NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Dapagliflozin with insulin for treating type 1 diabetes

1 Recommendations

1.1 Dapagliflozin with insulin is recommended as an option for treating type 1 diabetes in adults with a body mass index (BMI), of at least 27 kg/m^2, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy, only if:

- they are on insulin doses of more than 0.5 units/kg of body weight/day and
- they have completed a structured education programme that includes information about:
  - the risk of diabetic ketoacidosis
  - how to recognise risk factors for diabetic ketoacidosis, and its signs and symptoms
  - how and when to monitor blood ketone levels
  - what actions to take for elevated blood ketones, and
- treatment is started and supervised in a hospital diabetes clinic.

1.2 Assess haemoglobin A1c (HbA1c) level after 6 months and regularly after this. Stop dapagliflozin if there has not been a sustained improvement in glycaemic control (that is, a fall in HbA1c level of at least 0.3%).

1.3 These recommendations are not intended to affect treatment with dapagliflozin that was started in the NHS before this guidance was

published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Evidence from the clinical trials shows small improvements in blood glucose (haemoglobin A1c [HbA1c] levels) and weight loss, and very small improvements in quality of life, when dapagliflozin plus insulin is compared with placebo plus insulin in adults with type 1 diabetes and inadequate blood glucose control despite optimised insulin therapy. The company extrapolates the effects of the small improvement in HbA1c level with dapagliflozin seen at 1 year in the trials to a lower risk of long-term complications over a patient's lifetime.

In the company's scenario that assumes no benefit from improved HbA1c levels beyond the trial period (1 year), the cost-effectiveness estimate for dapagliflozin plus insulin compared with insulin alone is within the range that NICE normally considers an acceptable use of NHS resources. Dapagliflozin with insulin is therefore recommended as an option for type 1 diabetes in adults. Because of the increased risk of diabetic ketoacidosis, dapagliflozin should be stopped if blood glucose control does not improve.

2 Information about dapagliflozin

Marketing authorisation	Dapagliflozin (Forxiga, AstraZeneca) is indicated for the treatment of 'type 1 diabetes mellitus as an adjunct to insulin in patients with a BMI ≥27 kg/m^2, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy'. Dapagliflozin should not be started in people with type 1 diabetes with a 'low insulin need'. It should not be started in people with a glomerular filtration rate [GFR] < 60 mL/min and should be stopped at GFR persistently below 45 mL/min. During treatment with dapagliflozin, insulin therapy should be continuously optimised to prevent ketosis and diabetic ketoacidosis, and the insulin dose should only be reduced to avoid hypoglycaemia. This treatment should only be 'started and supervised by specialist doctors'. Patients should be able and committed to control ketone levels in their body. They should be

	educated about risk factors for diabetic ketoacidosis and how to recognise its signs and symptoms.
Dosage in the marketing authorisation	Administered orally at a dosage of 5 mg once daily.
Price	The list price of dapagliflozin is £36.59 for 28 tablets (excluding VAT; British National Formulary online, accessed April 2019). The treatment cost at list price is £477.30 per year. Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The appraisal committee (section 6) considered evidence submitted by AstraZeneca, a review of this submission by the evidence review group, and the technical report developed through engagement with stakeholders. See the committee papers for full details of the evidence.

Clinical management

People normally have structured education and optimised insulin therapy

3.1 Type 1 diabetes is an autoimmune metabolic disease that destroys insulin-producing cells of the pancreas. This raises the levels of blood glucose, which increases the risk of long-term diabetes-related complications. These include, but are not limited to, retinopathy, neuropathy, cardiovascular disease and death. People with type 1 diabetes manage their condition by injecting insulin, and by making choices about diet and physical activity. The NICE guideline on type 1 diabetes in adults recommends that people have individualised care including structured education (for example, the Dose Adjustment For Normal Eating [DAFNE] programme), and advice on diet and physical activity (that is, lifestyle), and on managing blood glucose. The guideline advises on targets for haemoglobin A1c (HbA1c) levels, self-monitoring of blood glucose, and preventing and managing hypoglycaemia and diabetic ketoacidosis. It also encourages people to identify and control risk factors for cardiovascular disease, manage diabetes-related complications and optimise their insulin therapy. Optimised management of insulin may include injection technique and sites, dosing of insulin, skills for self-

monitoring and using continuous subcutaneous insulin infusion ('insulin pump'). The clinical experts explained that people who optimally manage insulin would normally have done a structured education course, and may be using an insulin pump or continuous blood glucose monitoring. For people who, despite best efforts, cannot reach optimal glycaemic control, or who cannot improve control without it causing disabling hypoglycaemia, there are no other options available.

Experience of people with type 1 diabetes

There is an unmet need for interventions that help people to reach good glycaemic control without complications

3.2 One clinical expert explained that managing blood glucose involves, for most people, multiple blood glucose finger prick testing and multiple insulin injections every day. The dose of insulin is adjusted according to an individual's diet, activity level and other circumstances such as stress and illness. A submission to NICE from a patient and carer organisation highlighted that managing the condition is demanding, and that the risk of hypoglycaemia from insulin and adjusting doses can considerably affect wellbeing and quality of life. The clinical expert explained that about 70% of people struggle to control blood glucose without developing hypoglycaemia and putting on weight. The committee concluded that there is an unmet need for interventions that could include medicines which help people to get good control of their diabetes without complications.

People who might take dapagliflozin

Safety concerns limit dapagliflozin to a subset of patients

3.3 The company explained that, because of safety concerns around diabetic ketoacidosis associated with dapagliflozin, the European Medicines Agency had restricted the marketing authorisation for dapagliflozin as an adjunct to insulin to a subset of people with type 1 diabetes (that is, with a BMI of 27 kg/m^2 or more), when insulin alone does not provide adequate

glycaemic control despite optimal insulin therapy. Advice from the summary of product characteristics further specifies that dapagliflozin is not recommended in people with a 'low insulin need'. The clinical experts helped clarify this for the committee. One clinical expert suggested that 'low insulin need' could be 0.5 units of insulin per kilogram of body weight per day. Another clinical expert explained that it is likely to be between 0.4 and 0.5 units of insulin per kilogram of body weight per day. In addition to having a BMI of 27 kg/m^2 or more and insulin needs above 0.5 units/kg of body weight/day, the clinical experts noted further criteria that would define the appropriate clinical population. They suggested people should:

- have completed a structured education course,
- have been offered an insulin pump if appropriate, and
- be able to do blood glucose and ketone testing to enable them to prevent, recognise and treat diabetic ketoacidosis and hypoglycaemia.

The committee noted that safety concerns limit the use of dapagliflozin to a subgroup of patients with type 1 diabetes. It concluded that, in the NHS, dapagliflozin would likely be offered to people with a BMI of 27 kg/m^2 or more, insulin needs above 0.5 units/kg of bodyweight/day, inadequate glycaemic control despite structured education and optimised insulin therapy, and who are aware of the increased risk of diabetic ketoacidosis.

Comparators

The relevant comparator is optimised insulin therapy

3.4 The NICE scope specified the comparator as insulin therapy with or without metformin. The company explained that it did not consider metformin as a comparator in its base case because recent randomised trial evidence (REMOVAL) found a small improvement in HbA1c levels with metformin plus insulin therapy compared with insulin therapy alone. In addition, the clinical experts suggested that, in the UK, less than 10% of

people with type 1 diabetes use metformin off-label. The clinical experts explained that, in practice, dapagliflozin would not be offered as an alternative to insulin-pump therapy. Rather, it would be offered when insulin pumps are not appropriate (but in people who could otherwise manage the increased risk of diabetic ketoacidosis associated with dapagliflozin) or to people on pump therapy. The committee concluded that the relevant comparator is optimised therapy with insulin in addition to lifestyle changes.

Blood glucose and risk of diabetes-related complications

Lowering blood glucose levels decreases the risk of diabetes-related complications

3.5 HbA1c is a recognised surrogate endpoint for long-term diabetes complications. Treatment to lower HbA1c levels in type 1 diabetes to near normal levels decreases the risk of complications. The Diabetes Control and Complications Trial (DCCT) showed an average relative decrease in HbA1c levels of 2 percentage points over 10 years in patients who had intensive therapy, that is, multiple daily insulin injections (or an insulin pump) compared with those who had conventional glycaemic control, that is, no more than 2 injections. This reduced the risk of microvascular complications by over half. The DCCT's 30-year, observational, follow-on study (Epidemiology of Diabetes Interventions and Complications, EDIC) showed that having been previously randomised to intensive therapy lowered the risk of macrovascular complications and death compared with having previously been randomised to conventional glycaemic control. The committee discussed whether the results of DCCT and EDIC were generalisable to therapies such as dapagliflozin that lower blood glucose by a much smaller magnitude and with only short-term evidence (see section 3.14). It concluded that this was an area of considerable uncertainty. The committee agreed that DCCT and EDIC provided evidence that lowering blood glucose levels decreases the risk of diabetes-related complications.

