

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Proposed Health Technology Appraisal

Dapagliflozin in combination therapy for the treatment of type 2 diabetes

Final scope

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 2.9 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 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. 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 (for example, gliclazide, glipizide, or glimepiride) may be needed. If these drugs are not suitable, a thiazolidinedione (pioglitazone) or a

dipeptidyl peptidase-4 (DPP-4) inhibitor (incretin enhancers) such as sitagliptin or vildagliptin can be used as an add-on therapy to metformin and/or a sulfonylurea as appropriate. The glucagon-like peptide-1 (GLP-1) analogues (exenatide and liraglutide) are recommended in NICE technology appraisals no. 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, the twice daily or the prolonged release regimens of exenatide (an incretin mimetic) may be prescribed in accordance with clinical guideline no. 87 and technology appraisal no. 248 'Diabetes (type 2) – exenatide (prolonged release)'. Exenatide is recommended as an option for triple therapy for people with a high body mass index ($>35 \text{ kg/m}^2$) 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 comorbidities. 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. 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.

The technology

Dapagliflozin (Forxiga, 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.

The Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion, recommending the granting of a marketing authorisation for dapagliflozin. The CHMP approved the use of dapagliflozin in adults with type 2 diabetes as monotherapy (when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance) and add-on therapy in combination with other glucose-lowering agents including insulin (when these, together with diet and exercise, do not provide adequate glycaemic control).

Dapagliflozin has been studied in clinical trials as monotherapy compared with placebo and metformin in adults with type 2 diabetes who have inadequate glycaemic control with diet and exercise. It has also been studied as second line add-on to metformin, glimepiride, and pioglitazone. Dapagliflozin is currently being trialled as third-line add-on to metformin and a sulfonylurea and to metformin and a DPP4-inhibitor. In addition to the trials studying

dapagliflozin alone or in combination with oral anti-diabetics, dapagliflozin has been studied in inadequately controlled patients on insulin (with one or more oral agents) compared with placebo.

<p>Intervention(s)</p>	<p>Dapagliflozin (in combination with oral anti-diabetic agents and/or insulin).</p>
<p>Population(s)</p>	<p>Dual therapy Adults with type 2 diabetes that is inadequately controlled on monotherapy with either metformin or a sulfonylurea.</p> <p>Triple therapy Adults with type 2 diabetes that is inadequately controlled on dual therapy with either of the following:</p> <ul style="list-style-type: none"> • metformin in combination with a sulfonylurea • metformin or a sulfonylurea in combination with a thiazolidinedione, a DPP-4 inhibitor, or a GLP-1 analogue. <p>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.</p>

Comparators	<p>Dual therapy</p> <p>For the combination of dapagliflozin and metformin, the comparators are:</p> <ul style="list-style-type: none"> • sulfonylureas (with metformin) • pioglitazone (with metformin) • DPP-4 inhibitors (with metformin) • GLP-1 analogues (with metformin). <p>For the combination of dapagliflozin and sulfonylurea, the comparators are:</p> <ul style="list-style-type: none"> • pioglitazone (with a sulfonylurea) • DPP-4 inhibitors (with a sulfonylurea) • GLP-1 analogues (with a sulfonylurea). <p>Triple therapy</p> <p>For the combination of dapagliflozin, metformin and a sulfonylurea, the comparators are:</p> <ul style="list-style-type: none"> • 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). <p>For the combination of dapagliflozin, metformin and pioglitazone, the comparators are:</p> <ul style="list-style-type: none"> • DPP-4 inhibitors (with metformin and pioglitazone) • GLP-1 analogues (with metformin and pioglitazone) • insulin (with metformin and pioglitazone). <p>For the use of dapagliflozin in any other triple therapy regimen, the comparator is:</p> <ul style="list-style-type: none"> • insulin (alone or in combination with one or more oral anti-diabetic agents). <p>Add-on therapy to insulin</p> <ul style="list-style-type: none"> • One or more oral anti-diabetic agents (in combination with insulin).
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<p>Outcomes</p>	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> • HbA1c/glycaemic control • frequency and severity of episodes of hypoglycaemia • calculated cardiovascular risk (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.
<p>Economic analysis</p>	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>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.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p>
<p>Other considerations</p>	<p>If evidence allows, subgroups based on the following criteria will be considered:</p> <ul style="list-style-type: none"> • body mass index • HbA1c • duration of diabetes • dose of insulin. <p>Guidance will only be issued in accordance with the marketing authorisation.</p>

<p>Related NICE recommendations</p>	<p>Related Technology Appraisals:</p> <p>Technology Appraisal No 203, October 2010, 'Liraglutide for the treatment of type 2 diabetes. Review date May 2012.</p> <p>Technology appraisal No.151, July 2008, 'Continuous subcutaneous insulin infusion for the treatment of diabetes (review) '. Guidance on static list.</p> <p>Technology Appraisal No.248, February 2002. 'Diabetes (type 2) – exenatide (prolonged release'. Review date May 2012.</p> <p>Related Guidelines:</p> <p>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.</p>
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