NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Empagliflozin for treating type 2 diabetes

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of empagliflozin within its licensed indication 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) plus a failure of insulin secretion to compensate for this and is associated with obesity and an increased cardiovascular risk. If not managed effectively, diabetes mellitus can lead to complications including 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.

There were approximately 2.9 million people in the UK aged 17 or over with diabetes mellitus in 2011, 90% of which had type 2 diabetes; however, there are many people with undiagnosed type 2 diabetes so this rate could be considerably higher. The prevalence of type 2 diabetes in the UK is rising due to the increased prevalence of obesity and decreased physical activity, but also increased longevity after diagnosis due to better cardiovascular risk protection. Type 2 diabetes is particularly prevalent in people of African, South Asian and Caribbean family origin. Life expectancy is reduced by up to 10 years in people with diabetes.

NICE clinical guideline no. 87 ‘Type 2 diabetes- newer agents’ recommends diet modifications to initially manage type 2 diabetes. If the disease progresses one or more oral anti-diabetic drugs, such as metformin or a sulfonylurea may be needed. If one of these drugs is not suitable, a thiazolidinedione (pioglitazone) or a dipeptidyl peptidase-4 (DPP-4) inhibitor (incretin enhancer) such as sitagliptin or vildagliptin can be used as an add-on therapy to metformin or a sulfonylurea as appropriate. The glucagon-like peptide-1 (GLP-1) analogues (exenatide and liraglutide) are recommended in NICE technology appraisals nos. 203 and 248 as options for dual therapy where metformin or a sulfonylurea is not tolerated or contraindicated and a thiazolidinedione and a DPP-4 inhibitor is contraindicated or not tolerated. For people whose disease is not controlled on dual therapy, triple therapy may be considered. This may include the twice daily or the prolonged release regimens of exenatide (an incretin mimetic) in accordance with clinical guideline no. 87 and technology appraisal no. 248. Liraglutide is

recommended in NICE technology appraisal no. 203 as a triple therapy if it is used as described for exenatide in clinical guideline no. 87. NICE clinical guideline no. 87 also recommends either sitagliptin or pioglitazone as options for adding onto metformin and sulfonylurea. Insulin therapy is recommended when the control of blood glucose remains or becomes inadequate with all other measures, or when blood glucose remains markedly high with dual therapy.

The technology

Empagliflozin (brand name unknown, Boehringer-Ingelheim) is a selective sodium glucose-cotransporter 2 (SGLT-2) inhibitor which blocks the reabsorption of glucose in the kidneys and promotes excretion of excess glucose in the urine. Empagliflozin is administered orally.

Empagliflozin does not have a UK marketing authorisation for the treatment of type 2 diabetes. It is being studied in clinical trials in adults with type 2 diabetes who have inadequate glycaemic control on a number of different regimens:

- For those on diet and exercise alone (drug naive patients), empagliflozin alone or in combination with metformin is being compared with metformin alone. It has also been compared with sitagliptin and placebo. It was also studied in fixed dose combination with linagliptin.

- For those on metformin monotherapy,

  - empagliflozin has been compared with glimepiride as an add on therapy

  - empagliflozin alone or in combination with linagliptin is being compared to linagliptin alone and placebo as an add on therapy.

- For those on monotherapy with any oral antidiabetic drug other than metformin, empagliflozin has been compared with metformin as an add on treatment.

- For those on metformin or metformin plus sulfonylurea, empagliflozin has been compared with placebo as an add on therapy

- For those on pioglitazone alone or in combination with metformin, empagliflozin has been compared with placebo as an add-on therapy.

- For those on insulin alone or in combination with metformin, empagliflozin is being compared to placebo as an add-on to insulin regimen.

Intervention(s)	Empagliflozin alone or in combination with oral anti-diabetic agents and/or insulin
Population(s)	**Monotherapy** Adults with type 2 diabetes that is inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance **Dual therapy** Adults with type 2 diabetes that is inadequately controlled on monotherapy with either metformin or a sulfonylurea. **Triple therapy** Adults with type 2 diabetes that is inadequately controlled on dual therapy with either: • metformin in combination with a sulfonylurea • metformin or a sulfonylurea in combination with a thiazolidinedione, a DPP-4 inhibitor, or a GLP-1 analogue. **Add-on therapy to insulin** Adults with type 2 diabetes that is inadequately controlled on monotherapy with insulin or on therapy with insulin and up to two other oral agents.
Comparators	**Monotherapy** • Sulfonylurea **Dual therapy** For the combination of empagliflozin and metformin, the comparators are: • sulfonylureas (with metformin) • pioglitazone (with metformin) • DPP-4 inhibitors (with metformin) • GLP-1 analogues (with metformin) • dapagliflozin or canagliflozin (with metformin) (subject to NICE appraisals). For the combination of empagliflozin and sulfonylurea, the comparators are: • pioglitazone (with a sulfonylurea) • DPP-4 inhibitors (with a sulfonylurea) • GLP-1 analogues (with a sulfonylurea) • dapagliflozin or canagliflozin (with a

