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Health Technology Briefing
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Empagliflozin for the treatment of acute myocardial infarction to reduce heart failure and mortality

Company/Developer	Boehringer Ingelheim Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 23819	NICE TSID: 11817	UKPS ID: 666370

Licensing and Market Availability Plans

Currently in phase III and IV clinical trials.

Summary

Empagliflozin is in clinical development for the treatment of patients at high-risk of developing new onset heart failure (HF) following acute myocardial infarction (AMI; also known as heart attack), in order to reduce the risk of mortality from this condition. AMI is a serious type of coronary heart disease where the blood supply to the heart is suddenly blocked, usually by a blood clot. Symptoms of AMI can include chest pain, shortness of breath, sweating, coughing and wheezing, and feeling light-headed or dizzy. AMI is the most common cardiovascular disease in the western world and leads to a high-risk of developing chronic HF. HF is a progressive clinical syndrome caused by structural or functional abnormalities of the heart, resulting in reduced cardiac output. Despite many medical interventions and therapies that reduce the risk for mortality in patients with AMI being available, there remains a significant unmet need in developing new and effective therapies in patients at high-risk of HF after AMI.

Empagliflozin is administered orally in the form of a tablet and works by inhibiting the sodium-glucose co-transporter 2 (SGLT2). It blocks glucose absorption in the kidney and increases the amount of glucose excreted in the urine. The ability of empagliflozin to induce changes to the sugar, salt and water metabolism in the body may contribute to the reductions in cardiovascular death. Empagliflozin has been shown to significantly reduce the risk of cardiovascular events and HF hospitalisations in patients with chronic HF regardless of diabetes status. If licensed, empagliflozin may offer an additional treatment option for patients following an AMI.

Proposed Indication

For the reduction of heart failure (HF), and the risk of mortality in patients with acute myocardial infarction (AMI).[1,2]

Technology

Description

Empagliflozin (Jardiance) is a reversible, highly potent (IC_{50} of 1.3 nmol) and selective competitive inhibitor of sodium-glucose co-transporter 2 (SGLT2). Empagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is 5000 times more selective for SGLT2 versus SGLT1, the major transporter responsible for glucose absorption in the gut. SGLT2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low.[3,4] It is responsible, as the predominant transporter, for the reabsorption of glucose from the glomerular filtrate back into the circulation.[3,4] By blocking SGLT2, empagliflozin inhibits the reabsorption of glucose from the glomerular filtrate in the proximal tubule of the kidney, leading to urinary glucose excretion. The use of empagliflozin increases urinary glucose excretion in patients with mild and moderate renal impairment.[5] The ability of empagliflozin to induce changes to the sugar, salt and water metabolism in the body may contribute to the reductions in cardiovascular death.[6] Empagliflozin interacts with the cardiac Na^+/H^+ exchanger NHE1 directly to inhibit its activity and reduce cardiac cytosolic Na^+ and cytosolic Ca^{2+}. Inhibition of NHE1 attenuates cardiomyocyte injury, remodelling systolic dysfunction and ultimately HF.[7]

Empagliflozin is currently in clinical development for the reduction of HF in adults with myocardial infarction (MI). In the phase III clinical trial (NCT03087773; EMMY) patients were given 10mg of empagliflozin by oral administration once daily, or matching placebo, for 26 weeks.[1] In a different phase III clinical trial (NCT04509674; EMPACT-MI) patients were administered empagliflozin, or matching placebo, in addition to usual standard of care until end of study (or in the event of premature discontinuation, defined as the time when permanent withdrawal takes place).[2] Additionally, in the phase IV clinical trial (NCT05020704; EMPRESS MI) patients were given 10mg of empagliflozin by oral administration once daily, or matching placebo, for 6 months in addition to usual standard of care.[8a]

Key Innovation

Empagliflozin was initially developed as a treatment for high blood sugar in people with diabetes but has been shown to have beneficial effects on both the heart and kidney. Empagliflozin causes blood sugar (~10 teaspoons a day) to pass into the urine. It likely also increases the amount of sodium passing into the urine.[9] This results in a small decrease in body weight and blood pressure. In the EMPA-REG OUTCOME trial, empagliflozin was associated with a reduced risk of cardiovascular (CV) death (and death from any cause) in people with type 2 diabetes (T2D) at high risk for CV events.[10] In the EMPEROR-Reduced trial, in patients with heart failure with reduced ejection fraction, left ventricular ejection fraction (LVEF) ≤40%, empagliflozin had a beneficial effect on the key efficacy outcomes.[11] Notably, reductions in the risks of death from cardiovascular causes and from any cause occurred early in the trial, and these benefits continued throughout the study.[10] In addition, empagliflozin was the first drug shown prospectively in the EMPEROR-Preserved trial to improve the primary outcome by reducing the risk of hospitalisation for HF and of cardiovascular death in HF patients with LVEF >40% (i.e. heart failure patients with mildly reduced or preserved ejection fraction).[12] The results from the EMPEROR-Reduced trial also showed that empagliflozin had a beneficial effect on the key efficacy outcomes in patients with heart failure with reduced ejection fraction.[11] Heart failure remains one of the leading causes of mortality and morbidity in

