Dapagliflozin: NICE guidance for use in combination therapy for the treatment of type 2 diabetes

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Dapagliflozin (Forxiga, Bristol-Myers Squibb and AstraZeneca)¹ is a competitive, reversible, and highly selective inhibitor of a major renal sodium glucose co-transporter (SGLT2) resulting in insulin-independent renal elimination of glucose (a glucuretic effect).² Paradoxically, the ensuing glucosuria, once an undesirable facet of diabetes, is now an innovative therapeutic mechanism utilised by dapagliflozin which is licensed for use as mono- and add-on therapy, including with insulin in adults with type 2 diabetes, but not with pioglitazone.³ Dapagliflozin appears on average to reduce HbA1c by 0.54% and weight by 1.8kg.⁴ Given SGLT2 inhibitors’ mechanism of action, there is a reported increased risk of urinary and genital tract infections (OR of 1.34).⁵

The recently renamed National Institute for Health and Care Excellence (NICE) issued its single technology appraisal (STA) on the clinical use of dapagliflozin in June 2013.⁶ Following its deliberation and evidence consideration, NICE has supported the selective use of dapagliflozin in adults with type 2 diabetes in dual therapy and with insulin. The summary of the recommendations is outlined in Table 1.

Review of the evidence behind the appraisal

NICE used its well-established STA process in its determination and consideration of the evidence submitted by the manufacturers of dapagliflozin.⁷ Five randomised controlled trials (RCTs) with a focus on the 10mg dose of dapagliflozin were included in the manufacturers’ submission.⁸–¹² Three of the studies were add-on to metformin, of which only one had an active comparator in the form of a sulphonylurea (SU, glipizide), and two studies as add-on to insulin. Broadly, when compared to placebo, the trials showed statistically significant reduction in HbA1c (~0.5%) and weight (~2kg). When compared to glipizide, dapagliflozin showed non-inferiority in terms of glycaemic control with more beneficial effect on weight (a difference of over 4kg) and significantly less hypoglycaemia. There was an increased risk of urinary and genital tract infections with dapagliflozin. The add-on to insulin use was associated with weight loss and reduction in insulin dose along with improvement in glycaemic control. These trials are summarised in Table 2.

NICE did not consider monotherapy submission in its evidence review, although it did not rule out future consideration. In line with its licence exclusion, the use of dapagliflozin in moderate to severe renal impairments was also not considered by NICE (i.e. patients with an eGFR less than 60ml/min/1.73m²), due to renal function efficacy dependence. The main short-coming in the evidence submitted for dapagliflozin was the absence of RCTs against many active comparators, and in particular against the DPP-4 inhibitors, which the Evidence Review Group (ERG) regarded as the key comparators. Given the absence of such head-to-head trials, the submission relied on a network meta-analysis by the manufacturers (NMA). The numerical results of the analysis for the add-on to metformin comparison with DPP-4 inhibitors were provided as academic in confidence. In February 2013, NICE delayed its verdict on dapagliflozin due to uncertainty surrounding the methodology used in this NMA and economic modelling that then excluded urinary and genital tract infection. The manufacturers subsequently submitted revised evidence to NICE.¹³,¹⁴

NICE concluded that dapagliflozin provided efficacy similar to DPP-4 inhibitors as dual therapy, and appeared to have greater benefit for weight reduction when used with insulin. The evidence for dapagliflozin in the triple therapy setting was less robust since no specific direct triple oral therapy studies had been completed at the time of submission. The submitted data (as an addendum) came from a subset of patients in ongoing phase 3 clinical studies which were designed to assess the efficacy and safety of dapagliflozin in older subjects with cardiovascular disease, and were deemed to be not representative of the overall population of those with type 2 diabetes.¹³,¹⁴

Critical appraisal

This guidance, notable for its omissions and prohibitions, at this stage should perhaps preliminarily be viewed as work in progress rather than the completed article, for some understandable reasons. There is no verdict on the use of dapagliflozin as monotherapy and...
the evidence behind this indication was not considered. NICE has cited such potential use is unlikely to be common practice considering its current diabetes type 2 guidance, which is being updated. One could argue that the focus of NICE remains glucocentric; with less attention given to potential weight benefit, although there are signals that a forthcoming guideline update may see some shift in that position – assuming recent uncertainties and controversies surrounding new therapies do not intervene.

In addition, combination therapy with SUs is not recommended; NICE cites lack of clinical-effectiveness data availability in patients inadequately controlled on SU monotherapy in the manufacturers’ submission, although there is the existence of some clinical trial data elsewhere. In that trial, dapagliflozin added to glimepiride was associated with significant weight and HbA1c reduction, although genital infections were reported more frequently. The ERG maintained its assertion that SUs should be used after metformin and before dapagliflozin as SUs, according to the ERG, are well-established, inexpensive and safe drugs. Nevertheless, the safety of SUs has been the subject of ongoing debate with a recent meta-analysis in which the authors concluded that the cardiovascular safety of SUs cannot be considered established without long-term cardiovascular outcome trials. The use of dapagliflozin is also not recommended in combination with pioglitazone given licence restrictions – attractive though it may be in opposing fluid retention with the latter – most likely due to concerns regarding bladder cancer risk.

A novel oral antidiabetic therapy that appears to improve glycaemic control with associated benefits in terms of weight reduction and fewer hypoglycaemic episodes would be a welcome development in the diabetes therapeutic field. The degree of the glycaemic control and other measured intermediate benefits, however, need to be objectively balanced against the short life span of a chronic disease drug in clinical trials, the uncertain significance of co-incident signals albeit sometimes muffled, the potential for significant rare and yet to be uncovered long-term adversity, the sustainability of benefit, and the hindsight controversy accumulated with other therapeutic innovations, such as rosiglitazone and, recently, GLP-1 analogues/gliptins.

Dapagliflozin in this regard is no different from other novel advances in antidiabetic ammunition, and NICE’s latest appraisal determination is a reassuring qualified step to many – patients and professionals – in recruiting this treatment into mainstream clinical diabetes. The combination with insulin and as a selective alternative to DPP-4 inhibitors is likely to draw the bulk of interest.
particularly in secondary care. However, there remain outstanding questions regarding dapagliflozin therapeutic use which include:

- The likely sustainability of weight loss with dapagliflozin, as some animal studies suggest the development of compensatory hyperphagia.

- The uncertainty concerning the proportional and temporal contributions of diuresis versus reduction in adiposity to total weight loss with dapagliflozin.

- The question regarding cardiovascular safety in the absence of long-term outcome trials. The manufacturers’ meta-analysis of the current short-term studies using a range of dapagliflozin doses showed no association with an increased cardiovascular risk.

- Potential safety issues associated in relation to tumour risk (bladder, particularly) and risk of serious liver injury in patients exposed to dapagliflozin. Such concerns were factors in the US Food and Drug Administration (FDA) not granting approval in 2011. The FDA noted, however, that the imbalance in bladder cancer cases might possibly be due to detection bias.

- The clinical relevance of a reduction in HbA1c of 0.5%, albeit statistically significant.

- Limited data on dapagliflozin use in patients at risk of volume depletion, especially in those over 75 years of age.

NICE has to balance the need for robust and comprehensive evidence of long-term safety reassurances against delays in the approval process of innovative and potentially useful therapeutic additions. Significant delays in endorsing mainstream clinical use of licensed medicines might inadvertently contribute to the decline of research into new diabetic therapies.

It is worth remembering that existing treatments – established and new – are not without their own concerns. History, no doubt, will pass its own verdict as to whether this latest technology appraisal is perhaps visionary and timely – or not.

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Declaration of interests
The authors have participated in educational meetings sponsored by the manufacturers of dapagliflozin, but not in relation to this drug.

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