NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Canagliflozin in combination therapy for treating type 2 diabetes

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of canagliflozin 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. 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, of whom 90% had type 2 diabetes. However, there are many people with undiagnosed type 2 diabetes so the true number could be considerably higher. 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. Life expectancy is reduced by up to 10 years in people with diabetes.

NICE clinical guideline 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 (liraglutide and exenatide) are recommended in NICE technology appraisal guidance 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.

NICE technology appraisal guidance 288 recommends dapagliflozin in combination with metformin in a dual-therapy regimen, if it is used as described for DPP-4 inhibitors in NICE clinical guideline 87.

For people whose disease is not controlled on dual therapy, triple therapy may be considered. NICE clinical guideline 87 recommends either sitagliptin or pioglitazone as options for adding onto metformin and sulfonylurea. Other add-on treatments may include the twice-daily or the prolonged-release regimens of exenatide (an incretin mimetic) in accordance with clinical guideline 87 and technology appraisal guidance 248. Liraglutide is recommended in NICE technology appraisal guidance 203 as a triple therapy if it is used as described for exenatide in clinical guideline 87. Dapagliflozin in combination with metformin and a sulfonylurea in a triple therapy regimen is not recommended in NICE technology appraisal guidance 288, except as part of a clinical trial. Insulin therapy is recommended when the control of blood glucose remains or becomes inadequate with all other measures. Dapagliflozin in combination with insulin with or without other antidiabetic drugs is recommended in technology appraisal guidance 288.

The technology

Canagliflozin (brand name unknown, Janssen-Cilag) 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. Through this mechanism, canagliflozin may help control glycaemia independently of insulin pathways. Canagliflozin is administered orally.

Canagliflozin does not have a UK marketing authorisation for treating 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, canagliflozin is being studied as monotherapy compared with placebo.
- For those on metformin monotherapy, canagliflozin is being studied as a dual therapy in comparison with placebo, a sulfonylurea (glimepiride) and a DPP-4 inhibitor (sitagliptin) in a series of trials.
- For those on sulfonylurea monotherapy, canagliflozin is being studied as a dual therapy in comparison with placebo.
- For those on metformin and sulfonylurea dual therapy, canagliflozin is being studied as a triple therapy in comparison with placebo and in comparison with a DPP-4 inhibitor (sitagliptin).
- For those on metformin and pioglitazone dual therapy, canagliflozin is being studied as a triple therapy in comparison with placebo.

- As an add-on therapy for adults who have inadequate glycaemic control on their current diabetes treatment regimen including insulin.

Intervention(s)	Canagliflozin (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 of the following: • 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	**Dual therapy** For the combination of canagliflozin 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 canagliflozin 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 canagliflozin, 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 canagliflozin, 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 canagliflozin 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: • HbA_{1c}/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 (for example, 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, subgroups based on the following criteria will be considered: • body mass index • baseline HbA_{1c} 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'. Proposed review date: December 2014. Technology Appraisal No. 248, February 2012. 'Diabetes (type 2) – exenatide (prolonged release)'. Guidance on static list. Technology Appraisal No. 203, October 2010, 'Liraglutide for the treatment of type 2 diabetes. Under consideration for review. Technology Appraisal No.151, July 2008, 'Continuous subcutaneous insulin infusion for the treatment of diabetes (review)'. Guidance on static list. Related Guidelines: Clinical Guideline No. 87 (partial update of Clinical Guideline No. 66), May 2009 'Type 2 diabetes- newer agents' Review in preparation. Publication date tbc. Clinical Guideline No. 66 (partially updated by Clinical Guideline No. 87), May 2008 'Type 2 diabetes: full guideline' Review in preparation. Publication date tbc. Related Quality Standards Quality Standard, 'Diabetes in adults'. Issued March 2011. http://www.nice.org.uk/guidance/qualitystandards/diabetesinadults/diabetesinadultsqualitystandard.jsp