

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Dapagliflozin in triple therapy regimens for treating type 2 diabetes

Draft scope

Remit

To appraise the clinical and cost effectiveness of dapagliflozin within its marketing authorisation for treating type 2 diabetes.

Appraisal objective

This appraisal is a part-review of NICE technology appraisal (TA) 288, dapagliflozin combination treatment. It will only consider recommendation 1.3 in TA288, dapagliflozin triple therapy. The other recommendations in TA288 remain extant.

Background

Type 2 diabetes is a chronic metabolic condition characterised by insulin resistance (that is, the body's inability to effectively use insulin) and insufficient pancreatic insulin production, resulting in high blood glucose levels (hyperglycaemia). Type 2 diabetes is commonly associated with obesity, physical inactivity, raised blood pressure, disturbed blood lipid levels and a tendency to develop thrombosis, and therefore is recognised to have an increased cardiovascular risk. It is associated with long-term microvascular and macrovascular complications, together with reduced quality of life and life expectancy

In 2014 there were approximately 2.8 million adults in England with diabetes, of whom 90% had type 2 diabetes¹. However, many people with type 2 diabetes are undiagnosed, and so the number of people with the condition may be higher than reported (it is estimated that there are around 590,000 people in the UK who have diabetes but have not been diagnosed¹). 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 origin¹.

NICE guideline (NG) 28 'Type 2 diabetes in adults: management' recommends an individualised approach to diabetes care that is tailored to the needs and circumstances of adults with type 2 diabetes. It recommends beginning with dietary advice and increasing physical activity for all people with type 2 diabetes. If blood glucose is not adequately controlled by lifestyle interventions alone, the guideline recommends one or more oral anti-diabetic drugs, beginning with metformin. If blood glucose is not adequately controlled

following monotherapy, dual therapy should be considered followed by either the addition of insulin or triple therapy. For triple therapy, NG28 recommends considering a combination of metformin with: a DPP-4 inhibitor and a sulfonylurea, and; pioglitazone and a sulfonylurea. TA315 and TA336 recommended canagliflozin and empagliflozin respectively for triple therapy in combination with metformin and a sulfonylurea, or metformin and a thiazolidinedione. TA288 recommended that dapagliflozin should not be used for triple therapy; this recommendation will be the subject of this appraisal (because there is new evidence now available about this recommendation).

The technology

Dapagliflozin (Forxiga, AstraZeneca) 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, dapagliflozin may help control glycaemia independently of insulin pathways. It is administered orally.

Dapagliflozin has a UK marketing authorisation in “adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control 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.
- Add-on combination therapy: In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control”

Intervention(s)	Dapagliflozin in combination with 2 other oral anti-diabetic agents
Population(s)	Adults with type 2 diabetes that is inadequately controlled on dual therapy with either: <ul style="list-style-type: none"> • metformin with a sulfonylurea • metformin with a DPP-4 inhibitor
Comparators	For the combination dapagliflozin, metformin and a sulfonylurea the comparators are: <ul style="list-style-type: none"> • other SGLT2 inhibitors (with metformin and a sulfonylurea) • DPP-4 inhibitors (with metformin and a sulfonylurea) • pioglitazone (with metformin and a sulfonylurea) • insulin (with metformin and a sulfonylurea) <p>For the combination dapagliflozin, metformin and a</p>

	<p>DPP-4 inhibitor the comparators are:</p> <ul style="list-style-type: none"> • other SGLT2 inhibitors (in combination with metformin and a DPP-4 inhibitor) • a sulfonylurea (in combination with metformin and a DPP-4 inhibitor) • pioglitazone (in combination with metformin and a DPP-4 inhibitor) • insulin (in combination with metformin and a DPP-4 inhibitor)
Outcomes	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> • mortality • complications of diabetes, including cardiovascular, renal and eye • HbA1c/glycaemic control • body mass index • frequency and severity of hypoglycaemia • changes in cardiovascular risk factors • adverse effects of treatment, including urinary tract infections, genital infections and malignancies • health-related quality of life.
Economic analysis	<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>
Other considerations	<p>Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.</p>
Related NICE recommendations and NICE	<p>Related Technology Appraisals:</p> <p>'Empagliflozin in combination therapy for treating type 2 diabetes' (2015). NICE Technology Appraisal 336.</p>

Pathways	<p>Review proposal date March 2018.</p> <p>'Canagliflozin in combination therapy for treating type 2 diabetes' (2014). NICE Technology Appraisal 315. Review proposal date May 2017.</p> <p>'Dapagliflozin in combination therapy for treating type 2 diabetes' (2013). NICE Technology Appraisal 288. Review Proposal Date TBC.</p> <p>Appraisals in development (including suspended appraisals)</p> <p>'Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes'. NICE technology appraisals guidance [ID756]. Publication expected May 2016.</p> <p>Related Guidelines:</p> <p>'Type 2 diabetes in adults: management' (2015). NICE guideline 28. Review date December 2017.</p> <p>'Diabetic foot problems: prevention and management' (2015). NICE Guideline 19. Review date February 2017.</p> <p>'Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period' (2015). NICE guideline 3. Review date TBC.</p> <p>'Diabetes in adults' (2011). NICE quality standard 6.</p> <p>Related NICE Pathways: Diabetes (2011). NICE pathway</p>
Related National Policy	<p>NHS England (2014) 'Manual for Prescribed Specialised Services'. Chapter 67.</p> <p>Department of Health (2001) 'National Service Framework: Diabetes'.</p> <p>Department of Health (2014) 'NHS Outcomes Framework 2015-16'. Domains 1 to 5.</p>

Questions for consultation

Have all relevant comparators for dapagliflozin in triple therapy regimens been included in the scope?

- Which treatments are considered to be established clinical practice in the NHS for type 2 diabetes?
- Should GLP 1 analogues be included as a comparator?
- Is it appropriate to compare adding dapagliflozin to dual therapy with a switch to insulin?
- Is pioglitazone (in combination with metformin and a DPP-4 inhibitor) routinely used in clinical practice in the NHS?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom dapagliflozin is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider dapagliflozin in triple therapy regimens will fit into the existing NICE pathway, [diabetes](#)?

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 dapagliflozin in triple therapy regimens are 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 dapagliflozin in triple therapy regimens 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 in triple therapy regimens 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.

References

ⁱ Diabetes UK (2015) '[Diabetes: Facts and Stats](#)'. Accessed December 2015.