NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Dapagliflozin in combination therapy for the treatment of type 2 diabetes

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Dr Peter Winocour

Name of your organisation : ABCD (Association of British Clinical Diabetologists) and RCPL (The Royal College of Physicians of London)

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? Yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? Yes
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? Yes – Clinical Director in East and North Herts NHS trust
- other? (please specify) Member of executive of ABCD and Secretary of RCPL Joint Speciality Committee in Diabetes and Endocrinology

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? **Type 2 diabetes is extremely common - affecting 5-7% of the adult population , with a projected prevalence of 10% by 2020. The vast majority of cases are managed within primary care. Recent National Diabetes audit shows significant geographical variation in care processes and outcomes. There is a clear evidence base demonstrating that early effective control of blood glucose can reduce the development and progression of microvascular (and potentially macrovascular) complications. Over-intensive glucose control with established Type 2 diabetes and large vessel complications in older patients has been linked to increased mortality.**

Are there differences of opinion between professionals as to what current practice should be?
The algorithm for placement of different therapies in Type 2 diabetes is consensus rather than evidence based . Although the American Diabetes Association and the European Association for the Study of Diabetes have produced broad guidance to help selection of therapy for diabetes , this is not synonomous with the older NICE guidelines for type 2 diabetes . The early use of injectable (insulin and GLP-1 analogue) therapy and the relative risks of weight gain and hypoglycaemia versus the established evidence base for the beneficial impact of glycaemic control with older sulfonylurea agents remains an area of contention amongst opinion leaders in diabetes .

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?
Type 2 diabetes can be treated with a range of oral and injectable therapies . The broad categories either enhance or replicate endogenous insulin action or enable more effective use of endogenous insulin. Considerations as to selection of different classes of agent may reflect cost , impact on weight , hypoglycaemia risk , efficacy and safety in renal disease , impact on established micro and macrovascular complications , risk of specific side effects such as pancreatitis . Key longer term safety-efficacy in respect of cardiovascular and cancer outcomes requires longer term large scale prospective surveillance.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?

Patients with a family history of diabetes with adverse outcomes, those with the 'full house' of features of metabolic syndrome , renal disease (assessed by albuminuria and eGFR) , smokers , early onset T2, consistent poor control all carry a worse prognosis

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Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Patients with CKD3-4 may respond less well to this class of therapy. Patients with established bladder dysfunction or other bladder pathology or recurrent genitourinary infections – including fungal infections may be more likely to display the more common side effects .

Patients on diuretics or at risk of intravascular volume depletion may be at greater risk of hypovolaemia and postural –blood pressure lowering effects .

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?

The commonest setting for initiation of this therapy will be primary care although use alongside insulin may be more likely in specialist care .

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Monitoring of patients initiated on other therapies such as diuretics or antibiotic-antifungal agents whilst on this agent could be highlighted by dispensing pharmacists .

If the technology is already available, is there variation in how it is being used in the NHS?
Not currently available

Is it always used within its licensed indications? If not, under what circumstances does this occur?

Therapy could have place in patients with type 1 diabetes especially if overweight-obese

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

NICE –Type 2 – under review

ADA-EASD best practice guidelines for T2DM 2012

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The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

Patients with obesity and/or at risk of hypoglycaemia may currently be considered for gliptins or GLP-1 analogues . Dapagliflozin could be considered an agent which may also be placed alongside these newer agents although patients with CKD3 -4 would be less likely to respond to dapa in contrast to gliptins .

Haematocrit , urate and renal function measures are likely to be considered with initial use especially if already at risk of dehydration , GU infection. Sterile urine without haematuria should be established at baseline given the potential impact of sustained marked glycosuria on urothelial cells and the need to avoid any concern regarding bladder cancer risk .

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Recurrent GU infections , hypovolaemia , acute kidney injury , newly developed haematuria requiring investigation .

Efficacy over 6 months evidenced by drop in HbA1c of at least 5 mmol/mol as basis for continued treatment .

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

Glycaemic benefits key outcome .

Unclear whether exclusion of those at highest risk of GU infections , use of diuretics would mean that the study patients were representative of wider

general practice based population. Long term efficacy and safety (CVD and cancer incidence) would require long term surveillance outwith initial phase II studies. Longer term outcome studies should be planned that evaluate all small and large vessel outcomes especially incidence of diabetic nephropathy, along with CVD and cancer outcomes .

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Unclear whether recurrent urinary bacterial and fungal infections – impact of urine volume-nocturia would preclude longer term use although evidence from trials suggest these effects are modest and reduce over time course of therapy .

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Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Updated published abstracts and presentations at recent international speciality meetings at – ADSA and EASD + papers published within last few months that might not have been included in systematic review if undertaken prior to meeting in January

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that

have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Education of primary health care teams of a new class of therapy would be important as well as enabling placement of the class of therapy within upcoming Type 2 DM guidelines .