

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**  
**Health Technology Appraisal**

**Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating  
type 2 diabetes**

**Final scope**

**Appraisal objective<sup>1</sup>**

To appraise the clinical and cost effectiveness of canagliflozin, dapagliflozin and empagliflozin monotherapy within their licensed indications for treating type 2 diabetes.

**Background**

Diabetes mellitus is a chronic metabolic disorder characterised by elevated blood glucose levels (hyperglycaemia) resulting from a lack of the hormone insulin or resistance to its action. Type 2 diabetes results from reduced insulin secretion or reduced tissue sensitivity to insulin (known as insulin resistance). If not managed effectively, diabetes mellitus can lead to kidney failure, blindness, limb amputation, and damage to the nervous system, peripheral vasculature and skin. Cardiovascular disease is the most common complication of type 2 diabetes and is the greatest cause of morbidity and premature death. Life expectancy is reduced by up to 10 years in people with diabetes.

There were approximately 2.7 million people aged 17 and over in England with diagnosed diabetes mellitus in 2013, of whom 90% had type 2 diabetes. However, many people with type 2 diabetes are undiagnosed, and so the number of people with the condition may be higher than reported. The UK prevalence of type 2 diabetes is rising because of increased prevalence of obesity, decreased physical activity and increased life expectancy after diagnosis because of better cardiovascular risk protection. Type 2 diabetes is particularly prevalent in people of African, South Asian and Caribbean family origin.

NICE clinical guideline (CG) 87 (a partial update of CG66) 'the management of type 2 diabetes' recommends dietary advice and increasing physical activity for all people with type 2 diabetes. If blood glucose is not adequately controlled by lifestyle interventions alone, the guideline recommends one or more oral anti-diabetic drugs, beginning with metformin. Alternatively, a sulfonylurea or rapid acting insulin secretagogue may be considered if metformin is unsuitable. A draft update to CG87, currently undergoing consultation, recommends considering repaglinide as the initial drug treatment

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<sup>1</sup> NICE has separate remits for 3 drugs to: appraise canagliflozin within its licensed indication for the treatment of type 2 diabetes; appraise dapagliflozin within its licensed indication for the treatment of type 2 diabetes; and appraise empagliflozin within its licensed indication for treating type 2 diabetes. To date NICE has only considered these drugs in combination therapy.

if metformin is unsuitable, and, if treatment with repaglinide does not control HbA1c, then pioglitazone, a sulfonylurea or a dipeptidyl peptidase-4 (DPP-4) inhibitor may be used. If blood glucose is not adequately controlled following monotherapy, dual therapy should be considered followed by either the addition of insulin or triple therapy.

**The technology**

Canagliflozin (Invokana, Janssen), dapagliflozin (Forxiga, AstraZeneca) and empagliflozin (Jardiance, Boehringer-Ingelheim and Lilly UK) are all selective sodium glucose-cotransporter 2 (SGLT-2) inhibitors, which block the reabsorption of glucose in the kidneys and promote excretion of excess glucose in the urine. Through this mechanism, canagliflozin, dapagliflozin and empagliflozin may help control glycaemia independently of insulin pathways. They are all administered orally.

Canagliflozin has a UK marketing authorisation for treatment “in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications”.

Dapagliflozin has a UK marketing authorisation for treatment “in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance”.

Empagliflozin has a UK marketing authorisation for the “treatment of type 2 diabetes mellitus to improve glycaemic control in adults as monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance”.

<b>Intervention(s)</b>	<ul style="list-style-type: none"> <li>• Canagliflozin monotherapy</li> <li>• Dapagliflozin monotherapy</li> <li>• Empagliflozin monotherapy</li> </ul>
<b>Population(s)</b>	People with type 2 diabetes for whom metformin is not tolerated or is contraindicated.

<b>Comparators</b>	<p>The following interventions as monotherapy:</p> <ul style="list-style-type: none"> <li>• Repaglinide</li> <li>• Sulfonylureas</li> <li>• Pioglitazone</li> <li>• DPP-4 inhibitors</li> <li>• The SGLT-2 inhibitors will be compared with each other</li> </ul>
<b>Outcomes</b>	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> <li>• mortality</li> <li>• complications of diabetes, including cardiovascular, renal and eye</li> <li>• HbA1c/glycaemic control</li> <li>• body mass index</li> <li>• frequency and severity of hypoglycaemia</li> <li>• changes in cardiovascular risk factors</li> <li>• adverse effects of treatment, including urinary tract infections, genital infections and malignancies</li> <li>• health-related quality of life.</li> </ul>
<b>Economic analysis</b>	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p>
<b>Other considerations</b>	<p>Guidance will only be issued in accordance with the marketing authorisation.</p>

<p><b>Related NICE recommendations and NICE Pathways</b></p>	<p>Related Technology Appraisals:</p> <p>Technology Appraisal No. 315, Jun 2014, 'Canagliflozin in combination therapy for treating type 2 diabetes'. Review proposal date May 2017.</p> <p>Technology Appraisal No. 288, Jun 2013, 'Dapagliflozin in combination therapy for treating type 2 diabetes'. Review Proposal Date TBC.</p> <p>Technology Appraisal No. 248, Feb 2012, 'Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes'. To be updated within update of CG87.</p> <p>Technology Appraisal No. 203, Oct 2010, 'Liraglutide for the treatment of type 2 diabetes mellitus'. To be updated within update of CG87.</p> <p>Technology appraisal in preparation, 'Empagliflozin combination therapy for treating type 2 diabetes'. Earliest anticipated date of publication Mar 2015.</p> <p>Related Guidelines:</p> <p>Clinical Guideline No. 87, May 2009, 'Type 2 diabetes – newer agents (partial update of CG66)'. Review in preparation. Publication date Aug 2015.</p> <p>Clinical Guideline No. 66, May 2008, 'Type 2 diabetes: the management of type 2 diabetes (update)'. Review in preparation. Publication date Aug 2015.</p> <p>Clinical Guideline No. G, Oct 2002, 'Management of type 2 diabetes – managing blood glucose levels'. Replaced by CG66 and CG87.</p> <p>Related Quality Standards:</p> <p>Quality Standard No. 6, Mar 2011, 'Diabetes in adults'.</p> <p>Related NICE Pathways:</p> <p>NICE Pathway: Diabetes, Pathway created: May 2011:  <a href="https://pathways.nice.org.uk/pathways/diabetes">https://pathways.nice.org.uk/pathways/diabetes</a>.</p>
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<p><b>Related National Policy</b></p>	<p>NHS England Manual for Prescribed Specialised Services ‘Insulin-resistant diabetes service (adults and children)’, section 67 (page 157).  <a href="http://www.england.nhs.uk/wp-content/uploads/2012/12/pss-manual.pdf">http://www.england.nhs.uk/wp-content/uploads/2012/12/pss-manual.pdf</a></p> <p>The national Program of Care for Internal Medicine (group A) covers ‘Specialised Diabetes’, which includes people with insulin-resistant diabetes.  <a href="http://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-a/a17/">http://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-a/a17/</a></p> <p>National Service Framework: Diabetes, Dec 2001.  <a href="https://www.gov.uk/government/publications/national-service-framework-diabetes">https://www.gov.uk/government/publications/national-service-framework-diabetes</a></p>
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