A minimum, clinically meaningful reduction in HbA1c should consider baseline HbA1c levels, variability in readings and how long the reduction is sustained

3.6 One clinical expert suggested that an absolute reduction of 0.3 percentage points in HbA1c levels may be considered clinically meaningful. In response to the technical engagement, another clinical expert explained that a clinically meaningful reduction will likely depend on the starting HbA1c level. This is because larger reductions are more difficult to reach at lower starting levels. He suggested that a reduction of 0.4 percentage points for a baseline HbA1c level of no more than 8.5% (69 mmol/mol) may be considered clinically meaningful. The committee was aware that the changes in HbA1c seen in the dapagliflozin clinical trials at 52 weeks were at the lower end of the range that the clinical experts would consider meaningful (see section 3.9). The committee appreciated that a minimum, clinically meaningful reduction in HbA1c should consider variability (both natural over time and laboratory), baseline HbA1c levels, and how long the reduction is sustained.

Clinical evidence

The DEPICT-1 and DEPICT-2 trials provide the key clinical evidence for dapagliflozin

3.7 The main evidence for dapagliflozin came from 2 trials, DEPICT-1 and DEPICT-2. These trials compared dapagliflozin plus insulin therapy at 2 doses (5 mg [licensed] or 10 mg [unlicensed]) with placebo plus insulin therapy over 52 weeks. They were randomised and double-blind and included a total of 1,591 patients with inadequately controlled type 1 diabetes despite optimised insulin therapy and HbA1c levels ranging from 7.5% (58.5 mmol/mol) to 10.5% (91.0 mmol/mol). Patients starting on systemic corticosteroid therapy were excluded from the trials. The committee agreed that it would focus only on the data for the licensed dose of dapagliflozin and in the 'indicated' subgroup, even though the data provided by the company at the first committee meeting included

patients with low insulin doses (see sections 3.3 and 3.9). The primary endpoint in both trials was change in HbA1c from baseline at 24 weeks.

The population in the 'indicated' subgroup does not reflect people who would be offered dapagliflozin in the NHS

3.8 The 'indicated' subgroup included patients who were on average 45 years old and had an average BMI of 32 kg/m^2. Also, 54% were women, 6% smoked, 43% were on an insulin pump and 49% were on a renin-angiotensin-aldosterone system (RAAS) inhibitor. Patients had type 1 diabetes for an average of 21 years, had an average baseline HbA1c level of 8.4% (68 mmol/mol) and used an average insulin dose of 0.8 units/kg of body weight/day. The clinical experts explained that, in the NHS, a much lower proportion of people use an insulin pump (10% to 15%), that the prevalence of smoking and use of RAAS inhibitors are higher, and that the baseline risk of diabetic ketoacidosis may differ. The committee considered that these characteristics are unlikely to be a treatment-effect modifier. However, the baseline level of risk for diabetic ketoacidosis could be higher in the NHS, making a relative increase in diabetic ketoacidosis more important. In response to the appraisal consultation document, the company highlighted that the risk of diabetic ketoacidosis in the NHS is similar to DEPICT based on a systematic review (Fazeli Farzani et al. 2017). The committee noted that the data for the UK was based on a study (Bryden et al. 2003) that included only 113 people with type 1 diabetes and had concerns about the data. The committee concluded that the 'indicated' subgroup from the trials did not reflect patients with type 1 diabetes who would be offered dapagliflozin in the NHS, but that it was unlikely to affect the company's estimates of clinical and cost effectiveness.

The benefit of dapagliflozin over the course of a lifetime is unknown

3.9 The pooled DEPICT trial results showed a larger reduction in HbA1c from baseline at 24 weeks in patients randomised to dapagliflozin plus insulin therapy than patients randomised to placebo plus insulin therapy.

However, after an initial reduction, HbA1c levels increased over time in both arms (see table 1). In addition, patients randomised to dapagliflozin plus insulin therapy lost more weight than patients randomised to placebo plus insulin therapy at 24 weeks, which patients sustained at 52 weeks. The committee acknowledged that the company's revised base case excluded people with 'low insulin need' (see section 3.10) but noted that this minimally affected the efficacy results. One clinical expert explained that, in the REMOVAL trial, which compared metformin plus insulin therapy with insulin therapy alone, HbA1c fell 0.13 percentage points from baseline in patients randomised to metformin at 3 years. However, this was accounted for by an initial reduction at 3 months of 0.24 percentage points that was not sustained. One clinical expert stated that the differences in HbA1c in REMOVAL were "statistically but not clinically significant". The committee noted that the pooled reduction in HbA1c at 52 weeks seen in DEPICT was similar in size (0.26 percentage points). In response to the appraisal consultation document, the company explained that, in trials of anti-hyperglycaemic drugs, HbA1c commonly initially drops, then gradually increases, then stabilises. The committee noted that, based on the DEPICT trials, it could not assess whether patients on dapagliflozin plus insulin lived longer than patients on insulin alone. It noted that the trials showed only a very small increase in quality of life for patients on dapagliflozin plus insulin therapy. The committee concluded that, in general, any decrease in HbA1c in the absence of substantial hypoglycaemia or weight gain is desirable. It questioned the importance of the modest improvements in HbA1c level seen in DEPICT, and whether these differences would be sustained over a lifetime.

Table 1 Adjusted mean change from baseline in HbA1c and weight at 24 and 52 weeks in the DEPICT trials (pooled results, full analysis set)

Outcome		24 weeks		52 weeks	
		Dapagliflozin 5 mg plus insulin	Placebo plus insulin	Dapagliflozin 5 mg plus insulin	Placebo plus insulin
Change in HbA1c	Percentage points, %	-0.44	-0.01	-0.26	0.08
	Difference from placebo	-0.44 (95% CI -0.55 to -0.32)		-0.34 (95% CI -0.48 to -0.20)	
Change in weight	%	-3.11	-0.01	-3.42	0.49
	Difference from placebo	-3.10 (95% CI -3.89 to -2.31)		-3.89 (95% CI -4.67 to -3.11)	
Abbreviations: CI, confidence interval; HbA1c, haemoglobin A1c					

Adverse events

Diabetic ketoacidosis is almost twice as common with dapagliflozin and baseline risk is likely to be higher in the NHS than in the trials

3.10 The committee noted that dapagliflozin was associated with an increased risk of adverse events including genital tract infection, urinary tract infection and, in particular, ketonaemia and diabetic ketoacidosis. The committee was aware that the European Medicines Agency limited the marketing authorisation to people with a BMI of 27 kg/m^2 or more, and excluded people with 'low insulin need' (see section 3.3) to reduce the risk of this potentially life-threatening adverse effect. However, dapagliflozin was still associated with a doubling of risk of confirmed diabetic ketoacidosis in this restricted population. The representative from the patient organisation explained that diabetic ketoacidosis negatively affects quality of life. The clinical experts explained that they would not offer dapagliflozin to someone who had not had structured education, and could not recognise the signs and symptoms of diabetic ketoacidosis. The committee questioned whether the modest improvement in HbA1c level and weight loss outweighed the risk of diabetic ketoacidosis. It was concerned that, because the baseline characteristics of patients in DEPICT did not reflect people with type 1 diabetes seen in the NHS, the

baseline risk of diabetic ketoacidosis could be higher (see section 3.8). In response to the appraisal consultation document, the company explained that, although the relative risk is high, the absolute risk of diabetic ketoacidosis is low. Nevertheless, in its revised base case, the company restricted the population to exclude patients with 'low insulin need', which further reduced the risk of diabetic ketoacidosis. The committee concluded that dapagliflozin would not be offered to someone without structured education and sufficient expertise to detect diabetic ketoacidosis. It also concluded that the absolute risk of diabetic ketoacidosis in the NHS would likely be higher than that seen in the trials.

Company's economic model

The model uses risk equations to link changes in HbA1c seen in the trial with diabetes complications over a lifetime

3.11 The company used a patient-level, microsimulation model (Cardiff Type 1 Diabetes Model) to simulate disease progression and complications over a lifetime horizon. The company derived risk equations from the DCCT/EDIC study for microvascular complications and from the Swedish National Diabetes Registry for some macrovascular complications to link the change in HbA1c to the risk of future complications. The company did not link change in body weight to changes in risk of complications, but the company did link lower BMI with an increase in quality of life. The committee understood that, despite presenting no clinical evidence that dapagliflozin extends life, the company's model predicted that dapagliflozin increased length of life, and substantially improved quality of life (see section 3.9). In response to the appraisal consultation document, the company noted that the DCCT investigators state that 'for a proportionate reduction in HbA1c, there is a constant proportionate reduction in risk for retinopathy and nephropathy' and that 'there is a constant relative risk relationship over the entire range of HbA1c values'. The company further highlighted that DCCT/EDIC showed a 'legacy effect' in which sustained reductions in complication risk were seen long

after the conclusion of DCCT, when HbA1c levels converged. The committee acknowledged that the evidence from DCCT/EDIC supports a 'legacy effect' but noted that there is no clinical evidence that dapagliflozin extends life or substantially improves quality of life.

The model outcomes have not been validated

3.12 The company explained that the available studies to validate the model's predictive performance were limited. The main source of data available was DCCT/EDIC, but, because the company used this study as the basis of its model's risk equations, it could not also use it to validate the model's outputs. The company further explained that it checked the model's predictions against 5 other type 1 diabetes models for external consistency, including the Sheffield and CORE models. The committee recognised the difficulty in validating the model. And, although the model's predictions were in line with other type 1 diabetes models, this did not reduce the uncertainty because all the models used similar DCCT/EDIC-derived risk equations. The committee concluded that uncertainty remained about whether the model predicted what might occur after a relatively short period of improved glycaemic control and an increased risk of adverse events.

The committee would have preferred the risk equations for macrovascular complications to be derived from the DCCT/EDIC data

3.13 The committee noted that DCCT/EDIC also provided data on macrovascular complications (for example, cardiovascular, cerebrovascular and peripheral vascular disease). It queried why the company had not used the original trial-based data in preference to the Swedish registry data that was used to model cardiovascular disease (myocardial infarction, stroke and cardiovascular vascular disease-related death). In response to the appraisal consultation document, the company explained that the Swedish registry risk equations were robustly derived and have been used in other models for type 1 diabetes (for example, Sheffield and PRIME). It further explained that they produced results that

the company considered consistent with other published risk equations (for example, QRisk320 and STENO19). It added that the Swedish registry data were more up to date than the DCCT/EDIC data, and may better reflect the current background risk of cardiovascular disease. The company acknowledged that it could have developed bespoke risk equations with DCCT/EDIC data, but explained that it could not access patient-level data within the consultation period. Instead, it provided sensitivity analyses varying the cardiovascular risks by ±20% from the Swedish registry and a scenario in which HbA1c level had no effect on cardiovascular risk. The committee concluded that it would have preferred that the risk equations for macrovascular complications to be derived from randomised data. However, it acknowledged that the scenario in which the company assumed that HbA1c level did not affect cardiovascular risk had not markedly affected the cost-effectiveness results.

It is unclear if the small HbA1c changes seen in the DEPICT trials would translate to a reduced risk of long-term complications

3.14 The committee noted that the improvement in HbA1c level seen in DCCT/EDIC was substantially bigger (about 2 percentage points reduction – intensive therapy relative to conventional glycaemic control), and sustained for substantially longer (over 10 years) than the improvement in HbA1c level seen in the pooled DEPICT trials (0.34 percentage points reduction over 1 year relative to placebo). It was concerned that the company had assumed that the benefit associated with the smaller and shorter reduction in HbA1c seen in DEPICT was proportional to the benefit of sustained lower HbA1c level seen in DCCT/EDIC in terms of fewer complications (see section 3.11). The company also explained that reductions in HbA1c levels in its model immediately lowered the risk of developing microvascular and macrovascular complications, which the committee questioned. In response to the appraisal consultation document, the company highlighted that other diabetes models take the same approach. The committee noted that virtually all improvements in quality-adjusted life

years (QALYs) were after the end of the dapagliflozin trials (in the extrapolated period of the model), for which there was no clinical evidence. In response to the appraisal consultation document, the company provided:

- a scenario in which it modelled no treatment effects in HbA1c or weight beyond the 52-week trial period for dapagliflozin plus insulin or insulin alone
- a scenario in which it modelled no change in HbA1c level from baseline in either arm (see section 3.20).

