Empagliflozin (Jardiance) for preventing cardiovascular death in patients with type 2 diabetes mellitus and high cardiovascular risk

LAY SUMMARY

Type 2 diabetes is a disease that results in the levels of sugar in the blood being too high. This can cause damage to the eyes, nerves, kidneys and other tissues, and can greatly increase the chances of heart attacks and strokes, especially when combined with high blood pressure and high blood cholesterol levels.

Empagliflozin is a drug currently used to treat type 2 diabetes. It is given as a tablet that is taken once daily. In a large study of patients, empagliflozin reduced the risk of getting high blood pressure, heart attacks and strokes in people with type 2 diabetes.

If licensed in the UK, empagliflozin will offer type 2 diabetes patients who are at risk of developing heart disease and strokes, an additional treatment option which can be used with other diabetes drugs.

NIHR HSRIC ID: 12145
TARGET GROUP

- Diabetes mellitus: type 2; with high cardiovascular risk – adjunct therapy.

TECHNOLOGY

DESCRIPTION

Empagliflozin (Jardiance; BI 10773) is a reversible, highly potent 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 5,000 times more selective for SGLT2 compared to SGLT1. SGLT2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low. It is responsible for the reabsorption of glucose from the glomerular filtrate back into the circulation. Empagliflozin improves glycaemic control in patients with type 2 diabetes by reducing renal glucose reabsorption.

Empagliflozin is administered orally as either a 10mg or 25mg single tablet taken once daily. It is expected that this treatment will continue indefinitely as part of long term diabetic glucose and complication management.

Empagliflozin is currently licensed in the EU for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control as a monotherapy and as an add-on combination therapy with other glucose-lowering medicinal products. Common adverse events include hypoglycaemia (when used with sulphonylurea or insulin), genital infections, urinary tract infections, pruritus and increased urination.

Empagliflozin is currently in phase III clinical trials for diabetes in patients with heart failure (with and without diabetes) and type 1 diabetes.

INNOVATION and/or ADVANTAGES

If licensed, empagliflozin will offer an additional treatment option to prevent cardiovascular death in patients with type 2 diabetes mellitus who are at high risk of cardiovascular disease.

DEVELOPER

Boehringer Ingelheim, co-marketed with Eli Lilly and Company Limited.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

* Company provided information.
Type 2 diabetes mellitus is a chronic metabolic disorder, the prevalence of which has been increasing steadily in all parts of the world. Type 2 diabetes mellitus consists of an array of dysfunctions characterised by hyperglycaemia and resulting from the combination of resistance to insulin action, inadequate insulin secretion, and excessive or inappropriate glucagon secretion. Symptoms of type 2 diabetes include: polyuria, polydipsia, polyphagia, weight loss, blurred vision, paraesthesia of the lower extremities and yeast infections.

Type 2 diabetes can cause serious long-term health problems such as diabetic retinopathy and kidney failure, and patients with type 2 diabetes are up to five times more likely to have cardiovascular diseases such as strokes or ischaemia.

Type 2 diabetes is due primarily to lifestyle factors and genetics. A number of lifestyle factors are known to be important to the development of type 2 diabetes such as physical inactivity, sedentary lifestyle, cigarette smoking and generous consumption of alcohol. Obesity has been found to contribute to approximately 55% of cases of type 2 diabetes. There is a strong inheritable genetic connection; having relatives with type 2 diabetes increases the risks substantially. Recently, genes discovered to be significantly associated with developing type 2 diabetes include: TCF7L2, PPARG, FTO, CDKAL1, KCNJ11, NOTCH2, WFS1, IGF2BP2, SLC30A8, JAZF1, and HHEX KCNJ11. However, individually these account for only a small proportion of cases.

It is estimated that more than 1 in 16 people in the UK has diabetes (diagnosed or undiagnosed). There are almost 3.5 million people diagnosed with diabetes in the UK, with 90% of these having type 2 diabetes. In addition, it is estimated that there are around 549,000 people in the UK who have diabetes but have not been diagnosed. Research suggests that people from South Asian and Black communities are two to four times more likely to develop type 2 diabetes than those from White ethnic groups. Diabetes care is estimated to account for up to 10% of NHS expenditure.

By 2025, it is estimated that five million people will have diabetes in the UK. In 2014-15, there were 20,971 hospital admissions for type 2 diabetes (ICD-10 E11) in England, resulting in 153,939 bed days and 34,028 finished consultant episodes. In the same year in England and Wales, 2,435 deaths were registered for type 2 diabetes (ICD-10 E11). Cardiovascular disease is a major cause of death and disability in people with diabetes, accounting for 52% of deaths in people with type 2 diabetes. There is a 138.8% increased risk of angina, a 94.2% increased risk of myocardial infarction, a 126.2% increased risk of heart failure and a 62.5% increased risk of stroke among people with both types of diabetes. People with type 2 diabetes have a two-fold increased risk of stroke within the first five years of diagnosis compared with the general population. Around one fifth of hospital admissions for heart failure, heart attack and stroke are in people with diabetes.
The population likely to be eligible to receive empagliflozin could not be estimated from available published sources.

## PATIENT PATHWAY

### RELEVANT GUIDANCE

**NICE Guidance**

**Other Guidance**
- Royal College of Nursing. Starting injectable treatment in adults with Type 2 diabetes. 2012.

## CURRENT TREATMENT OPTIONS

Treatments for type 2 diabetes take an individualised approach that is tailored to the needs and circumstances of the patient, taking into account their personal preferences, comorbidities, risks from polypharmacy, and ability to benefit from long-term interventions because of reduced life expectancy. Educating the patient in managing their diabetes, alongside dietary advice, and weight loss targets for patients who are overweight is often the first approach in managing this condition.
Pharmacological treatment options include\textsuperscript{6,9}:

- Standard-release metformin is the initial drug offered. The dose is gradually increased over several weeks to minimise the risk of gastrointestinal side effects. If gastrointestinal effects do occur, a modified-release formulation of metformin can be trialled.

- If metformin is contraindicated or not tolerated, the initial treatments can be a dipeptidyl peptidase-4 inhibitor (DPP-4, or ‘gliptin’), pioglitazone or sulfonylurea. Pioglitazone should not be offered to diabetic patients with a history of heart failure, hepatic impairment, diabetic ketoacidosis, history of bladder cancer or macroscopic haematuria.

- Drug treatment intensification with metformin in combination with either a DPP-4 inhibitor, pioglitazone, sulfonylurea or SGLT2 inhibitor (such as canagliflozin, dapagliflozin and empagliflozin), for patients whose glycosylated haemoglobin (HbA1c) has not been controlled by metformin alone. For patients who are not taking metformin as the initial drug treatment, combinations of either a DPP-4 inhibitor, pioglitazone or sulfonylurea can be used.

- If dual therapy with metformin and other oral drugs has not worked, triple therapy with a combination of metformin, DPP-4 inhibitor, pioglitazone, sulfonylurea or SGLT2 inhibitor may be used.

- A structured programme of insulin therapy is usually offered with continuing support and self-monitoring if triple therapy has not been effective. Insulin based therapy may be used in combination with any aforementioned drugs.

For the primary prevention of cardiovascular disease in primary care, a systematic strategy to identify and prioritise people at risk is carried out\textsuperscript{17}. Lifestyle changes to reduce risk are suggested such as alterations in diet, physical activity, smoking and alcohol consumption. Lipid modification therapy may be offered for primary or secondary prevention of cardiovascular disease\textsuperscript{17}. NICE recommends offering atorvastatin 20mg for the primary prevention of cardiovascular disease to people with type 2 diabetes who have a 10\% or greater 10-year risk of developing cardiovascular disease using the QRISK2 assessment tool\textsuperscript{17}.

### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>EMPA-REG OUTCOME; NCT01131676, EudraCT 2009-106178-33, 1245.25, BI 10773 vs placebo; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Boehringer Ingelheim.</td>
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<tr>
<td>Status</td>
<td>Published.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Publication\textsuperscript{18}, trial registry\textsuperscript{19}.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
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<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
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<tr>
<td>Participants</td>
<td>n=7,020; aged 18 yrs or older; type 2 diabetes mellitus; drug naïve patients or unchanged antidiabetic therapy for 12 wks prior to randomisation; HbA1c ≥7% and ≤10% for patients on background therapy or ≥7% and ≤9% for drug naïve patients; body mass index ≤45; high cardiovascular risk; no uncontrolled hyperglycaemia with a glucose level &gt;240mg/dl after an overnight fast during placebo run-in confirmed by a second measurement; no indication of liver disease; no planned cardiac surgery or angioplasty within 3 mths; glomerular filtration rate (eGFR) &lt;30 ml/min; no bariatric surgery within past 2 yrs; no treatment with anti-obesity drug 3 mths prior to screening; no current treatment with systemic steroids or change in dose of thyroid hormones within 6 wks; no acute coronary syndrome, stroke or TIA within 2 mths.</td>
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<tr>
<td>Schedule</td>
<td>Randomised to BI 10773 10mg taken orally once daily, or BI 10773 25mg taken orally once daily, or placebo taken orally once daily.</td>
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<tr>
<td>Follow-up</td>
<td>Median active treatment was 2.6 yrs, with a median follow-up observation time of 3.1yrs</td>
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### Primary outcome/s

Time to the first occurrence of any of the following adjudicated components of the primary composite endpoint: cardiovascular death (including fatal stroke and fatal myocardial infarction), non-fatal myocardial infarction and non-fatal stroke.

### Secondary outcome/s

**Key secondary cardiovascular-endpoint:** Time to the first occurrence of the following adjudicated events (treated as a composite): cardiovascular death (including fatal stroke and fatal myocardial infarction [MI]), non-fatal MI (excluding silent MI), non-fatal stroke and hospitalisation for unstable angina pectoris.

**Further secondary endpoints:** silent MI, heart failure requiring hospitalisation, new onset albuminuria (ACR >30mg/g), new onset macroalbuminuria (>300mg/g), composite microvascular outcome defined as need for initiation of retinal photocoagulation, vitreous haemorrhage, diabetes related blindness OR new or worsening onset nephropathy (defined as new onset or macroalbuminuria or doubling of serum creatinine level accompanied by an eGFR ≤45ml/min or need for initiation of continuous renal replacement therapy or death due to renal disease). No quality of life measurement included in trial outcomes.

### Key results

For empagliflozin vs placebo group, respectively: the primary outcome occurred in 490 of 4,687 patients (10.5%) compared to 282 of 2,333 patients (12.1%), (hazard ratio 0.86; 95.02% confidence interval, 0.74 to 0.99); no significant between-group differences in the rates of myocardial infarction or stroke, but in the empagliflozin group there were significantly lower rates of death from cardiovascular causes, 3.7% vs. 5.9% (38% relative risk reduction), hospitalisation for heart failure 2.7% vs 4.1% (35% relative risk reduction), and death from any cause 5.7% vs 8.3% (32% relative risk reduction).

### Adverse effects (AEs)

There was an increased rate of genital infection among patients receiving empagliflozin.

### ESTIMATED COST and IMPACT

#### COST

The cost of empagliflozin is not yet known.

#### IMPACT - SPECULATIVE

**Impact on Patients and Carers**

- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- No impact identified
- Other

**Impact on Health and Social Care Services**

- Increased use of existing services
- Decreased use of existing services: If successful in reducing cardiovascular events.
- Re-organisation of existing services
- Need for new services
- Other
- None identified
Impact on Costs and Other Resource Use

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs
- Other reduction in costs
- Other
  - None identified

Other Issues

- Clinical uncertainty or other research question
  - None identified

REFERENCES