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Newcastle University

Health Technology Briefing
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Empagliflozin for treating chronic kidney disease

Company/Developer	Boehringer Ingelheim Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 24239	NICE ID: 10698	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Empagliflozin is in clinical development for the treatment of adult patients with chronic kidney disease (CKD). In CKD, the kidneys do not function as well as they should. This leads to the leakage of blood and protein into the urine. CKD can be developed due to age, but the main risk factors are diabetes, hypertension, acute kidney disease and cardiovascular disease. Some of the symptoms expressed in patients with CKD are headaches, blood in the urine, weight loss and loss of appetite. CKD can occur in both diabetes and non-diabetes mellitus patients. CKD affects around 3 million individuals in the UK therefore additional treatment options are needed.

Empagliflozin is administered orally in the form of a tablet and works by inhibiting the sodium-glucose co-transporter 2 (SGLT2), thus inhibiting the reabsorption of glucose from the glomerular filtrate in the proximal tubule of the kidney, leading to urinary glucose excretion. Potential mechanisms for the kidney benefits of SGLT2 inhibition include a reduction in cell and kidney damage. Evidence from trials in patients with type 2 diabetes and in patients with heart failure suggest empagliflozin has beneficial effects on renal outcomes, both in patients with and without CKD. If licensed empagliflozin will offer an additional treatment for patients with CKD.

Proposed Indication

For the treatment of adults with chronic kidney disease (CKD).[1]

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.[2,3] It is responsible, as the predominant transporter, for the reabsorption of glucose from the glomerular filtrate back into the circulation. 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.[4] Potential mechanisms for benefits of SGLT2 inhibition for the kidneys include, a reduction in single nephron hyperfiltration, decreased tubulointerstitial damage, suppression of hyperglycaemia-induced production of reactive oxygen species and angiotensinogen, reduction of mitochondrial damage, and enhanced nutrient deprivation signalling.[5]

Empagliflozin has been studied in a phase III clinical trial for the treatment of adult patients with CKD (NCT03594110). In this trial, empagliflozin 10 mg once daily was administered orally.[1]

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.[6] 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.[6] The study also demonstrated that empagliflozin, in patients with T2D and high CV risk, was associated with slower progression of kidney disease and lower rates of clinically relevant renal events than placebo when added to standard care.[7,8] In the EMPEROR-Reduced trial, in patients with heart failure with reduced ejection fraction, empagliflozin had a beneficial effect on the key efficacy outcomes and slowed the rate of kidney function decline in patients with and without CKD, and regardless of the severity of kidney impairment at baseline.[5]

Empagliflozin is currently being studied in patients with CKD at risk of progression, in the EMPA-Kidney trial. The primary outcome of the trial is a composite of kidney disease progression or cardiovascular death EMPA-Kidney has wide eligibility criteria and has recruited a broad range of people with CKD, including those underrepresented in reported SGLT2 inhibitor trials.[9] Studies show empagliflozin can be used in patients with an eGFR ≥ 45 mL/min/1.73 m2 and compared to similar SGLT2 inhibitors, other hypoglycemic drugs may be factors that affect the efficacy of sugar-lowering treatments in patients with diabetes. Empagliflozin reduces glucose toxicity of proximal tubular cells therefore, it has potential renal protective effect in patients with type 2 diabetes.[10] Currently recommended SGLT2 inhibitor, empagliflozin demonstrates fewer renal events and can be given to patients that have a lower eGFR.[11] From a clinical perspective, there is growing evidence for the protection of the kidney in non-diabetes mellitus patients.[12]

Regulatory & Development Status

Empagliflozin currently has Marketing Authorisation in the EU/UK for the following indications:[13,14]

- Type 2 diabetes
- Symptomatic chronic heart failure
    - In the EU, empagliflozin is indicated in adults for the treatment of symptomatic chronic heart failure;
    - In the UK, empagliflozin is indicated in adults for the treatment of symptomatic chronic heart failure with reduced ejection fraction.