The committee agreed that there was still uncertainty about whether the small HbA1c changes seen in the DEPICT trials would translate to a reduced risk of long-term complications over a lifetime. It appreciated that the gains in QALYs in these scenarios were derived largely from quality-of-life gain in people who lost weight. It concluded that the scenarios modelling no treatment benefit related to glycaemic control and complications beyond the trial period might provide some reassurance about whether the cost-effectiveness estimates were robust, and would consider these in its decision making.

Assumptions in the economic model

The population in the company's model is appropriate for decision making

3.15 In its revised base case for the second committee meeting, the company used the baseline characteristics derived from the pooled DEPICT data for the 'indicated' subgroup but excluded patients with 'low insulin need' from the model (see section 3.10). The committee recalled its concerns about the generalisability of the trial population to patients in the NHS likely to be offered dapagliflozin (see section 3.8). In response to the appraisal consultation document, the company provided sensitivity analyses varying the proportions of patients who smoked; used RAAS inhibitors; or had microalbuminuria, hypertension, dyslipidaemia or other co-morbidities. It also provided sensitivity analyses in which it increased

the baseline risk of diabetic ketoacidosis up to 5 times higher than the base case. The committee noted that these did not have a large effect on the cost-effectiveness estimates. It concluded that the population included in the company's model was appropriate for decision making.

Dapagliflozin's treatment effect on HbA1c level is likely to wane after 1 year

3.16 In its base case, the company assumed that dapagliflozin's treatment effects on HbA1c level and body weight seen at 52 weeks were maintained for the remainder of the 79-year time horizon of the model as long as patients stayed on treatment. The committee questioned the plausibility of the company's assumption. It noted that the effect on weight appeared to be maintained in the trials, but the effect on HbA1c had already waned between 24 weeks and 52 weeks (see table 1). Also, it had not seen any evidence that the attenuation in effects on HbA1c had plateaued by 52 weeks. The committee concluded that the treatment effect of dapagliflozin is likely to wane further beyond year 1. In response to the appraisal consultation document, the company highlighted that there is no biological basis for waning of effect. The clinical experts suggested that most patients whose condition responds to treatment would probably maintain benefit. The committee noted that the company provided a range of scenarios in which the effect of dapagliflozin on HbA1c level diminished over time. These included scenarios in which the effect of dapagliflozin on HbA1c level was lost after 2 or 3 years, or in which the company extrapolated the diminishing effect seen in the 24-week and 52-week data from DEPICT over time. In these scenarios, the company assumed that patients maintained their weight loss while taking dapagliflozin over the long term. The committee agreed that, given the lack of evidence, the model should include dapagliflozin's treatment effects diminishing over time. However, the committee acknowledged that none of these scenarios had a large effect on the cost-effectiveness estimates. This was largely because when the effect on HbA1c level is lost, people stop treatment, so no further cost of treatment is incurred.

People should stop dapagliflozin if glycaemic control does not improve

3.17 The committee discussed stopping 'rules' and how they differed from stopping rates (stopping the drug for any reason including adverse effects). The company did not include any 'rules' about when to stop treatment in its model because it considered that this decision should be left to the physician and individual patient. The committee recognised that, in general, drugs do not work in all people, and on-going treatment in the absence of a clinically meaningful improvement in HbA1c level would subject the patient to risks and the NHS to costs. The committee recognised that the trials did not include stopping rules. One clinical expert explained that, in practice, it might be difficult to stop treatment for people who had lost weight but had little improvement in HbA1c level. The committee acknowledged this, but noted that, while weight loss did not lessen the risk of complications in the company's model, it improved quality of life. However, it highlighted that dapagliflozin does not have a marketing authorisation for weight loss. It also noted that, during the technical engagement, clinical experts suggested a range of stopping rules based on safety and treatment effectiveness, demonstrated by improvements in HbA1c level alone or in combination with weight loss. The committee concluded that it was reasonable that dapagliflozin would be stopped if it did not result in improved glycaemic control, and that this should be assessed at 6 months (see section 3.7) and regularly after this. It concluded that, given the increased risk of diabetic ketoacidosis (see section 3.10), if glycaemic control does not improve, it would not be appropriate for people to continue taking dapagliflozin.