	sulfonylurea) (subject to NICE appraisals). **Triple therapy** For the combination of empagliflozin, metformin and a sulfonylurea, the comparators are: • pioglitazone (with metformin and a sulfonylurea) • DPP-4 inhibitors (with metformin and a sulfonylurea) • GLP-1 analogues (with metformin and a sulfonylurea) • dapagliflozin or canagliflozin (with metformin and a sulfonylurea) (subject to NICE appraisals) • insulin (with metformin and a sulfonylurea) For the combination of empagliflozin, metformin and pioglitazone, the comparators are: • DPP-4 inhibitors (with metformin and pioglitazone) • GLP-1 analogues (with metformin and pioglitazone) • dapagliflozin or canagliflozin (with metformin and pioglitazone) (subject to NICE appraisals) • insulin (with metformin and pioglitazone). For the use of empagliflozin in any other triple therapy regimen, the comparator is • insulin (alone or in combination with one or more oral anti-diabetic agents). **Add-on therapy to insulin** • one or more oral anti-diabetic agents (in combination with insulin).

Outcomes	The outcome measures to be considered include: • HbA1c/glycaemic control • frequency and severity of episodes of hypoglycaemia • change in cardiovascular risk factors (including blood pressure and/or serum lipids) • weight change • complications of diabetes e.g. cardiovascular, renal and eye • mortality • adverse effects of treatment (including genitourinary tract infection) • 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	If evidence allows, following subgroups will be considered: • body mass index • HbA1c Guidance will only be issued in accordance with the marketing authorisation. *Subject to referral by the Department of Health, the invite for participation in this technology appraisal is anticipated for after January 2014, when new arrangements for the pricing of pharmaceuticals are expected to be in place. Consequences for this appraisal will be explored through further consultation on the scope pre invitation.*

Related NICE recommendations	Related Technology Appraisals: Technology Appraisal No.248, February 2012. 'Diabetes (type 2) – exenatide (prolonged release)'. Review ongoing: included in update of Clinical Guidelines No. 66 and 87. Publication date TBC. Technology Appraisal No. 203, October 2010, 'Liraglutide for the treatment of type 2 diabetes. Review ongoing: included in update of Clinical Guidelines No. 66 and 87. Publication date TBC. Technology Appraisal No.151, July 2008, 'Continuous subcutaneous insulin infusion for the treatment of diabetes (review) '. Guidance on static list. Technology Appraisal in Preparation, 'Dapagliflozin for the treatment of type 2 diabetes' Earliest anticipated date of publication June 2013 Technology Appraisal in Preparation, 'Canagliflozin for the treatment of type 2 diabetes' Earliest anticipated date of publication June 2014. Related Guidelines: Clinical Guideline No. 87 (partial update of Clinical Guideline No. 66), May 2009 'Type 2 diabetes-newer agents' Review ongoing. Publication TBC. Clinical Guideline No. 66 (partially updated by Clinical Guideline No. 87), May 2008 'Type 2 diabetes: full guideline' Review ongoing. Publication TBC. Related Quality Standards Quality Standard No.6, March 2011 'Diabetes in adults'. Review Proposal Date: March 2016 http://publications.nice.org.uk/diabetes-in-adults-quality-standard-qs6 Related NICE Pathways NICE Pathway: Diabetes, Pathway created: May 2011(last updated January 2013) http://pathways.nice.org.uk/pathways/diabetes

Questions for consultation

Is it appropriate to include the use of empagliflozin as monotherapy in the scope?

The comparators in the scope include combinations that are reflected in NICE guidance or NICE clinical guidelines. Have the most appropriate comparators for empagliflozen for the treatment of type 2 diabetes been included in the scope? Are the comparators listed routinely used in clinical practice?

Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately?

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 the technology 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 the technology 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

Where do you consider empagliflozin will fit into the existing NICE pathway: Diabetes (http://pathways.nice.org.uk/pathways/diabetes)?

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/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp)