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NICE guidance on dapagliflozin for type 1 diabetes

On August 28, 2019, the National Institute for Health and Care Excellence (NICE) published guidance recommending dapagliflozin (a sodium-glucose co-transporter-2 inhibitor) for treating type 1 diabetes in adults with a BMI of at least 27 kg/m^2 when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy.[1] However, the guidance applies only if patients are on insulin doses of more than 0.5 units per kg body weight per day; they have completed a structured education programme that includes information about diabetic ketoacidosis (DKA) such as recognising its risk factors, signs, and symptoms, how and when to monitor blood ketones, and what actions to take; and, treatment is started and supervised by a consultant physician specialising in endocrinology and diabetes. The structured education course, in line with the NICE Quality Standard for diabetes[2] should be evidence based and quality-assured, and be delivered by trained educators.

The NICE appraisal focused on the newer indication of type 1 diabetes. AstraZeneca (Cambridge, UK) submitted clinical and cost-effectiveness evidence, which an independent appraisal committee considered during two public meetings; clinical and patient experts attended the first meeting.

The committee was aware that the European Medicines Agency had limited the dapagliflozin license because of safety concerns about DKA to people with a BMI of at least 27 kg/m, adequate education about DKA, and without low insulin needs. It also limited the license to a glomerular filtration rate ≥60 mL/min per 1.73 m^2 when starting treatment. The committee took advice on how to define low insulin needs from the clinical experts and concluded that it was appropriate to evaluate dapagliflozin in people in whom, despite structured education, insulin alone did not control blood glucose; the comparator, therefore, was optimised treatment with insulin.

As evidence of clinical effectiveness, AstraZeneca presented data from the DEPICT-1[3] [and DEPICT-2[4] randomised trials, which compared dapagliflozin plus insulin therapy at 5 mg [licensed] or 10 mg [unlicensed] doses with placebo plus insulin therapy over 52 weeks in patients with inadequately controlled type 1 diabetes despite optimised insulin therapy and with HbA_{1c} levels ranging from 7.5% (59 mmol/mol) to 10.5% (91 mmol/mol). The license, and the evidence presented to the committee, reflects a subset of the trial participants (n=561). The committee recognised that more people used continuous subcutaneous insulin infusion (pumps) and fewer used renin-angiotensin-aldosterone system inhibitors than NHS

patients who might receive dapagliflozin, but considered that this was unlikely to modify dapagliflozin's effect.

The primary measure of effectiveness in both trials was the change in HbA_{1c} from baseline to 24 weeks, whereas NICE's measure of effectiveness is the quality-adjusted life year (QALY).[5] The DEPICT trials showed no evidence that dapagliflozin prolongs life, but showed a small increase in quality of life. Yet, AstraZeneca proposed that dapagliflozin plus insulin increases both length and quality of life compared with insulin alone over a lifetime. The committee noted that the pooled reduction in HbA_{1c} at 52 weeks from the DEPICT trials was modest at 0.34% relative to placebo, and questioned whether it was important, and would be sustained. People randomized to dapagliflozin lost weight at 24 weeks, which was sustained at 52 weeks. The committee concluded that, in general, any decrease in HbA_{1c} without substantial hypoglycaemia or weight gain is desirable.

To support its case that dapagliflozin prolongs life and improves quality of life, AstraZeneca used a patient-level model[6] to simulate disease progression and complications over a lifetime. The company derived risk equations linking HbA_{1c} to future complications using the randomised Diabetes Control and Complications Trial (DCCT)[7] and its follow-on observational study, the Epidemiology of Diabetes Interventions and Complications (EDIC)[8] for microvascular complications, and the Swedish National Diabetes Registry[9] for macrovascular complications. AstraZeneca did not link changes in body weight to changes in the risk of complications, but did link changes to an increase in quality of life. Because studies in other populations to validate the model were limited, the committee concluded that it was uncertain how well the model predicted long-term complications following a relatively short observed period of modestly improved glycaemic control.

The committee queried why AstraZeneca had not used DCCT/EDIC-based data to model cardiovascular disease. The company explained that it could not access the patient-level data within the consultation period and the committee acknowledged that a scenario in which HbA_{1c} did not affect cardiovascular risk had not markedly changed the cost-effectiveness results.

The committee noted that nearly all modelled improvements in QALYs occurred in the extrapolated period after the end of the DEPICT trials, for which there was no observed evidence. In response, AstraZeneca provided scenarios in which it modelled varying degrees of treatment effect waning over time for HbA_{1c} and for weight loss with dapagliflozin

plus insulin. The committee appreciated that the gains in QALYs were largely from quality-of-life gains in people who lost weight.

The model presented by AstraZeneca at the second committee meeting included people who need more than 0.5 units of insulin per kg body weight per day; a progressive increase in HbA_{1c} of 0.045% per year and in body weight of 0.1 kg per year for both arms; a stopping rate in year 1 and beyond for dapagliflozin based on DEPICT; and mortality and disutility associated with severe hypoglycaemia, DKA, and life-threatening urogenital infections, such as Fournier's gangrene. AstraZeneca modelled scenarios using both additive and multiplicative approaches to apply disutilities associated with complications[10] and costs related to increased blood glucose testing, additional ketone monitoring and visits to diabetes specialist teams. The committee noted that the deterministic incremental cost-effectiveness ratio (ICER) for AstraZeneca's revised base case was below the range that NICE considers to be cost effective; that is, below £20,000 per QALY gained.

The committee noted that AstraZeneca provided two scenarios in which it modelled: first, no treatment effects affecting HbA_{1c} or weight beyond the 52 week trial for either treatment and stopping dapagliflozin; and second, no change in HbA_{1c} from baseline for either treatment, but maintaining a weight benefit and not stopping dapagliflozin. The committee acknowledged that both of the scenarios tested resulted in ICERs that fell within the range NICE normally considers to be cost effective.

The committee recognised that if HbA_{1c} did not improve, ongoing treatment with dapagliflozin would likely subject the patient to risks. The committee recognised that dapagliflozin did not have an indication for weight loss, and that the trials did not include stopping 'rules'. The committee concluded that if glycaemic control does not improve, it would not be appropriate to continue dapagliflozin.

The committee concluded that dapagliflozin with insulin appears to be a cost-effective use of NHS resources for treating type 1 diabetes in adults with a BMI of at least 27 kg/m^2 when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy, subject to the above-listed conditions. The guidance also states that people should stop dapagliflozin if they do not see a sustained improvement in glycaemic control when assessed after 6 months and regularly thereafter.

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