Ertugliflozin for type 2 diabetes mellitus

NIHR HSRIC ID: 7712; 11910; 12223; 12238

Lay summary

Ertugliflozin is a new drug to treat type 2 diabetes. Type 2 diabetes is a disease that results when the level of sugar in the blood is too high. This can cause damage to the eyes, nerves, kidneys and other tissues. It also greatly increases the chance of heart attacks and strokes. Ertugliflozin is taken as a tablet once a day and works by increasing the amount of sugar that passes out of the body in urine.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

- Diabetes mellitus: type 2; in adults aged 18 years and older; in patients for whom diet and exercise do not provide adequate glycaemic control –
  - As monotherapy, in patients for whom use of metformin is considered inappropriate due to intolerance or contraindications.
  - As add-on combination therapy, with other glucose-lowering medicinal products, including insulin.

TECHNOLOGY

DESCRIPTION

Ertugliflozin (MK-8835; PF-4971729) is an orally active inhibitor of the sodium glucose co-transporter type 2 (SGLT2). SGLT2 is responsible for 80-90% of renal glucose re-absorption and is often overexpressed and over activated in patients with type 2 diabetes. SGLT2 inhibitors reduce renal glucose reabsorption in the proximal convoluted tubule, leading to increased urinary glucose excretion. In phase III clinical trials, ertugliflozin is administered orally at 5mg or 15mg once daily.

Ertugliflozin does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, ertugliflozin will offer an additional treatment option for patients with type 2 diabetes mellitus.

DEVELOPER

Merck Sharp and Dohme Corp.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

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 (glycosylated haemoglobin [HbA1c] >48mmol/mol or random plasma glucose >11mmol/L), resulting from the combination of resistance to insulin action, inadequate insulin secretion, and excessive or inappropriate glucagon secretion. Type 2 diabetes is the most common form of diabetes, accounting for about 90% of cases. Symptoms of type 2 diabetes include polyuria, polydipsia, polyphagia, weight loss, blurred vision, paraesthesia of the lower extremities and yeast infections.
Complications of type 2 diabetes include:\(^5\):
- Microvascular complications – retinopathy, nephropathy and neuropathy.
- Macrovascular complications – cardiovascular disease, cerebrovascular disease, and peripheral arterial disease.
- Metabolic complications – dyslipidaemia, hyperosmolar state, and diabetic ketoacidosis.
- Psychological complications – including anxiety and depression.

Type 2 diabetes is due primarily to lifestyle and genetic factors. A number of lifestyle factors are known to be important to the development of this condition, such as physical inactivity, poor diet, cigarette smoking and excessive consumption of alcohol\(^3,4\). Obesity has been found to contribute to approximately 55% of cases of type 2 diabetes\(^3\). There is a strong heritable genetic predisposition; having relatives with type 2 diabetes increases the risks substantially. The risk of developing type 2 diabetes is about 15% if one parent has type 2 diabetes and 75% if both parents have type 2 diabetes\(^5\). However, individually these account for only a small proportion of cases. Lifestyle interventions (such as diet and physical activity) are recommended initially to manage type 2 diabetes and reduce the risk of complications. However, over time, many people will require antidiabetic drug treatments\(^5\).

**CLINICAL NEED and BURDEN OF DISEASE**

It is estimated that more than 1 in 16 people in the UK has diabetes (diagnosed or undiagnosed), which equates to approximately 4 million people aged 16 years and over in England, of whom around 90% have type 2 diabetes\(^7,8\). By 2035, it is estimated that 4.9 million people will have diabetes in England\(^8\). 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\(^7\).

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\(^9\). In the same year in England and Wales, 2,435 deaths were registered for type 2 diabetes (ICD-10 E11)\(^10\). Diabetes is costly to the NHS, with a recent study estimating that 10% of all NHS expenditure is for diabetes\(^11\). In 2013-14, it was estimated that 9.5% of prescribing costs were for diabetes, including pharmaceutical treatment and blood glucose testing strips\(^12\).

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\(^7\). There is a 139% increased risk of angina, a 94% increased risk of myocardial infarction, a 126% increased risk of heart failure, and a 63% increased risk of stroke among people with diabetes\(^7\). 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\(^7\). Around one fifth of hospital admissions for heart failure, heart attack and stroke are in people with diabetes\(^7\).

It is estimated that 56% of patients receiving pharmacological treatment for type 2 diabetes are receiving first-line treatment, which equates to approximately 1.2 million people in England. It is also estimated that 25% of patients receiving pharmacological treatment for type 2 diabetes are receiving second-line treatment, which equates to approximately 517,000 people in England\(^13\).

\(^a\) Expert personal communication.
PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- NICE technology appraisal in development. Diabetes (type 2) - canagliflozin, dapagliflozin and empagliflozin (monotherapy) (ID756). Expected May 2016.


NHS England Policies and Guidance


Other Guidance

- Royal College of Nursing. Starting injectable treatment in adults with Type 2 diabetes. 2012.
Treatments for type 2 diabetes should adopt 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:

- 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 recommended treatment options are 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, 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), is recommended for patients whose 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, or SGLT2 inhibitor can be used.
- If dual therapy with metformin and other oral drugs is insufficient, triple therapy with a combination of metformin, DPP-4 inhibitor, pioglitazone, sulfonylurea, or SGLT2 inhibitor may be used.
- A structured programme of insulin therapy may be offered in combination with continuing support and self-monitoring if triple therapy has not been effective. Insulin based therapy may be used in combination with any of the aforementioned drugs.

**EFFICACY and SAFETY**

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01958671, 8835-003, 2013-002519-90, B1521022; ertugliflozin vs placebo; phase III.</th>
<th>NCT02226003, 8835-017, 2014-001049-25, B1521047; ertuglizoflozin in combination with sitagliptin vs placebo; phase III.</th>
<th>NCT01999218, 8835-002, 2013-003582-34, B1521013; ertugliflozin vs glimepiride; phase III.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Merck Sharp &amp; Dohme Corp.</td>
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<tr>
<td>Source of information</td>
<td>Trial registry, manufacturer.</td>
<td>Trial registry, manufacturer.</td>
<td>Trial registry, manufacturer.</td>
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<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
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<td>EU (not UK), USA, Canada and other countries.</td>
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<p>| Participants | n=464; aged 18 yrs and older; type 2 diabetes mellitus; no oral antihyperglycaemic agents for at least 8 wks prior to study participation. | n=292; aged 18 yrs and older; type 2 diabetes mellitus; no oral antihyperglycaemic agents for at least 8 wks prior to study participation and HbA1c ≥8% and ≤10.5%; or on a single allowable antihyperglycaemic agent (metformin, α-glucosidase inhibitors, sulfonylureas and glinides) and HbA1c ≥7.5% and ≤10%; or on low dose dual combination therapy with allowable antihyperglycaemic agents and HbA1c ≥7.5% and ≤10%. | n=1,230 (planned); aged 18 yrs and older; type 2 diabetes mellitus; on metformin monotherapy or metformin in combination with a single allowable antihyperglycaemic agent (dipeptidyl peptidase-4 inhibitor, glinides and α-glucosidase inhibitors). |
| Schedule | Part A: Randomised to ertugliflozin 5mg oral once daily for 26 wks; or ertugliflozin 15mg oral once daily; or placebo once daily for 26 wks. Part B: Pts requiring rescue with metformin in part A continue to receive metformin in addition to their original randomised treatment, once daily for 26 wks. Pts not requiring rescue with metformin in part A receive metformin placebo in addition to their original randomised treatment, once daily for 26 wks. | Randomised to ertugliflozin 5mg oral once daily for 26 wks; or ertugliflozin 15mg oral once daily; both in combination with sitagliptin 100mg oral once daily; or ertugliflozin placebo and sitagliptin placebo oral once daily for 26 wks. | Randomised to ertugliflozin 5mg oral once daily; or ertugliflozin 15mg oral once daily; or glimepiride 8mg oral once daily. |
| Follow-up | Active treatment for 52 wks. | Active treatment for 26 wks. | Active treatment for 26 wks. |
| Primary outcomes | HbA1c; adverse effects (AEs). | HbA1c; AEs. | HbA1c; AEs. |
| Secondary outcomes | Fasting plasma glucose, body weight, 2-hrs postprandial plasma glucose, and blood pressure; number of pts with HbA1c &lt;7%. | Fasting plasma glucose, body weight, 2-hrs postmeal glucose, body weight, and blood pressure; number of pts with HbA1c &lt;7%. | Body weight; systolic blood pressure; number of pts with symptomatic hypoglycaemia. |
| Key results | Not reported. | Not reported. | - |
| Adverse effects (AEs) | Not reported. | Not reported. | - |
| Expected reporting date | Previously reported as July 2016. | Previously reported as Feb 2016. | Study completion date reported as April 2017. |</p>
<table>
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<tr>
<th>Trial</th>
<th>NCT02033889, 8835-007, 2013-003290-955, B1521017; ertugliflozin vs placebo; phase III.</th>
<th>NCT02099110, 8835-005; ertugliflozin vs sitagliptin; phase III.</th>
<th>NCT02036515, 8835-006, 2013-003697-26, B1521015; ertugliflozin vs placebo; phase III.</th>
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<td>Trial registry&lt;sup&gt;30&lt;/sup&gt;, manufacturer.</td>
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<td>EU (not UK), USA and other countries.</td>
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<td>Participants</td>
<td>n=600 (planned); aged 18 yrs and older; type 2 diabetes mellitus; on metformin monotherapy for &lt;8 wks prior to study participation; HbA1c ≥7% and ≤10.5%.</td>
<td>n=1,291; aged 18 yrs and older; type 2 diabetes mellitus; on metformin monotherapy (≥1,500mg/day) with HbA1c ≥7.5% and ≤11%; or on metformin monotherapy (&lt;1,500mg/day) with HbA1c ≥8% and ≤11.5%.</td>
<td>n=462; aged 18 yrs and older; type 2 diabetes mellitus; on metformin monotherapy with either sitagliptin or another dipeptidyl peptidase-4 inhibitor or a sulfonylurea.</td>
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<tr>
<td>Schedule</td>
<td>Randomised to ertugliflozin 5mg oral once daily; or ertugliflozin 15mg once daily; or placebo oral once daily; all in combination with metformin 1,500mg oral once daily.</td>
<td>Randomised to ertugliflozin 5mg oral once daily; or ertugliflozin 15mg oral once daily; or ertugliflozin 5mg once daily in combination with sitagliptin 100mg oral once daily; or ertugliflozin 15 mg once daily in combination with sitagliptin 100mg oral once daily; or sitagliptin 100mg oral once daily; all in combination with metformin 1,500mg oral once daily.</td>
<td>Randomised to ertugliflozin 5mg oral once daily; or ertugliflozin 15mg oral once daily; or placebo oral once daily. Pts are to remain on their stable doses of metformin and sitagliptin, and receive glimepiride and insulin glargine rescue medication as required.</td>
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<td>Follow-up</td>
<td>Active treatment for 104 wks.</td>
<td>Active treatment for 52 wks.</td>
<td>Active treatment for 52 wks.</td>
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<tr>
<td>Primary outcomes</td>
<td>HbA1c; AEs.</td>
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</tr>
<tr>
<td>Secondary outcomes</td>
<td>Fasting plasma glucose, body weight, blood pressure, bone mineral density, and bone biomarkers; number of pts with HbA1c &lt;7%; number of pts with HbA1c &lt;6.5%; number of pts requiring glycaemic rescue therapy.</td>
<td>Fasting plasma glucose, body weight, blood pressure and beta-cell function; number of pts with HbA1c &lt;7%.</td>
<td>Fasting plasma glucose, body weight, and blood pressure; number of pts with HbA1c &lt;7%.</td>
</tr>
<tr>
<td>Key results</td>
<td>-</td>
<td>Not reported.</td>
<td>Not reported.</td>
</tr>
<tr>
<td>AEs</td>
<td>-</td>
<td>Not reported.</td>
<td>Not reported.</td>
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<tr>
<td>Expected reporting date</td>
<td>Study completion date reported as Aug 2017.</td>
<td>Previously reported as May 2016.</td>
<td>Previously reported as June 2016.</td>
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</tbody>
</table>
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ESTIMATED COST and IMPACT

