Empagliflozin (Jardiance) for type 1 diabetes – adjunctive therapy

LAY SUMMARY

Type 1 diabetes occurs when the person’s own immune system attacks the pancreas and destroys the cells that produce a hormone called insulin, which is needed to regulate the body's sugar levels. Without insulin, there is too much sugar in the blood. This can cause damage to the eyes, nerves, kidneys and other tissues, and can increase the chances of heart attacks and strokes.

Empagliflozin is a drug currently used to treat type 2 diabetes. It is given as a tablet that is taken once daily. Empagliflozin is currently being studied to see if it would also work in patients with type 1 diabetes, to be taken alongside the insulin injections that patients already take.

If licensed in the UK, empagliflozin will offer type 1 diabetes patients an additional treatment option alongside insulin to maintain stable sugar levels.

NIHR HSRIC ID: 11033
TARGET GROUP

- Type 1 diabetes mellitus – adjunct to insulin 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 (the major transporter responsible for glucose absorption in the gut) 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 diabetes by reducing renal glucose reabsorption.

Empagliflozin is administered orally as either 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 therapy in combination 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 type 2 diabetes with high cardiovascular risk and in heart failure patients, both with and without diabetes.

INNOVATION and/or ADVANTAGES

If licensed, empagliflozin will offer an additional oral treatment option for patients with type 1 diabetes who require an additional therapy alongside insulin.

DEVELOPER

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

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

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* Company provided information.
Type 1 diabetes is a chronic autoimmune disorder that may be precipitated by environmental factors in genetically susceptible individuals. The immune system attacks the beta-cells in the islets of Langerhans of the pancreas, destroying or damaging them sufficiently to reduce and eventually eliminate insulin production. The disease is most often diagnosed in children and adolescents, but it can also develop in adults in their late 30s and early 40s. Type 1 diabetes usually presents with the classic trio of symptoms; polydipsia, polyphagia and polyuria alongside overt hyperglycemia. This sequence is a consequence of hepatic overproduction of glucose via glycogenolysis and gluconeogenesis pathways and decreased cellular uptake of glucose by peripheral tissues such as muscle and adipose tissue. In addition, excessive fat breakdown and fatty acid oxidation may lead to hyperlipidaemia and ketosis. Type 1 diabetes patients have an immediate need for exogenous insulin replacement, which will be required for life. Over years, type 1 diabetes causes tissue damage which, if not detected and managed early, can result in disability, blindness, kidney failure and foot ulceration leading to amputation, as well as premature heart disease, stroke and death.

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 over 370,000 having type 1 diabetes. Diabetes care is estimated to account for up to 10% of NHS expenditure.

In 2014-15, there were 25,800 hospital admissions for type 1 diabetes (ICD-10 E10) in England, resulting in 91,803 bed days and 37,534 finished consultant episodes. In the same year in England and Wales, 344 deaths were registered for type 1 diabetes (ICD-10 E10).

The population likely to be eligible to receive empagliflozin could not be estimated from available published sources.

• NICE guideline. Diabetes (type 1 and type 2) in children and young people: diagnosis and management (NG18). August 2015.
• NICE guideline. Type 1 diabetes in adults: diagnosis and management (NG17). August 2015.
• NICE guideline. Diabetes in pregnancy: management from pre-conception to the postnatal period (NG3). February 2015.

Other Guidance

• British Medical Journal. Diagnosis and management of type 1 diabetes in adults: summary of updated NICE guidance. 201511.
• International Society for Pediatric and Adolescent Diabetes. ISPAD clinical practice consensus guidelines. 201413.
• NHS University Hospitals Leicester. Diabetes mellitus guidelines. 201315.
• Trend UK. Diabetes and Dementia Guidance on Practical Management. 201316.
• The Royal College of Ophthalmologists. Diabetic Retinopathy Guidelines. 201218.

