(s)	Time to first event of adjudicated cardiovascular death or adjudicated hospitalisation for heart failure in patients with HFrEF [Time Frame: Up to 38 months] See trial record for full list of outcome measures
Results (efficacy)	-
Results (safety)	-

Trial	**EMPERIAL-reduced, NCT03448419, Eudra CT 2017-004073-14; A Phase III Randomised, Double-blind Trial to Evaluate the Effect of 12 Weeks Treatment of Once Daily Empagliflozin 10mg Compared With Placebo on Exercise Ability and Heart Failure Symptoms, In Patients With Chronic Heart Failure With Reduced Ejection Fraction (HFrEF) (EMPERIAL-reduced)** **Phase III - ongoing** **Locations: 7 EU (not incl UK), USA, Canada and other countries**
Trial design	Parallel assignment, Double blind, Randomised
Population	Adults aged 18 years and older; 6-minute walk test (6MWT) <350m at screening and at baseline; chronic HF diagnosed for at least 3 months before visit 1 and currently in NYHA class II-IV; chronic HF with reduced EF defined as LVEF < 40% as per echocardiography at visit 1; clinically stable and on appropriate and stable dose of medical therapy for HF with no signs of heart failure decompensation
Intervention(s)	Empagliflozin 10mg (oral tablet)
Comparator(s)	Placebo
Outcome(s)	Change from baseline to week 12 in exercise capacity as measured by the distance walked in 6 minutes in standardised conditions [Time Frame: Up to week 0 and up to week 12] See trial record for full list of outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**Empire HF, NCT03198585, Eudra CT 2017-001341-27; Empagliflozin in Heart Failure Patients With Reduced Ejection Fraction: A Randomized Clinical Trial (Empire HF)**

	Phase II – completed **Location: Denmark**
Trial design	Parallel assignment, Double blind
Population	Adults aged 18 years and older; optimal heart failure therapy in accordance with European and national guidelines; LVEF < 0.40; estimated glomerular filtration rate (eGFR > 30ml/min/1.73 m^2; NYHA class I-III
Intervention(s)	Empagliflozin 10mg (oral tablet)
Comparator(s)	Placebo
Outcome(s)	Between-group difference in the change of plasma concentrations of NT-proBNP [Time Frame: 90 days] See trial record for full list of outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of 28 empagliflozin tablets (10 mg and 25 mg concentrations) is £36.59.[23]

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
- NICE medical technologies guidance. ENDURALIFE powered CRT-D devices for treating heart failure (MTG33). 2017.[24]

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England service specification. Cardiac surgery – adults. A10/S/a.
- 2013/14 NHS Standard Contract for Cardiology: Implantable cardioverter defibrillator (ICD) and cardiac resynchronisation therapy (CRT) (Adult). A09/S/a.
- 2013/14 NHS Standard Contract for ventricular assist devices (VADS) as a bridge to heart transplantation or myocardial recovery (All ages). A18/S(HSS)/b.

OTHER GUIDANCE

- European Society of Cardiology (ESC). European Society of Cardiology Guidelines 2016.[14]
- Scottish Intercollegiate Guidelines Network (SIGN). SIGN 147: Management of chronic heart failure. March 2016.[11]

ADDITIONAL INFORMATION

REFERENCES

1 American College of Cardiology. *A promising EMPRISE: Empagliflozin and Heart Failure Outcomes in Type 2 Diabetes Patients.* 2019. Available from: https://www.acc.org/latest-in-cardiology/articles/2019/09/17/15/02/a-promising-emprise [Accessed 20 May 2020].

2 Boehringer Ingelheim. *Boehringer Ingelheim and Lilly provide update on empagliflozin phase III exercise ability studies in chronic heart failure.* 2019. Available from: https://www.boehringer-ingelheim.com/press-release/emperial-heart-failure-toplineresults [Accessed 28 May 2020].

3 Iborra-Egea, O., Santiago-Vacas E., Yurista S. R., Lupón J., Packer M., Heymans S., et al. *Unraveling the Molecular Mechanism of Action of Empagliflozin in Heart Failure With Reduced Ejection Fraction With or Without Diabetes*. JACC Basic Transl Sci. 2019 Nov;4(7):831-40. Available from: https://pubmed.ncbi.nlm.nih.gov/31998851/

4 Clinicaltrials.gov. *A Phase III Randomised, Double-blind Trial to Evaluate Efficacy and Safety of Once Daily Empagliflozin 10mg Compared to Placebo, in Patients With Chronic Heart Failure With Reduced Ejection Fraction (HFrEF). Trial ID*. 2017. Status: Available from: https://clinicaltrials.gov/ct2/show/NCT03057977?id=NCT03057977&draw=2&rank=1&load=cart [Accessed 20 May 2020].

5 EU Clinical Trials Register. *A Phase III randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10mg compared to placebo, in patients with chronic Heart Failure with reduced Ejection Fraction (HFrEF). Trial ID*. 2018. Status: Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-002280-34/GB [Accessed 20 May 2020].

6 Westphal, J. G., Bekfani T., Schulze P. C. *What's new in heart failure therapy 2018?* Interactive CardioVascular and Thoracic Surgery. 2018;27(6):921-30. Available from: https://doi.org/10.1093/icvts/ivy282

7 Hinder, M., Yi B. A., Langenickel T. H. *Developing Drugs for Heart Failure With Reduced Ejection Fraction: What Have We Learned From Clinical Trials?* Clinical Pharmacology & Therapeutics. 2018 2018/05/01;103(5):802-14. Available from: https://doi.org/10.1002/cpt.1010

8 Electronic Medicines Compendium (EMC). *Jardiance 10mg film-coated tablets.* 2019. Available from: https://www.medicines.org.uk/emc/product/5441/smpc [Accessed 21 May 2020].

9 Clinicaltrials.gov. *Search for Empagliflozin studies: Phase II or III.* 2020. Available from: https://clinicaltrials.gov/ct2/results?intr=Empagliflozin&age_v=&gndr=&type=&rslt=&phase=1&Search=Apply [Accessed 21 May 2020].

10 National Institute for Health and Care Excellence (NICE). *Chronic heart failure.* 2020. Available from: https://bnf.nice.org.uk/treatment-summary/chronic-heart-failure.html [Accessed 20 May 2020].

11 Scottish Intercollegiate Guidelines Network (SIGN). *SIGN Management of chronic heart failure.* 2016. Available from: https://www.sign.ac.uk/assets/sign147.pdf [Accessed 20 May 2020].

12 National Health service (NHS). *Heart Failure: Overview.* 2018. Available from: https://www.nhs.uk/conditions/heart-failure/ [Accessed 20 May 2020].

13 Cleveland Clinic. *Ejection Fraction.* 2019. Available from: https://my.clevelandclinic.org/health/articles/16950-ejection-fraction [Accessed 05 May 2020].

14 Ponikowski, P., Voors A. A., Anker S. D., Bueno H., Cleland J. G. F., Coats A. J. S., et al. *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: 10.1093/eurheartj/ehw128 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5947521/

15 National Institute for Health and Care Excellence (NICE). *Chronic heart failure in adults (QS9)*. Last Update Date: 29 June 2011. Available from: https://www.nice.org.uk/guidance/qs9/resources/chronic-heart-failure-in-adults-pdf-58304464837 [Accessed 20 May 2020].

16 NHS Digital. *Recorded disease prevalence, achievements and exceptions. GP practice level*. Available from: https://digital.nhs.uk/pubs/qof1718 [Downloaded 26 October 2018].

17 National Cardiac Audit Programme. *National Heart Failure Audit 2016/17 Summary Report*. 2017. Available from: https://www.nicor.org.uk/wp-content/uploads/2018/11/Heart-Failure-Summary-Report-2016-17.pdf [Accessed 21 May 2020].

18 NHS Digital. *Hospital Admitted Patient Care Activity 2018-19: Diagnosis*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19 [Downloaded 19 September 2019].

19 National Institute for Health and Care Excellence (NICE). *Chronic heart failure in adults: diagnosis and management (NG106)*. Last Update Date: Available from: https://www.nice.org.uk/guidance/ng106/resources/chronic-heart-failure-in-adults-diagnosis-and-management-pdf-66141541311685 [Accessed 21 May 2020].

20 National Health Service (NHS). *Heart Failure: Treatment*. 2018. Available from: https://www.nhs.uk/conditions/heart-failure/treatment/ [Accessed 20 May 2020].

21 National Institute for Health and Care Excellence (NICE). *Interactive flowchart: Chronic heart failure*. 2020. Available from: https://pathways.nice.org.uk/pathways/chronic-heart-failure#path=view%3A/pathways/chronic-heart-failure/treating-chronic-heart-failure-with-reduced-ejection-fraction.xml&content=view-node%3Anodes-surgical-interventions [Accessed 21 May 2020].

22 National Institute for Health and Care Excellence (NICE). *Interactive Flowchart: Treating chronic heart failure with reduced ejection fraction*. 2020. Available from: https://pathways.nice.org.uk/pathways/chronic-heart-failure#path=view%3A/pathways/chronic-heart-failure/treating-chronic-heart-failure-with-reduced-ejection-fraction.xml&content=view-index [Accessed 21 May 2020].

23 National Institute for Health and Care Excellence (NICE). *Empagliflozin*. 2020. Available from: https://bnf.nice.org.uk/medicinal-forms/empagliflozin.html [Accessed 21 May 2020].

24 National Institute for Health and Care Excellence (NICE). *ENDURALIFE powered CRT-D devices for treating heart failure (MTG33)*. Last Update Date: 17 March 2017. Available from: https://www.nice.org.uk/guidance/mtg33 [Accessed 28 May 2020].

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.