NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Empagliflozin for reducing the risk of death from cardiovascular disease in people with type 2 diabetes

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of empagliflozin within its marketing authorisation for reducing the risk of death from cardiovascular disease in people with type 2 diabetes.

Background

Type 2 diabetes is a chronic metabolic condition characterised by insulin resistance (that is, the body's inability to effectively use insulin) and insufficient pancreatic insulin production, resulting in high blood glucose levels (hyperglycaemia). It is commonly associated with obesity, physical inactivity, raised blood pressure, disturbed blood lipid levels and a tendency to develop thrombosis, and therefore is recognised to have an increased cardiovascular risk. It is also associated with long-term microvascular and macrovascular complications, together with reduced quality of life and life expectancy.

In 2015, there were approximately 2.9 million adults in England with diabetes, of whom 90% had type 2 diabetes[1]. However, many people with type 2 diabetes are undiagnosed, and so the number of people with the condition may be higher than reported. The 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. Cardiovascular disease (CVD) is a major cause of death and disability in people with diabetes and accounts for 52% of deaths.[1]

NICE guideline (NG) 28 'Type 2 diabetes in adults: management' recommends an individualised approach to diabetes care that is tailored to the needs and circumstances of adults with type 2 diabetes. It recommends beginning with dietary advice and increasing physical activity. 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 blood glucose is not adequately controlled following monotherapy, dual therapy with metformin and another oral drug (a dipeptidyl peptidase-4 (DPP-4) inhibitor, pioglitazone or a sulfonylurea) should be considered, followed by insulin-based treatment or triple therapy (such as metformin with: a DPP-4 inhibitor and a sulfonylurea, and; pioglitazone and a sulfonylurea). Selective sodium glucose-cotransporter 2 (SGLT-2) inhibitors are also recommended by NICE for some people with type 2 diabetes: technology appraisal (TA) 390 recommends canagliflozin, dapagliflozin and empagliflozin monotherapies as

options in adults for whom metformin is contraindicated or not tolerated, and if a DPP-4 inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate. These treatments are also recommended in TA 315, TA 288, and TA 336, respectively, as options in a dual therapy regimen with metformin if a sulfonylurea is contraindicated or not tolerated, or the person is at significant risk of hypoglycaemia or its consequences; and as options in combination with insulin, with or without other antidiabetic drugs. In addition, canagliflozin and empagliflozin are recommended in triple therapy regimens with metformin and a sulfonylurea or a thiazolidinedione.

Lipid modification therapy for the primary and secondary prevention of CVD is also recommended for some people with type 2 diabetes. NICE clinical guideline 181 on CVD recommends atorvastatin for people with type 2 diabetes who have a 10% or greater 10-year risk of developing CVD and for people who have CVD. This is in addition to lifestyle interventions such as changes to diet, physical activity, smoking and alcohol consumption.

The technology

Empagliflozin (Jardiance, Boehringer Ingelheim and Eli Lilly) is a SGLT-2 inhibitor, which lowers blood glucose in people with type 2 diabetes by blocking the reabsorption of glucose in the kidneys and promoting excretion of excess glucose in the urine. It is administered orally.

Empagliflozin does not currently have a marketing authorisation in the UK for reducing the risk of death from CVD in people with type 2 diabetes. It has been studied in a randomised, placebo-controlled trial in adults with type 2 diabetes who have established CVD, in addition to standard care.

Empagliflozin has a marketing authorisation in the UK for treating type 2 diabetes to improve glycaemic control in adults: as monotherapy when metformin is considered inappropriate, and with other glucose–lowering medicinal products when these do not provide adequate glycaemic control.

Intervention(s)	Empagliflozin
Population(s)	People with type 2 diabetes who have established cardiovascular disease
Comparators	Established clinical management without empagliflozin

Outcomes	The outcome measures to be considered include: • fatal and non-fatal cardiovascular events including myocardial infarction and stroke • other complications of diabetes, including renal and eye • HbA1c/glycaemic control • mortality • 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. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: 'Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes (2016). NICE technology appraisal 390. Review date May 2019. 'Empagliflozin in combination therapy for treating type 2 diabetes' (2015). NICE technology appraisal 336. Review date March 2018. Canagliflozin in combination therapy for treating type 2 diabetes' (2014). NICE technology appraisal 315. Review date May 2017. **'**Dapagliflozin in combination therapy for treating type 2 diabetes' (2013). NICE technology appraisal 288. Review date June 2016. Appraisals in development (including suspended

	appraisals): 'Cardiovascular events (reducing, high risk) – ticagrelor' NICE technology appraisal ID813. Publication expected December 2016. Related Guidelines: 'Type 2 diabetes in adults: management' (2015). NICE guideline 28. Review date December 2017. 'Cardiovascular disease: risk assessment and reduction, including lipid modification' (2014). Clinical guideline 181. Review date 2018. Related public health guidelines: 'Type 2 diabetes prevention: population and community-level interventions' (2011). NICE public health guideline 35. 'Type 2 diabetes: prevention in people at high risk (2012). NICE public health guideline 38. Related Quality Standards: 'Diabetes in adults' (2011). NICE quality standard QS6. Related NICE Pathways: Diabetes (2011). NICE pathway.
Related National Policy	Department of Health (2016) 'NHS Outcomes Framework 2015-2016'. Domains 1 to 5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017. NHS England (2016) 'Manual for Prescribed Specialist Services'. Chapter 67. https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/06/pss-manual-may16.pdf NHS England (2014) Action on diabetes https://www.england.nhs.uk/wp-content/uploads/2014/01/act-for-diabetes.pdf

Questions for consultation

- Are the comparators included in the scope appropriate? Have all relevant comparators for empagliflozin been included? Which treatments are considered to be established clinical practice in the NHS for reducing the risk of death from cardiovascular disease in people with type 2 diabetes?

- Would treatment with empagliflozin (for reducing the risk of death from cardiovascular disease in people with type 2 diabetes) be expected to displace any existing treatments, or would it be given in addition to existing treatments?

- Are the outcomes listed appropriate?

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

- Where do you consider 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 empagliflozin will be 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 empagliflozin to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it 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 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.

- NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's

Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction)

References

1. Diabetes UK. Facts and Stats November 2015. https://www.diabetes.org.uk/Documents/Position%20statements/Diabetes%20UK%20Facts%20and%20Stats_Dec%202015.pdf. Accessed 06 October 2016.