CURRENT TREATMENT OPTIONS

Type 1 diabetes is treated by insulin replacement, supported by active management of other cardiovascular risk factors such as hypertension and high circulating lipids6. NICE recommends offering all adults with type 1 diabetes a structured education programme in the self-management of flexible insulin therapy (for example the DAFNE [dose adjustment for normal eating] programme) for 6 to 12 months as well as education about self-monitoring blood glucose levels6,11. NICE recommends offering dietary advice about matters that are not solely about blood glucose control, but include weight control and cardiovascular risk management as well6,11.

NICE recommends multiple daily injection basal-bolus insulin regimens6. Insulin detemir is offered twice daily as basal insulin therapy, or insulin glargine if insulin detemir is not tolerated; with bolus rapid acting insulin injected before meals. In flexible therapy, doses of basal insulin are based on fasting glucose readings and readings made five or more hours after eating; doses for meal insulin are based on the current blood glucose test result and the amount of carbohydrate the patient plans to eat11. Twice daily mixed insulin may be offered if multiple daily injections are not possible6. Continuous subcutaneous insulin infusion treatment is also available20. Metformin adjunct therapy alongside insulin can also be given for improvement of blood glucose control while minimising effective insulin dose6.
**EFFICACY and SAFETY**

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT02580591, 1245.72, EudraCT 2014-005256-26; empagliflozin vs placebo; phase III.</th>
<th>NCT02414958, 1245.69, EudraCT 2014-001922-14; empagliflozin vs placebo; phase III.</th>
<th>NCT01969747, 1245.78, EudraCT 2011-004354-25; empagliflozin vs placebo; phase II.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Boehringer Ingelheim.</td>
<td>Boehringer Ingelheim.</td>
<td>Boehringer Ingelheim.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Ongoing.</td>
<td>Published.</td>
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<tr>
<td>Source of information</td>
<td>Trial registry(^{21}), manufacturer.</td>
<td>Trial registry(^{22}), manufacturer.</td>
<td>Publication(^{23}), trial registry(^{24}), manufacturer.</td>
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<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
<td>Austria and Germany.</td>
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<tr>
<td>Participants</td>
<td>n=960 (planned); aged 18 yrs or older; receiving insulin for type 1 diabetes &gt;1yr; C-peptide &lt;0.7ng/ml; using multiple daily injections of insulin or insulin pump with total daily insulin ≥0.3 and ≤1.5 U/kg; HbA1c ≥7.5% and ≤10.0%; body mass index (BMI) ≥18.5kg/m(^2); estimated glomerular filtration rate (eGFR) ≥30ml/min/1.73m(^2); compliance with trial medication administration between 80% and 120% during placebo run-in period; no type 2 diabetes, maturity onset diabetes of the young, pancreatic surgery or chronic pancreatitis; no pancreas, pancreas islet cells or renal transplant; no treatment with any other anti-hyperglycaemic drug except insulin within last 3 mths; no severe hypoglycaemia within last 3 mths; no diabetic ketoacidosis within 3 mths.</td>
<td>n=720 (planned); aged 18 yrs or older; receiving insulin for type 1 diabetes ≥1yr; C-peptide &lt;0.7ng/ml; HbA1c ≥7.5% and ≤10.0%; BMI ≥18.5kg/m(^2); no type 2 diabetes, maturity onset diabetes of the young, pancreatic surgery or chronic pancreatitis; no pancreas, pancreas islet cells or renal transplant; no treatment with any other anti-hyperglycaemic drug except insulin within last 3 mths; no severe hypoglycaemia within last 3 mths; no diabetic ketoacidosis within 3 mths.</td>
<td>n=75; aged 18 to 65 yrs; receiving insulin for type 1 diabetes ≥1yr; C-peptide &lt;1.5ng/ml; using multiple daily injections of insulin; HbA1c ≥7.5% and ≤10.5%; BMI ≥18.5kg/m(^2) and ≤35.0kg/m(^2); eGFR 60 to 150ml/min/1.73m(^2); compliance with trial medication administration between 80% and 120% during placebo run-in period; patients receiving multiple daily injections of insulin consisting of basal insulin and ≥3 daily bolus injections for ≥12 months before screening; no type 2 diabetes, maturity onset diabetes of the young, pancreatic surgery or chronic pancreatitis; no pancreas, pancreas islet cells or renal transplant; no treatment with any other anti-hyperglycaemic drug except insulin within last 3 mths; no severe hypoglycaemia within last 3 mths; no diabetic ketoacidosis within 3 mths.</td>
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<tr>
<td>Schedule</td>
<td>Randomised to oral empagliflozin at 2.5mg, 10mg or 25mg once daily; or oral placebo once daily.</td>
<td>Randomised to oral empagliflozin at 10mg or 25mg once daily; or oral placebo once daily.</td>
<td>Randomised to oral empagliflozin at 2.5mg, 10mg or 25mg once daily; or oral placebo once daily; alongside their insulin regime.</td>
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<td>Follow-up</td>
<td>Active treatment for 26 wks, follow-up 3 wks after final dose.</td>
<td>Active treatment for 52 wks, follow-up 3 wks after final dose.</td>
<td>Active treatment for 28 days, follow-up 7 days after final dose.</td>
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<tr>
<td>Primary outcome/s</td>
<td>Change from baseline in HbA1c.</td>
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<td>Urinary glucose excretion (UGE) in 24hrs on day 7.</td>
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<td>Secondary outcome/s</td>
<td>Percentage of time spent in target glucose range 70-180mg/dl as determined by continuous glucose monitoring (CGM); body weight; total daily insulin dose; symptomatic hypoglycaemic adverse effects (AEs) with confirmed plasma glucose &lt;54mg/dl and/or severe hypoglycaemic AEs; systolic blood pressure; interstitial glucose variability as determined by CGM; area under the curve; diastolic blood pressure. No quality of life measurement included in trial outcomes.</td>
<td>Percentage of time spent in target glucose range 70-180mg/dl as determined by CGM; body weight; total daily insulin dose; symptomatic hypoglycaemic AEs with confirmed plasma glucose &lt;54mg/dl and/or severe hypoglycaemic AEs; systolic blood pressure; diastolic blood pressure. No quality of life measurement included in trial outcomes.</td>
<td>No quality of life measurement included in trial outcomes. Other trial outcomes include: change in 24hr UGE; change in HbA1c; change in fasting plasma glucose on days 7 and 28; change in mean daily glucose (MDG; eight-point profile) on days 7 and 28; change in weekly mean recorded total insulin use in wk 4; change in weight; and changes from baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP).</td>
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<tr>
<td>Key results</td>
<td>-</td>
<td>-</td>
<td>Empagliflozin significantly increased 24hr UGE versus placebo on days 7 and 28. On day 28, adjusted mean difference for empagliflozin group vs placebo in change from baseline in: HbA1c, −0.35 to −0.49% (−3.8 to −5.4 mmol/mol, all p&lt;0.05 vs placebo); total daily insulin dose, −0.07 to −0.09 U/kg (all p&lt;0.05 vs placebo); and weight, −1.5 to −1.9 kg (all p&lt;0.001 vs placebo).</td>
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<td>Adverse effects</td>
<td>-</td>
<td>-</td>
<td>For the placebo, empagliflozin 2.5mg, 10mg and 25 mg groups, respectively, AEs were reported in 94.7, 89.5, 78.9 and 100.0%; rate of symptomatic hypoglycaemic episodes with glucose ≤3.0 mmol/l not requiring assistance was 1.0, 0.4, 0.5 and 0.8 episodes per 30 days.</td>
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</table>
Expected reporting date | The estimated primary completion date is reported as Oct 2017. | The estimated primary completion date is reported as Jan 2018. | -

**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
- Other
  - Reduced symptoms or disability
  - No impact identified

**Impact on Health and Social Care Services**
- Increased use of existing services
- Re-organisation of existing services
- Other.
  - Decreased use of existing services
  - Need for new services
  - 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 identified
  - None identified

**REFERENCES**