COST

The cost of ertugliflozin is not yet known. The cost of other selected treatments for type 2 diabetes include[^1]:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Annual cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1,500mg oral once daily</td>
<td>£32.85</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>100mg oral once daily</td>
<td>£433.57</td>
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<tr>
<td>Glimepiride</td>
<td>4mg oral once daily</td>
<td>£12.90</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>10mg oral once daily</td>
<td>£475.67</td>
</tr>
</tbody>
</table>

IMPACT - SPECULATIVE

Impact on Patients and Carers
- [ ] Reduced mortality/increased length of survival
- [ ] Reduced symptoms or disability
- [ ] Other
- [ ] No impact identified

Impact on Health and Social Care Services
- [ ] Increased use of existing services
- [ ] Decreased use of existing services
- [ ] 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: uncertain unit cost compared to existing alternative treatment options.
- [ ] None identified

Other Issues
- [ ] Clinical uncertainty or other research question identified: expert opinion states that they believe ertugliflozin will add little to an already crowded field of SGLT2 inhibitors. Recent data suggest empagliflozin has a strong link with reduced cardiovascular events and mortality in patients with diabetes and high risk cardiovascular disease. Ertugliflozin will therefore have to demonstrate very significant benefits to be prescribed before other SGLT2 inhibitors[^2].
- [ ] None identified

[^1]: Reference
[^2]: Expert personal communication.
REFERENCES


