Appendix B

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Empagliflozin combination therapy for treating type 2 diabetes

Final scope

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 whom 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. NICE technology appraisal no. 288 recommends dapagliflozin in a dual therapy regimen in combination with metformin and in combination with insulin with or without other antidiabetic drugs.

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.

Intervention(s)	Empagliflozin in combination with oral anti-diabetic agents and/or insulin
Population(s)	**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 one or more other oral agents.

Comparators	**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 (with metformin). 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) **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) • 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) • 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 estimated glomerular filtration rate, albumin creatinine ratio, 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: • baseline body mass index • baseline HbA1c Guidance will only be issued in accordance with the marketing authorisation.

Related NICE recommendations	Related Technology Appraisals: Technology Appraisal No.288, June 2013, 'Dapagliflozin in combination therapy for treating type 2 diabetes'. Review Proposal Date December 2014 Technology Appraisal No.248, February 2012. 'Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes'. Review ongoing: included in update of Clinical Guidelines No. 66 and 87. Publication date August 2015. 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 August 2015. Technology Appraisal No.151, July 2008, 'Continuous subcutaneous insulin infusion for the treatment of diabetes (review)'. Guidance on static list. 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 August 2015. Clinical Guideline No. 66 (partially updated by Clinical Guideline No. 87), May 2008 'Type 2 diabetes: full guideline' Review ongoing. Publication August 2015. 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 November 2013) http://pathways.nice.org.uk/pathways/diabetes