[a] Information provided by Boehringer Ingelheim Ltd

developed countries and contributes significantly to the economic burden of modern health care systems.[13] If licensed empagliflozin will provide an additional treatment for patients at high-risk of HF after an AMI.

Regulatory & Development Status

Empagliflozin currently has Marketing Authorisation in the EU/UK for the following indications:[3,4,14]

- T2D
- Symptomatic chronic heart failure

Empagliflozin received FDA Fast Track designation in 2019 for the treatment of chronic heart failure.[15]

Empagliflozin is currently in phase II and phase III clinical trials for chronic kidney disease.[16]

Patient Group

Disease Area and Clinical Need

AMI is a serious medical emergency in which the supply of blood to the heart is suddenly blocked, usually by a blood clot.[17] MI is the most prevalent cardiovascular disease in the western world and HF is one of the most common and severe complications of AMI, which subsequently leads to a higher risk of mortality and disability. It has a destructive potential for heart cells and abruptly reduces the cardiac output, a clinical condition known as heart dysfunction that might progress to HF.[18] 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 such as shortness of breath, persistent coughing or wheezing, ankle swelling, reduced exercise tolerance, fatigue, and signs such as pulmonary oedema, pulmonary crepitations and elevated jugular venous pressure.[19,20] Several overlapping mechanisms contribute to HF following AMI. HF during the index MI occurs due to a combination of myocardial stunning, myocyte necrosis, decompensation of pre-existing HF or acute mitral regurgitation due to papillary muscle dysfunction. HF during hospitalisation may also be due to any of the above, compounded by fluid or contrast overload, renal dysfunction, or complications such as ventricular septal defect or cardiac tamponade. Late HF reflects the consequences of cardiomyocyte death and scar formation occurring alongside ventricular remodelling. AMI-induced myocardial injury triggers ventricular remodelling leading to an increased risk of HF.[21]

In England in 2021-22 there were 5,848 finished consultant episodes (FCE) for AMI (ICD-10; I21.9) resulting in 2,838 hospital admissions and 20,985 FCE bed days.[22] Primary care data from 2013 in the UK suggests that the prevalence of AMI in men is about three-fold greater than for women, and that overall 915,000 people in the UK have had an AMI.[23]

Recommended Treatment Options

For secondary prevention and rehabilitation in patients who have had an MI to reduce or prevent complications, their impact, and further cardiovascular events and mortality, NICE recommends:[24]

- ACE inhibitors (or angiotensin-II receptor antagonists)
- aldosterone antagonists in people with HF with reduced ejection fraction
- dual anti-platelet therapy
- β-blockers
- calcium channel blockers such as diltiazem or verapamil may be considered if β-blockers are contraindicated or need to be discontinued
- statins

Clinical Trial Information	
Trial	NCT03087773; **EMMY;** Impact of Empagliflozin on Cardiac Function and Biomarkers of Heart Failure in Patients With Acute Myocardial Infarction **Phase III–** Completed **Location(s):** Austria **Completion date:** May 2022
Trial Design	Randomised, quadruple blind, parallel assignment
Population	N=476 (actual); Subjects aged 18 to 80 years with myocardial infarction with evidence of significant myocardial necrosis defined as a rise in creatinine kinase >800 U/l and a troponin T-level (or troponin I-level) >10x ULN (upper limit of normal). In addition, at least 1 of the following criteria must be the met: Symptoms of ischemia/ ECG (electrocardiogram) changes indicative of new ischemia (new ST-T changes or new LBBB)/Imaging evidence of new regional wall motion abnormality
Intervention(s)	Empagliflozin 10 mg orally once daily for 26 weeks
Comparator(s)	Matched placebo
Outcome(s)	Change of nt-proBNP levels [Time Frame: 26 weeks] - Difference in the change of nt-proBNP levels between treatment groups from randomization to week 26 See trial record for full list of other outcomes
Results (efficacy)	Baseline median (interquartile range) NT-proBNP was 1294 (757–2246) pg/mL. NT-proBNP reduction was significantly greater in the empagliflozin group, compared with placebo, being 15% lower [95% confidence interval (CI) −4.4% to −23.6%] after adjusting for baseline NT-proBNP, sex, and diabetes status (P=0.026)[25]
Results (safety)	Serious adverse event (SAE) rates did not differ between the empagliflozin and the placebo groups. There was a total of 72 SAEs with 63 participants hospitalised, out of which seven participants were hospitalised for heart failure (three in the empagliflozin group, four in placebo group). Three deaths occurred during the study, all in the empagliflozin group. Two participants died within 5 days after enrolment in the trial secondary to large MIs and subsequent cardiogenic shock. One participant died 149 days after enrolment due to lung cancer. All three fatalities were considered by the adjudication committee prior to unblinding to be unrelated to study medication[25]

