NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Proposed Health Technology Appraisal

Dapagliflozin for the treatment of type 2 diabetes

Draft scope (Pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of dapagliflozin within its licensed indication for the treatment of 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. There are two main types of diabetes: Type 1 diabetes is due to an absolute loss of insulin production and therefore administration of insulin is necessary for survival. Type 2 diabetes is associated with obesity and results from reduced tissue sensitivity to insulin (known as insulin resistance) plus a failure of insulin secretion to compensate for this.

In people with untreated type 2 diabetes, typical symptoms are excessive production of urine (polyuria), thirst, weight loss and fatigue. Type 2 diabetes is associated with an increased cardiovascular risk. This can manifest as coronary artery disease (heart attacks, angina), peripheral artery disease (leg claudication, gangrene), and carotid artery disease (strokes, dementia). If not managed effectively, diabetes can also lead to complications including kidney failure, blindness, limb amputation, and damage to the nervous system, peripheral vasculature and skin.

There were approximately 2.8 million people in the UK with diabetes mellitus in 2010, 85% 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 increasing 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. Cardiovascular disease is the most common complication of type 2 diabetes and is the greatest cause of morbidity and premature death.

NICE clinical guideline no. 66 ‘The management of type 2 diabetes’ recommends diet modifications to initially manage type 2 diabetes. If the disease progresses one or more oral antidiabetic drugs, such as metformin or a sulphonylurea may be needed. If patients are unable to tolerate these drugs as combination therapy, or if one of the drugs is contraindicated, or where the combination is considered ineffective, a thiazolidinedione (pioglitazone) can

be used as an add-on therapy to metformin and/or a sulphonylurea as appropriate. Other options for dual and triple therapy include glucagon-like peptide-1 analogues (incretin mimetics) and dipeptidyl peptidase-4 (DPP-4) inhibitors (incretin enhancers). Exenatide (twice daily), an incretin mimetic, is recommended in NICE clinical guideline no. 87 (CG87, 'Type 2 diabetes – newer agents') as an option for triple therapy for people with a high body mass index (>35 kg/m^2) in those of European descent (with an adjustment for other ethnic groups) where certain criteria are met, and blood glucose control remains/becomes inadequate on metformin and sulfonylurea treatment. It is also recommended for use in patients with a body mass index less than 35 kg/m^2 if therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related co-morbidities. Liraglutide is recommended in NICE technology appraisal no. 203 as a triple therapy for the treatment of type 2 diabetes if it is used as described for exenatide in CG87. Insulin therapy is recommended in CG87 when the control of blood glucose remains or becomes inadequate with all other measures.

The technology

Dapagliflozin (Brand name unknown, Bristol-Myers Squibb and AstraZeneca) is a 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. Through this mechanism, dapagliflozin may help control glycaemia independently of insulin pathways. Dapagliflozin is administered orally.

Dapagliflozin does not have a UK marketing authorisation for the treatment of type 2 diabetes. It has been studied in clinical trials as monotherapy compared with placebo in adults with type 2 diabetes who have inadequate glycaemic control with diet and exercise. It has also been studied as dual therapy in combination with metformin, insulin, glipizide or a thiazolidinedione compared with placebo in adults with type 2 diabetes that is inadequately controlled on metformin, insulin, glipizide or thiazolidinione monotherapy, respectively.

Intervention(s)	• Dapagliflozin monotherapy • Dapagliflozin as dual therapy in combination with either metformin, a sulphonylurea, a thiazolidinedione or insulin
Population(s)	**Monotherapy** Adults with type 2 diabetes that is inadequately controlled despite lifestyle modifications **Dual therapy** Adults with type 2 diabetes that is inadequately controlled on monotherapy with either metformin, a sulphonylurea, a thiazolidinedoine or insulin at the maximal tolerated dose
Comparators	**Monotherapy** • Metformin • Sulphonylureas (including gliclazide, glibenclamide, glipizide, chloropropamide, tolbutamide, glimepiride) **Dual therapy** The following agents used in combination, in accordance with their marketing authorisations: • Metformin • Sulphonylureas (including gliclazide, glibenclamide, glipizide, chloropropamide, tolbutamide, glimepiride) • Thiazolidinediones (pioglitazone) • Dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin, vildagliptin, saxagliptin) • Insulins and insulin analogues

Outcomes	The outcome measures to be considered include: • HbA1c/glycaemic control • Frequency and severity of episodes of hypoglycaemia • Weight change and its consequences • Complications of diabetes e.g. cardiovascular, renal and eye • 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	If evidence allows, subgroups based on the following criteria will be considered: • Body mass index • HbA1c Guidance will only be issued in accordance with the marketing authorisation.

Related NICE recommendations	Related Technology Appraisals: Technology Appraisal No 203, October 2010, 'Liraglutide for the treatment of type 2 diabetes. Review date May 2012. Technology appraisal No.151, July 2008, 'Continuous subcutaneous insulin infusion for the treatment of diabetes (review)'. Review date February 2011. Technology appraisal No.60, April 2003, 'Diabetes (types 1 and 2) - patient education models'. Recommendations on type 2 diabetes updated within Clinical Guideline 66. Technology appraisal No.53, December 2002, 'Diabetes (types 1 and 2) - long acting insulin analogues'. Recommendations on type 2 diabetes updated within Clinical Guideline 66. Technology Appraisal in Preparation, 'Long-acting exenatide for the second-line (dual therapy) or third-line (triple therapy) treatment of type 2 diabetes. Earliest date of publication TBC. Related Guidelines: Clinical Guideline No. 87, May 2009, 'Type 2 diabetes: newer agents (partial update of CG 66)'. Clinical Guideline No. 66, May 2008, 'Type 2 diabetes: the management of type 2 diabetes'. This guideline replaces TA53 and TA63. Clinical Guideline No. 63, March 2008, 'Diabetes in pregnancy: management of diabetes and its complications from pre-conception to the postnatal period'. Clinical Guideline No. 10, January 2004, 'Type 2 diabetes: prevention and management of foot problems'.

Questions for consultation

Is dapagliflozin more likely to be used as monotherapy or dual therapy in routine clinical practice?

Have the most appropriate comparators for the treatment of type 2 diabetes been included in the scope? Are the comparators listed routinely used in clinical practice?

- Should liraglutide be included as a comparator for dual therapy considering the restricted recommendation for its use within NICE technology appraisal no. 203?

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?

What do you consider to be the relevant clinical outcomes and other potential health related benefits of dapagliflozin for the treatment of type 2 diabetes, particularly when compared with currently used treatment options?

Please consider whether in the remit or the scope there are any issues relevant to equality. Please pay particular attention to whether changes need to be made to the remit or scope in order to promote equality, eliminate unlawful discrimination, or foster good relations between people who share a characteristic protected by the equalities legislation and those who do not share it, or if there is information that could be collected during the assessment process which would enable NICE to take account of equalities issues when developing guidance.

Do you consider dapagliflozin 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 dapagliflozin 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/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp)