Empagliflozin for type 2 diabetes mellitus

April 2012

This technology summary 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.

The NIHR Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Empagliflozin for type 2 diabetes mellitus

Target group
- Type 2 diabetes mellitus.

Technology description
Empagliflozin (BI-10773) is a sodium glucose co-transporter type 2 (SGLT-2) inhibitor. It acts by blocking renal glucose re-absorption from the renal filtrate, thereby increasing urinary glucose excretion. SGLT-2 inhibitors are also associated with weight loss and reductions in blood pressure. Empagliflozin is intended to treat and improve the glycaemic control of adults with type 2 diabetes mellitus. In the phase III clinical trial, empagliflozin was administered orally at 10mg or 25mg once daily.

Empagliflozin is in phase III clinical trials for patients with type 2 diabetes and hypertension, a high risk of cardiovascular events or renal impairment, and is in phase II clinical trials for type 1 diabetes.

Innovation and/or advantages
If licensed, empagliflozin would offer an additional oral treatment option for patients with type 2 diabetes mellitus.

Developer
Boehringer-Ingelheim.

Availability, launch or marketing dates, and licensing plans
In phase III clinical trials.

NHS or Government priority area
This topic is relevant to The National Service Framework for Diabetes (2007).

Relevant guidance
Clinical need and burden of disease

The prevalence of diabetes in the UK is increasing, but not accurately known, and varies with factors including age, ethnic group and social deprivation. In 2010, the prevalence of diabetes (diagnosed and undiagnosed) in adults was estimated to be 7.4\% in England, which equates to 3,009,853 people above the age of 16 years. In Wales, the prevalence was estimated to be 9\%, equating to 218,956 people above the age of 16 years. More than 85\% of people with diabetes are expected to have type 2 diabetes and in 2009 it was estimated that there were 821,800 adults in England with diabetes who were not diagnosed. The prevalence of diabetes among adults is estimated to rise to 8.5\% by 2020 and 9.5\% by 2030.

In England in 2005, there were 26,300 deaths between the ages of 20 and 79 years which were registered as due to diabetes (11.6\% of all deaths in this age group). However, clinical coding practice means that only a minority of deaths among people with diabetes from causes that can be associated with the disease have diabetes identified as the primary cause of death. Life expectancy is reduced by up to 10 years in this patient group. Cardiovascular disease is a common complication of type 2 diabetes and a significant cause of death and disability, accounting for around 52\% of all deaths from diabetes. Other long-term complications associated with diabetes include: nephropathy, retinopathy and neuropathy, leading respectively to renal failure, reduced vision or blindness, and foot ulceration and amputation.

Existing comparators and treatments

Current treatment options, alone or in combination, include:

**Oral antidiabetic drugs**
- Metformin – first line.
- Sulphonylureas: gliclazide, glibenclamide, glipizide, tolbutamide, glimepiride.
- DPP-4 inhibitors: sitagliptin, vildagliptin, saxagliptin, linagliptin.
- Thiazolidinediones (glitazones): pioglitazone.
- Alpha-glucosidase inhibitors: acarbose.

**Injectable antidiabetic drugs**
- Short-acting insulin.
- Long-acting (basal) insulin.
- Insulin secretagogues: liraglutide, exenatide.

Current practice is that treatment with any agent other than insulin or sulphonylureas should aim to reduce the HbA1c level to as low as 6.5\%. Treatment with insulin or sulphonylureas should aim to achieve a target HbA1c level of 7% to avoid the risk of hypoglycaemia. For longer duration patients and those with co-morbidities such as cardiovascular disease and/or renal impairment, a target of 7.5\% is recommended. Current NICE guidelines recommend a target HbA1c of <6.5\% for first and second line therapy, with a target of <7.5\% for third or later line therapy.

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\(a\) Uncertainty limits 5.3\%-10.8\%.
\(b\) Uncertainty limits 6.9\%-11.9\%.
\(c\) Not currently licensed for use in combination with insulin.
\(d\) Glycosylated haemoglobin.
\(e\) Expert opinion.
### Efficacy and safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01177813, 2009-016243-20, 1245.20; empagliflozin vs placebo vs sitagliptin; phase III.</th>
<th>NCT01159600, 2009-016258-41, 1245.23; empagliflozin vs placebo, both with metformin alone or in combination with a sulfonylurea; phase III.</th>
<th>NCT01368081, 1245.52; empagliflozin with an oral antidiabetic drug vs metformin; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Boehringer Ingelheim Pharmaceuticals.</td>
<td>Boehringer Ingelheim Pharmaceuticals.</td>
<td>Boehringer Ingelheim Pharmaceuticals.</td>
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<tr>
<td>Source of information</td>
<td>Trial registry.</td>
<td>Trial registry.</td>
<td>Trial registry.</td>
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<tr>
<td>Location</td>
<td>EU, USA, Canada, India, China and Japan.</td>
<td>EU, USA, Canada and other countries.</td>
<td>Japan.</td>
</tr>
<tr>
<td>Participants and schedule</td>
<td>n=986 (planned); adults; type 2 diabetes mellitus; drug naive; HbA1c ≥7% and ≤10%. Randomised to empagliflozin, 10mg or 25mg; placebo; sitagliptin, 100mg; or empagliflozin open-label, 25mg. All administered orally once daily.</td>
<td>n=1,504; adults; type 2 diabetes mellitus; insufficient glycaemic control; pre-treatment with metformin or metformin with a sulfonylurea unchanged for 12 weeks prior to randomisation; HbA1c ≥7% and ≤11%. Randomised to empagliflozin, 10mg or 25mg; or empagliflozin open-label 25mg; or placebo. All administered orally once daily in combination with metformin ≥1,500mg daily or metformin with a sulfonylurea, administered at least half of the maximum recommended dose.</td>
<td>n=1,122 (planned), 20 years and older; type 2 diabetes mellitus; pre-treated with an oral anti-diabetic drug; HbA1c ≥7% and ≤10%. Randomised to empagliflozin, 10mg or 25mg oral once daily; or metformin, 500-2,250mg, oral daily.</td>
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<tr>
<td>Follow-up</td>
<td>Active treatment period 24 weeks.</td>
<td>Active treatment period 24 weeks.</td>
<td>Active-treatment period 52 weeks.</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>HbA1c.</td>
<td>HbA1c.</td>
<td>Adverse events (AEs); hypoglycaemic events; protocol specified significant AEs; cardiovascular events; change in BP; change in laboratory values.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Body weight; systolic and diastolic blood pressure (BP).</td>
<td>Body weight; mean change in daily plasma glucose; target response (HbA1c &lt;7%); relative efficacy response</td>
<td>HbA1c.</td>
</tr>
<tr>
<td>Expected reporting date</td>
<td>Previously reported as Mar 2012.</td>
<td>Previously reported as Feb 2012.</td>
<td>Estimated study completion date, Mar 2013.</td>
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<tr>
<td><strong>Trial</strong></td>
<td><strong>NCT01210001, 2009-016154-40, 1245.19; empagliflozin vs placebo, both with pioglitazone alone or with metformin; phase III.</strong></td>
<td><strong>NCT01167881, 2009-016244-39, 1245.28; empagliflozin vs glimepiride, both with metformin; phase III.</strong></td>
<td><strong>NCT01289990, 2010-022718-17, 1245.31; empagliflozin vs placebo, both with sitagliptin alone or with different background therapies; phase III extension.</strong></td>
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<tr>
<td><strong>Sponsor</strong></td>
<td>Boehringer Ingelheim Pharmaceuticals.</td>
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<tr>
<td><strong>Status</strong></td>
<td>Ongoing.</td>
<td>Ongoing.</td>
<td>Ongoing.</td>
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<td><strong>Location</strong></td>
<td>EU, USA, Canada and other countries.</td>
<td>EU (inc UK), USA, Canada and other countries.</td>
<td>EU, USA, Canada and other countries.</td>
</tr>
<tr>
<td><strong>Participants and schedule</strong></td>
<td>n=468 (planned); adults; type 2 diabetes mellitus; insufficient glycaemic control; pre-treatment with pioglitazone or pioglitazone with metformin unchanged for 12 weeks prior to randomisation; HbA1c ≥7% and ≤10%. Randomised to empagliflozin, 10mg or 25mg; or placebo. All administered orally once daily in combination with pioglitazone ≥30mg daily, alone or with metformin ≥1,500mg daily, unchanged throughout trial.</td>
<td>n=1,400; adults; type 2 diabetes mellitus; pre-treated with metformin 12 weeks prior to randomisation; HbA1c ≥7% and ≤10%. Randomised to empagliflozin 25mg; or glimepiride 1-4mg, both oral once daily with metformin ≥1,500mg daily.</td>
<td>n=1,920 (planned); adults; type 2 diabetes mellitus; completed trials NCT01210001, NCT01177813, NCT01159600. Empagliflozin 10mg, 25mg; or placebo, all oral once daily, each arm alone or in combination with pioglitazone, metformin, metformin and sulphonylurea, or sitagliptin monotherapy 100mg, oral once daily.</td>
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<tr>
<td><strong>Follow-up</strong></td>
<td>Active treatment period 24 weeks.</td>
<td>Active treatment period 104 weeks.</td>
<td>Active treatment period minimum of 76 weeks.</td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td>HbA1c.</td>
<td>HbA1c.</td>
<td>Safety; tolerability; AEs; changes in albumin/creatinine ratio; use of rescue therapy.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>FPG.</td>
<td>Body weight; BP; hypoglycaemic events; AEs; cardiovascular events.</td>
<td>HbA1c; body weight; waist circumference; FPG; composite endpoint of decrease in HbA1c by ≥0.5%, decrease in systolic BP by ≥3mmHg and decrease in body weight by &gt;2%; BP.</td>
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<td>Expected reporting date</td>
<td>Estimated study completion date, Apr 2012.</td>
<td>Estimated study completion date, Aug 2015.</td>
<td>Estimated study completion date, Apr 2013.</td>
</tr>
<tr>
<td>Trial</td>
<td>NCT01306214, 2010-019968-37, 1245.49; empagliflozin vs placebo, both with insulin alone or with metformin; phase III.</td>
<td>NCT01370005, 2011-000347-25, 1245.48; empagliflozin vs placebo; phase III.</td>
<td>NCT01164501, 2009-016179-31, 1245.36; empagliflozin vs placebo; phase III.</td>
</tr>
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<tr>
<td>Location</td>
<td>EU, USA and other countries.</td>
<td>EU, USA, Canada, Norway and Lebanon.</td>
<td>EU (inc UK), USA, Canada and other countries.</td>
</tr>
<tr>
<td>Participants and schedule</td>
<td>n=555 (planned); adults; type 2 diabetes mellitus; pre-treated with multiple daily injections of insulin alone or with stable metformin ≥1,500mg daily; HbA1c ≥7.5% and ≤10%. Randomised to empagliflozin, 10mg or 25mg; or placebo, all oral once daily with insulin or insulin with metformin, ≥1,500mg daily. Insulin dose unchanged for 18 weeks, then adjusted during weeks 19-40 to achieve defined glucose target levels. During weeks 41-50, background insulin dose kept unchanged except adjustments for safety reasons.</td>
<td>n=816 (planned); adults; type 2 diabetes mellitus; hypertension; HbA1c ≥7.0% and ≤10%; mean systolic BP 130-159mmHg and diastolic BP 80-99mmHg. Randomised to empagliflozin 10mg, 25mg; or placebo, all oral once daily.</td>
<td>n=682 (planned); adults; type 2 diabetes; renal impairment; estimated glomerular filtration rate of &lt;90ml/min; HbA1c ≥7.0% and ≤10%; pre-treated with any antidiabetic therapy and on maximum tolerated dose that has been unchanged for 12 weeks. Randomised to empagliflozin 10mg, 25mg; or placebo, all oral once daily in combination with pre-existing antidiabetic therapy.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment period 52 weeks.</td>
<td>Active treatment period 12 weeks.</td>
<td>Active treatment period 52 weeks.</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>HbA1c.</td>
<td>HbA1c; mean 24 hour systolic BP.</td>
<td>HbA1c.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Change in insulin dose; body weight; HbA1c.</td>
<td>Mean 24 hour diastolic BP; proportion of patients</td>
<td>-</td>
</tr>
</tbody>
</table>
with HbA1c <7%; FPG; body weight; daytime systolic and diastolic BP; night time systolic and diastolic BP; trough mean sitting systolic and diastolic BP; orthostatic BP; proportion of patients with BP <130/80mmHg; composite endpoint of decrease in HbA1c by ≥0.5%, decrease in systolic BP by ≥3mmHg and decrease in body weight by >2%.

<table>
<thead>
<tr>
<th>Expected reporting date</th>
<th>Estimated study completion date, Apr 2013.</th>
<th>Estimated study completion date, Jun 2012.</th>
<th>Estimated study completion date, Jul 2012.</th>
</tr>
</thead>
</table>

**Trial**

| NCT00749190, 2008-000641-54, 1245.10; empagliflozin vs placebo vs sitagliptin, all with metformin; phase II. |
| NCT00789035, 2008-000640-14, 1245.9; adults; empagliflozin vs placebo vs metformin; phase Ib. |

**Sponsor**

Boehringer Ingelheim Pharmaceuticals.

**Status**

Complete and published in abstract.

**Source of information**

Trial registry"*, abstract"**.

**Location**

EU, USA and other countries.

**Design**

Randomised, placebo-controlled.

**Participants and schedule**

n=495; adults; type 2 diabetes; stable metformin therapy of ≥1,500mg/day alone (HbA1c ≥7% and ≤10%) or with one other oral antidiabetic drug (HbA1c ≥6.5% and ≤9.0%). Randomised to empagliflozin 1mg, 5mg, 10mg, 25mg, 50mg; or placebo; all oral once daily; or sitagliptin open label, 100mg once daily. All arms with stable dose metformin as before trial entry.

n=408; adults; type 2 diabetes; HbA1c between 7% and 10%. Randomised to empagliflozin 5mg, 10mg, 25mg; or placebo, all oral once daily; or metformin, 1,000mg twice daily or maximum tolerated dose.

**Follow-up**

Active treatment period 12 weeks.

**Primary outcomes**

HbA1c.

**Secondary outcomes**

FPG; HbA1c; proportion with HbA1c ≤7%; HbA1c lowering >0.5%; fasting plasma insulin; body weight.

**Key results**

For empagliflozin 1mg, 5mg, 10mg, 25mg, 50mg and sitagliptin, respectively (p value vs placebo): HbA1c vs placebo, -0.24%, -0.39%, -0.71%, -0.70%, -0.64%, -0.58% (all p<0.05). Significant decrease in body weight reported with empagliflozin 5mg, 10mg, 25mg and 50mg vs placebo. Non-significant trend towards dose-dependent decrease in BP, greatest decrease on empagliflozin 25mg.

For empagliflozin 5mg, 10mg, 25mg and metformin, respectively (p values vs placebo): HbA1c vs placebo, -0.52%, -0.57%, -0.72%, -0.82% (all p<0.001); FPG (mg/dl), -23.3, -28.9, -31.1, -29.7 (all p<0.001); body weight (kg), -1.81 (p<0.001), -2.33 (p<0.001), -2.03 (p<0.001), -1.32 (p>0.05).