Trial	NCT04509674; Eudra CT 2019-001037-13; **EMPACT-MI;** A Streamlined, Multicentre, Randomised, Parallel Group, Double-blind Placebo-controlled Superiority Trial to Evaluate the Effect of Empagliflozin on Hospitalisation for Heart Failure and Mortality in Patients With Acute Myocardial Infarction **Phase III-** Recruiting **Location(s):** 9 EU countries, US, Canada and other countries

	Primary completion date: March 2023
Trial Design	Randomised, quadruple blind, parallel assignment
Population	N=6500 (estimated); Subjects aged 18 and over with a diagnosis of spontaneous Acute Myocardial Infarction (AMI): ST-Elevation Myocardial Infarction (STEMI) or Non-ST Elevation Myocardial Infarction (NSTEMI) with randomisation to occur no later than 14 calendar days after hospital admission. For patients with an in-hospital Myocardial Infarction (MI) as qualifying event, randomization must still occur within 14 days of hospital admission
Intervention(s)	Empagliflozin
Comparator(s)	Matched placebo
Outcome(s)	Composite of time to first heart failure hospitalisation or all-cause mortality [Time Frame: up to 26 months] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	NCT05020704; **EMPRESS MI**; Empagliflozin to Prevent Worsening of Left Ventricular Volumes and Systolic Function After Myocardial Infarction **Phase IV**- Recruiting **Location:** UK **Primary completion date:** October 2023
Trial Design	Randomised, quadruple blind, parallel assignment
Population	N=100 (estimated); Subjects aged 18 and over with a diagnosis of STEMI or NSTEMI AMI and with left ventricular ejection fraction ≤40% as measured by cardiac MRI performed ≥12 hours and ≤14 days following hospital admission with an acute type 1 MI
Intervention(s)	Empagliflozin 10mg orally once daily
Comparator(s)	Matched placebo
Outcome(s)	Change in left ventricular end diastolic volume indexed to body surface area [Time Frame: 24 weeks] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Empagliflozin is already marketed in the UK; a 10mg pack of 28 tablet costs £36.59 and a 25mg pack of 28 tablets also costs £36.59.[26]

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Empagliflozin for treating chronic heart failure with reduced ejection fraction (TA773). March 2022.
- NICE technology appraisal. Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction (TA388). April 2016.
- NICE technology appraisal. Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome (TA335). March 2015.
- NICE technology appraisal. Ivabradine for treating chronic heart failure (TA267). November 2012.
- NICE clinical guideline. Acute coronary syndromes (NG185). November 2020.
- NICE clinical guideline. Chronic heart failure in adults: diagnosis and management (NG106). September 2018.
- NICE quality standard. Secondary prevention after a myocardial infarction (QS99). September 2015.

NHS England (Policy/Commissioning) Guidance

- NHS England service specification. Cardiac surgery – adults. A10/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cardiology: Implantable cardioverter defibrillator (ICD) and cardiac resynchronisation therapy (CRT) (Adult). A09/S/a.
- NHS England. 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.
- NHS England. 2013/14 NHS Standard Contract for Cardiology: Inherited Cardiac Conditions (All Ages). A09/S/c.
- NHS England. 2013/14 NHS Standard Contract for Cardiology: Primary Percutaneous Coronary Intervention (PPCI) (Adult). A09/S/d.

Other Guidance

- British Journal of General Practice. Secondary prevention following myocardial infarction: a clinical update. 2018.[27]
- European Society of Cardiology. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). 2017.[28]

Additional Information

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