NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE
Health Technology Appraisal

Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes

Draft scope (pre-referral)

Appraisal objective[1]

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 87 (a partial update of clinical guideline 66) '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 if the person is overweight. Alternatively:

- a sulfonylurea may be considered if

[1] 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.

    - the person is not overweight
    - metformin is not tolerated or is contraindicated, or
    - a rapid therapeutic response is required because of hypoglycaemic symptoms
- metformin may be considered even if the person is not overweight
- a rapid acting insulin secretagogue may be considered for a person with an erratic lifestyle
- acarbose may be considered if a person is unable to use other oral-glucose lowering agents.

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”.

Intervention(s)	• Canagliflozin monotherapy • Dapagliflozin monotherapy • Empagliflozin monotherapy

Population(s)	People with type 2 diabetes for whom metformin is not tolerated or is contraindicated.
Comparators	• Sulfonylureas • The SGLT-2 inhibitors will be compared with each other
Outcomes	The outcome measures to be considered include: • mortality • complications of diabetes, including cardiovascular, renal and eye • HbA1c/glycaemic control • body mass index • frequency and severity of hypoglycaemia • changes in cardiovascular risk factors • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. 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. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation.

Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Technology Appraisal No. 288, Jun 2013, 'Dapagliflozin in combination therapy for treating type 2 diabetes'. Review Proposal Date Dec 2014 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. Technology Appraisal No. 203, Oct 2010, 'Liraglutide for the treatment of type 2 diabetes mellitus'. To be updated within update of CG87. Technology appraisal in preparation, 'Empagliflozin combination therapy for treating type 2 diabetes'. Earliest anticipated date of publication Dec 2014. Technology appraisal in preparation, 'Canagliflozin in combination therapy for treating type 2 diabetes'. Earliest anticipated date of publication June 2014. Related Guidelines: Clinical Guideline No. 87, May 2009, 'Type 2 diabetes – newer agents (partial update of CG66)'. Review in preparation. Publication date Aug 2015. Clinical Guideline No. 66, May 2008, 'Type 2 diabetes: the management of type 2 diabetes (update)'. Review in preparation. Publication date Aug 2015. Clinical Guideline No. G, Oct 2002, 'Management of type 2 diabetes – managing blood glucose levels'. Replaced by CG66 and CG87. Related Quality Standards: Quality Standard No. 6, Mar 2011, 'Diabetes in adults'. Related NICE Pathways: NICE Pathway: Diabetes, Pathway created: May 2011: https://pathways.nice.org.uk/pathways/diabetes.

Related National Policy	NHS England Manual for Prescribed Specialised Services 'Insulin-resistant diabetes service (adults and children)', section 67 (page 157). http://www.england.nhs.uk/wp-content/uploads/2012/12/pss-manual.pdf The national Program of Care for Internal Medicine (group A) covers 'Specialised Diabetes', which includes people with insulin-resistant diabetes. http://www.england.nhs.uk/ourwork/commissioning/spec-services/npc-crg/group-a/a17/ National Service Framework: Diabetes, Dec 2001. https://www.gov.uk/government/publications/national-service-framework-diabetes

Questions for consultation

Have all relevant comparators for canagliflozin, dapagliflozin and empagliflozin been included in the scope?

- Which treatments are considered to be established clinical practice in the NHS for use as monotherapy in type 2 diabetes?
- Should rapid acting insulin secretagogues, acarbose or DPP-4 inhibitors be included as comparators?

Are there any subgroups of people in whom canagliflozin, dapagliflozin and empagliflozin are expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider canagliflozin, dapagliflozin and empagliflozin will fit into the existing NICE pathway, diabetes?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which canagliflozin, dapagliflozin and empagliflozin are licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider canagliflozin, dapagliflozin and empagliflozin to be innovative in their potential to make a significant and substantial impact on health-related benefits and how they might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of canagliflozin, dapagliflozin and empagliflozin can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.