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

Patient Group

Disease Area and Clinical Need

CKD is a long-term condition where the kidneys do not work as well as they should. CKD is a common condition that is often developed due to age and is most common in individuals of black or south Asian origin. CKD can worsen over time and eventually the kidneys may stop working altogether, but this is uncommon.[16] In CKD, damage to the kidney's filter system has been sustained which allows blood and protein to leak into the urine. This is not always visible but can be found with a urine test.[17] Symptoms are not usually expressed in the early stages of CKD but in the later stages common symptoms include weight loss and poor appetite, oedema, blood in urine, insomnia, muscle cramps, headaches, and erectile dysfunction in men.[18]

Approximately 10% of people in the UK have CKD.[17] According to the Quality and Outcomes Framework the prevalence of CKD (stage 3-5) in 2020/21 in England was 3.96 per 100 in adults aged 18 and above.[19] In England, in 2020-21, there were 45,692 finished consultant episodes (FCE) for CKD (ICD-10; N18) resulting in 34,372 hospital admissions and 88,826 FCE bed days.[20]

Recommended Treatment Options

The current treatment option recommended by NICE NG203 are:[11,21]

- Angiotensin-receptor blockers (ARB) or an angiotensin-converting enzyme (ACE) inhibitor (titrated to the highest licensed dose that the person can tolerate) if ACR is 3 mg/mmol or more for adults with CKD and diabetes (type 1 or type 2)
- Referral for nephrology assessment and offer an ARB or an ACE inhibitor (titrated to the highest licensed dose that they can tolerate), if ACR is 70 mg/mmol or more for with CKD but without diabetes

NICE NG28 guidelines recommend:[22]

- For adults with type 2 diabetes and CKD who are taking an ARB or an ACE inhibitor (titrated to the highest licensed dose that they can tolerate), offer an SGLT2 inhibitor (in addition to the ARB or ACE inhibitor) if:
    - ACR is over 30 mg/mmol and
    - they meet the criteria in the marketing authorisation (including relevant estimated glomerular filtration rate [eGFR] thresholds).

- For adults with type 2 diabetes and CKD who are taking an ARB or an ACE inhibitor (titrated to the highest licensed dose that they can tolerate), consider an SGLT2 inhibitor (in addition to the ARB or ACE inhibitor) if:
  - ACR is between 3 and 30 mg/mmol and
  - they meet the criteria in the marketing authorisation (including relevant eGFR thresholds).

NICE TA775 recommendations (for dapagliflozin in patients with CKD):[11]

- Dapagliflozin is recommended as an option for treating CKD in adults. It is recommended only if:
  - it is an add-on to optimised standard care including the highest tolerated licensed dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), unless these are contraindicated, and
  - people have an estimated glomerular filtration rate (eGFR) of 25 ml/min/1.73 m^2 to 75 ml/min/1.73 m^2 at the start of treatment and:
    - have type 2 diabetes or
    - have a urine albumin-to-creatinine ratio (uACR) of 22.6 mg/mmol or more.

Clinical Trial Information

Trial	**EMPA-KIDNEY;** NCT03594110, 2017-002971-24**;** A Multicentre International Randomized Parallel Group Double-blind Placebo-controlled Clinical Trial of EMPAgliflozin Once Daily to Assess Cardio-renal Outcomes in Patients With Chronic KIDNEY Disease **Phase III** – Active, Not recruiting **Location(s):** 2 EU, UK, USA, Canada, Malaysia, Japan and China **Primary completion date:** June 2022[a23]
Trial Design	Randomised, double blind, parallel assignment
Population	N=6609 (actual); subjects aged 18 and older with evidence of CKD at risk of kidney disease progression
Intervention(s)	Empagliflozin 10 mg taken daily with or without food.
Comparator(s)	Matching placebo taken with or without food.
Outcome(s)	The primary (composite) outcome is defined as time to first occurrence of (i) kidney disease progression (defined as ESKD, a sustained decline in eGFR to <10 mL/min/1.73m^2, renal death, or a sustained decline of ≥40% in eGFR from randomization) or (ii) Cardiovascular death [Time frame: median follow-up approx. 3.1 years]. See trial record for full list of all outcomes.

[a] On 16th March 2022 it was announced that Independent Data Monitoring Committee recommended that the trial be stopped early due to clear evidence of positive efficacy of empagliflozin, following a formal interim assessment.

Results (efficacy)	-
Results (safety)	-

Estimated Cost

Empagliflozin is already marketed in the UK; a 10mg pack of 28 tablet costs £36.59.[24]

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance. Dapagliflozin for treating chronic kidney disease (TA775). March 2022.
- NICE clinical guideline. Chronic kidney disease in adults: assessment and management (NG203). November 2021.
- NICE clinical guideline. Type 2 diabetes in adults: management (NG28). March 2022.
- NICE quality standard. Chronic kidney disease in adults (QS5). July 2017.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- Kidney Disease Improving Global Outcomes (KDIGO). Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. 2012.[25]

Additional Information

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