Cost-effectiveness estimate

The company's revised base case includes many of the committee's preferences

3.18 The company's revised base case included:

- people with insulin needs of more than 0.5 units/kg of body weight/day (see section 3.10)

- a progressive increase in HbA1c level of 0.045 percentage points per year and in body weight of 0.1 kg/year after 52 weeks (the duration of the trials) for both arms
- a stopping rate in year 1 for dapagliflozin based on the stopping rate seen in DEPICT for any reason at 52 weeks and, for subsequent years, a lower stopping rate based on the stopping rate for adverse events from DEPICT
- mortality and disutility associated with severe hypoglycaemia, diabetic ketoacidosis and life-threatening urogenital infections, such as Fournier's gangrene
- scenarios using both additive and multiplicative approach to disutilities
- utility values from 1 source (Peasgood et al. 2016)
- costs related to increased blood glucose testing, additional ketone monitoring and visits to diabetes specialist teams for dapagliflozin.

The committee concluded that these changes were appropriate as a basis for its decision making, but not in line with all its preferences (see section 3.19). It noted that the probabilistic and deterministic estimates of cost effectiveness for dapagliflozin plus insulin therapy compared with insulin therapy alone in the company's revised base case were £14,344 and £13,775 per QALY gained respectively.

The company provides scenario analyses to address concerns about extrapolating the trial results over a patient's lifetime

3.19 The committee continued to have concerns about the company's revised base-case analysis, in which the company:

- assumed that the degree and duration of improvement in HbA1c level seen in DEPICT (0.34 percentage point reduction over 1 year) would lead to a proportional reduction in long-term complications based on the DCCT/EDIC data, despite these studies reporting a much larger reduction (about 2 percentage points sustained over 10 years; see section 3.14)

- assumed that the effect on the risk of developing diabetes-related complications occurred immediately when HbA1c changes (see section 3.14)
- assumed no waning of treatment effect over time (see section 3.16)
- did not include any treatment stopping rules (see section **Error! Reference source not found.**).

To address these concerns, the company provided scenario analyses in which it did not model any:

- treatment effects in HbA1c or weight beyond the 52-week trial period for dapagliflozin plus insulin and insulin alone, at which point everyone stopped dapagliflozin (see section 3.14)
- change in HbA1c level from baseline in either arm (the benefit of dapagliflozin on weight was retained and people continued dapagliflozin treatment in this scenario; see section 3.14).

These scenarios resulted in deterministic incremental cost-effectiveness ratios of £6,385 and £19,122 per QALY gained respectively, relative to the company's original base case (£6,618 per QALY gained).

Dapagliflozin with insulin appears to be cost effective when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy

3.20 The committee considered the company's revised base case and the scenario analyses. It 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 27 kg/m^2 or more when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy, only if:

- they are on insulin doses of more than 0.5 units/kg of body weight/day (see section 3.3) and

- they have completed a structured education programme such as DAFNE, that includes training on diabetes ketoacidosis before starting treatment (see section 3.3) and
- treatment is started and supervised in a hospital diabetes clinic and
- HbA1c level is assessed after 6 months (and regularly after this) and dapagliflozin is stopped if there has not been a sustained improvement in glycaemic control (that is, a fall in HbA1c level of at least 0.3%).

Other factors

No equality issues were identified

3.21 No equality issues were raised by stakeholders.

There are no additional benefits not adequately captured in the QALY

3.22 The committee recognised that there is an unmet need for people with inadequately controlled type 1 diabetes despite optimised insulin therapy. It agreed that dapagliflozin is innovative but may not be considered a step change in managing type 1 diabetes because of the modest benefits seen in the clinical trials (see section 3.9). In response to the appraisal consultation document, stakeholders indicated that they considered there were additional gains in health-related quality of life over those already included in the QALY calculations. These included benefits on glycaemic variability and preventing weight gain. The committee concluded that there were no additional benefits not adequately captured in the QALY.

4 Implementation

Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.1 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.2 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has type 1 diabetes not controlled by insulin therapy alone and the doctor responsible for their care thinks that dapagliflozin is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, Appraisal Committee
July 2019

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Sharlene Ting
Technical lead

Ross Dent
Technical adviser

Jeremy Powell
Project manager

ISBN: [to be added at publication]