**Adverse AEs empagliflozin vs placebo vs AEs frequently reported included frequent**
effects (AEs) sitagliptin, respectively: frequent urination, 2.5% vs 1.4% vs 0%; urinary tract infection, 4.0% vs 2.8% vs 4.2%; genital infection, 4.0% vs 0% vs 2.8%; hypoglycaemia, 1.1% vs 0% vs 2.8%. urination, thirst and nasopharyngitis. Rates of hypoglycaemia similar between groups. Low incidence of genital infections and urinary tract infections.

Expected reporting date Previously reported as Oct 2009. Previously reported as Oct 2009.

Trial NCT00881530, 2008-007938-21, 1245.24; adults; empagliflozin vs sitagliptin vs metformin; phase II extension.

Sponsor Boehringer Ingelheim Pharmaceuticals.

Status Completed but unpublished.

Source of information Trial registry.

Location EU, USA and other countries.

Design Randomised, active-controlled.

Participants and schedule n=660 (planned); adults; type 2 diabetes; completed trial NCT00789035 or NCT00749190. Randomised to empagliflozin 10mg or 25mg, oral once daily; or sitagliptin 100mg, oral once daily; or metformin, 2,000mg, oral daily.

Follow-up Active treatment period 78 weeks.

Primary outcomes Safety; AEs; hypoglycaemic events; use of rescue therapy; vital signs; body weight; waist circumference; lipid parameters; clinical laboratory changes.

Secondary outcomes HbA1c; % treated to target <7%; FPG; additional treat to target response; relative efficacy response.

Expected reporting date Previously reported as May 2011.

Estimated cost and cost impact
The cost of empagliflozin is not yet known. The cost of selected comparator treatments are as follows:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>500mg oral three times daily.</td>
<td>£19.89 per year.</td>
</tr>
<tr>
<td>Sitagliptin (Januvia)</td>
<td>100mg oral once daily.</td>
<td>£432.38 per year.</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>5mg-15mg oral once daily.</td>
<td>£12.48-£37.44 per year.</td>
</tr>
<tr>
<td>Pioglitazone (Actos)</td>
<td>15-45mg oral once daily according to response.</td>
<td>£335.79-£514.15 per year.</td>
</tr>
<tr>
<td>Liraglutide (Victoza)</td>
<td>1.2-1.8mg subcutaneous injection once daily.</td>
<td>£941.76-£1,412.64 per year.</td>
</tr>
<tr>
<td>Insulin (Actrapid)</td>
<td>According to blood glucose.</td>
<td>£7.48 per 1,000 units.</td>
</tr>
<tr>
<td>Insulin glargine (Lantus)</td>
<td>According to blood glucose.</td>
<td>£30.68 per 1,000 units</td>
</tr>
</tbody>
</table>

Claimed or potential impact – speculative

Patients
☐ Reduced mortality or increased length of survival
☐ Reduction in associated morbidity or improved quality of life for patients and/or carers
☐ Quicker, earlier or more accurate diagnosis or identification of disease
☐ Other:
☐ None identified
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Services

☐ Increased use
☐ Service organisation
☐ Staff requirements

☐ Decreased use
☐ Other:
☑️ None identified

Costs

☐ Increased unit cost compared to alternative

☑️ New costs: Additional treatment option.

☐ Increased costs: more patients coming for treatment

☐ Increased costs: capital investment needed

☐ Savings:

☐ Other:

Other issues

☑️ Clinical uncertainty or other research question identified: Expert opinion suggests there remains clinical uncertainty regarding the long-term adverse effects on the kidney, the mechanism of blood pressure lowering and the increased risk of genital or urinary infections. There are potential safety concerns in patients who are fluid depleted and careful study will also be needed following concerns that SGLT-2 inhibitors may increase the incidence of cancers.

References

33. Ferrannini E, Seman LJ, Seewaldt-Becker E et al. The potent and highly selective sodium-glucose co-transporter (SGLT-2) inhibitor BI 10773 is safe and efficacious monotherapy in patients with type 2 diabetes mellitus. ESAD 2010; Abstract 877.