

**NATIONAL INSTITUTE FOR HEALTH AND CARE  
EXCELLENCE**

**Appraisal consultation document**

**Dapagliflozin with insulin for treating type 1  
diabetes**

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using dapagliflozin in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

**This document has been prepared for consultation with the consultees.**

It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the [committee papers](#)).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

**Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.**

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using dapagliflozin in the NHS in England.

For further details, see NICE's [guide to the processes of technology appraisal](#).

**The key dates for this appraisal are:**

Closing date for comments: 15<sup>th</sup> May 2019

Second appraisal committee meeting: 30<sup>th</sup> May 2019

Details of membership of the appraisal committee are given in section 5.

# 1 Recommendations

- 1.1 The committee was minded not to recommend dapagliflozin with insulin as an option for treating type 1 diabetes in adults with a BMI of at least 27 kg/m<sup>2</sup>, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy.
- 1.2 The committee recommends that NICE requests clarification and analyses from the company for the second appraisal committee meeting, including:
- a clear presentation of the risk equations in the model and their sources (see section 3.11)
  - scenario analyses in which the source of risk equations for macrovascular complications is varied (see section 3.13)
  - a clear presentation of the relationship assumed between the degree and duration of improvement in HbA1c seen in the DEPICT trials, and the reduction in long-term complications based on the data from the Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC) study (see sections 3.13 and 3.14)
  - scenario analyses in which the benefit associated with the degree and duration of improvement in HbA1c seen in the DEPICT trials is not proportional to that resulting from the larger, sustained reduction in HbA1c seen in DCCT/EDIC (see section 3.14)
  - scenario analyses in which the risk of developing diabetes-related complications does not change immediately when HbA1c changes (see section 3.14)
  - analyses that include the baseline characteristics that reflect people in England with type 1 diabetes likely to have dapagliflozin (see sections 3.8 and 3.15), and excludes people with a 'low insulin need' defined as 0.5 units/kg of body weight (see sections 3.3 and 3.15)
  - analyses that include a progressive increase in HbA1c and weight over time in the model (see section 3.16)

- scenario analyses that include a waning over time of the treatment effect for dapagliflozin (see section 3.17)
- scenario analyses that include criteria defining when to stop treatment (see section 3.18)
- analyses that include a stopping rate for dapagliflozin based on the probability of stopping for any reason from the DEPICT trials in year 1, and decreased rates in subsequent years (see section 3.19)
- analyses that include a stopping rate for the standard of care arm of 0 (see section 3.19)
- analyses that include the disutility and risk of death from Fournier's gangrene, severe hypoglycaemia and diabetic ketoacidosis (see section 3.20)
- analyses using disutilities with face validity for minor and major amputations (see section 3.22)
- analyses that include additional ketone monitoring, increased blood glucose testing and additional visits to diabetes specialist teams for people having dapagliflozin (see section 3.23)
- the results of probabilistic sensitivity analyses (see section **Error! Reference source not found.**)
- both the additive and multiplicative approach to disutilities (see section 3.21)
- scenario analyses including EQ-5D data from DEPICT (see section 3.22)
- a clear presentation of the different utility values available from the literature and sensitivity analyses exploring the effect of using values from different sources (see section 3.22).

Where appropriate, these analyses should be combined to give cumulative results.

### **Why the committee made these recommendations**

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

There is no clinical evidence to show that dapagliflozin increases how long people live, but this assumption is included in the economic model. The model and other assumptions, such as how treatment effects are likely to change after 1 year, lack credibility. Therefore, the committee is minded not to recommend dapagliflozin as an option for type 1 diabetes in the NHS.

## 2 Information about dapagliflozin

<b>Marketing authorisation</b>	Dapagliflozin (Forxiga, AstraZeneca) is indicated for the treatment of 'type 1 diabetes mellitus as an adjunct to insulin in patients with a BMI $\geq 27$ kg/m <sup>2</sup> , 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. 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.
<b>Dosage in the marketing authorisation</b>	Administered orally at a dosage of 5 mg once daily.
<b>Price</b>	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 5) considered evidence submitted by AstraZeneca, a review of this submission by the evidence review group, and the technical report

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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, physical activity and managing blood glucose. The guideline advises on targets for HbA1c, 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 their insulin would normally have done a structured education course and may be using an insulin pump. 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 medicines that help people to reach good glycaemic control without complications**

3.2 One clinical expert explained that managing blood glucose levels involves 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 medicines that help people to get good control of their diabetes without complications.

## ***Positioning of dapagliflozin in the treatment pathway***

### **The position of dapagliflozin in the treatment pathway is appropriate**

3.3 The company explained that the European Medicines Agency restricted the marketing authorisation for dapagliflozin to a subset of people with type 1 diabetes, that is, as an adjunct to insulin in people with a BMI of 27 kg/m<sup>2</sup> 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 aim of both these criteria is to manage the safety concerns of an increased risk of diabetic ketoacidosis associated with dapagliflozin. One clinical expert suggested that a threshold for 'low insulin need' could be 0.5 units/kg of body weight. Another clinical expert explained that it is difficult to define, but could be less than 0.4 units/kg to 0.5 units/kg. In addition to having a BMI of 27 kg/m<sup>2</sup> or more and insulin needs above 0.5 units/kg, the clinical experts noted further criteria that would define the appropriate clinical

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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 and recognise hypoglycaemia and diabetic ketoacidosis. The committee concluded that, in the NHS, dapagliflozin would likely be offered to people with a BMI over 27 kg/m<sup>2</sup>, insulin needs above 0.5 units/kg, inadequate glycaemic control despite structured education and optimised insulin therapy, and who are aware of the increased risk of diabetic ketoacidosis. It further concluded that this is an appropriate positioning of dapagliflozin in the treatment pathway.

## **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 only a transient and minimal improvement in HbA1c with metformin plus insulin therapy compared with insulin therapy alone. The clinical experts agreed that the trial results showed insulin plus metformin improved glycaemic control to a 'statistically significant but not a clinically significant' degree 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 to people on pump therapy, or when insulin pumps are not appropriate (but in people who could otherwise manage the increased risk of diabetic ketoacidosis associated with dapagliflozin). The committee concluded that the relevant comparator is optimised insulin therapy.



## ***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 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 of 2% over 10 years in patients who had multiple daily insulin injections (or an insulin pump) compared with those who had 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 multiple daily insulin injections lowered the risk of macrovascular complications and death compared with having previously been randomised to fewer daily insulin injections. 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% in HbA1c 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% for a baseline HbA1c of no more than 69 mmol/mol (8.5%) may be considered clinically meaningful.

The committee was aware that the changes in HbA1c seen in the dapagliflozin clinical trials 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 58.5 mmol/mol (7.5%) to 91.0 mmol/mol (10.5%). 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 (see section 3.3). 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<sup>2</sup>. Also, 54% were women, 6% smoked, 43% were on an insulin pump and 49% were on a renin-angiotensin-aldosterone system inhibitor (RAASi). Patients had had type 1 diabetes for an average of 21 years, had an average baseline HbA1c of 68 mmol/mol (8.4%) and used an average insulin dose of 0.8 units/kg. The clinical experts explained that, in the NHS, a much lower proportion of people use an insulin pump (10% to 15%) and that the prevalence of

smoking is higher. While this is unlikely to be a treatment-effect modifier, the baseline level of risk for complications such as diabetic ketoacidosis could be higher in the NHS. The committee concluded that the 'indicated' subgroup did not reflect patients with type 1 diabetes who would be offered dapagliflozin in the NHS.

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

3.9 The pooled DEPICT trial results showed a statistically significantly larger reduction in HbA1c from baseline at 24 weeks in patients having dapagliflozin plus insulin therapy than patients having placebo plus insulin therapy. However, after an initial reduction, HbA1c increased over time in both arms (see table 1). In addition, patients on dapagliflozin plus insulin therapy lost more weight than patients on placebo plus insulin therapy at 24 weeks, which was sustained at 52 weeks. One clinical expert explained that, in the [REMOVAL](#) trial, which compared metformin plus insulin therapy with insulin therapy alone, there was a reduction in HbA1c of 0.13% from baseline in patients having metformin at 3 years. However, this was accounted for by an initial reduction at 3 months of 0.24% that was not sustained. The committee recalled the clinical expert's view that the differences in HbA1c in REMOVAL were 'statistically but not clinically significant' (see section 3.4). It noted that the pooled reduction in HbA1c at 52 weeks seen in DEPICT was similar in size (0.26%). The committee also noted that, in the DEPICT trials, it was not possible to assess whether patients on dapagliflozin plus insulin lived longer than patients on insulin alone. In addition, 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. However, it questioned the importance of the modest improvements in HbA1c seen in DEPICT, and whether these differences would be sustained over a lifetime.

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

Change	24 weeks		52 weeks	
	Dapagliflozin 5 mg plus insulin	Placebo plus insulin	Dapagliflozin 5 mg plus insulin	Placebo plus insulin
HbA1c (%)	-0.44 (0.05)	-0.01 (0.05)	-0.26 (0.06)	0.08 (0.06)
Weight (%)	-3.11 (0.29)	-0.01 (0.30)	-3.42 (0.29)	0.49 (0.30)
Weight (kg)	-2.86 (0.27)	-0.01 (0.27)	-3.15 (0.26)	0.45 (0.28)

### **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<sup>2</sup> or more, and excluded people with ‘low insulin needs’ (without explicitly defining this) to reduce the risk of this potentially life-threatening adverse effect. Nonetheless, in this restricted population, people having dapagliflozin plus insulin therapy were almost twice as likely to have proven diabetic ketoacidosis than people having insulin therapy only. The representative from the patient organisation explained that diabetic ketoacidosis has a substantial negative impact on 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 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). The committee concluded that dapagliflozin

would not be offered to someone without sufficient education and expertise to detect diabetic ketoacidosis. It also concluded that the absolute risk of diabetic ketoacidosis in the NHS was likely 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; its output lacks credibility**

3.11 The company used a patient-level, microsimulation model (Cardiff type 1 diabetes model) to simulate disease progression and complications over a life-time horizon. The company derived risk equations from the DCCT/EDIC study for microvascular complications and from the Swedish National Diabetes Registry for macrovascular complications to link the change in HbA1c to the risk of developing complications over a lifetime. Change in body weight was not linked to changes in risk of complications, but lower BMI was associated 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). The committee questioned the face validity of the model output.

#### **The model outcomes have not been validated**

3.12 The company explained that the available studies to validate the model's predictive performance are limited in type 1 diabetes. The main source of data available is DCCT/EDIC but, because the company used this study as the basis of most of the risk equations, it could not use it to validate the model 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 externally validating the model. However, 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 it was still uncertain whether the model predicted what might occur after a relatively short period of improved glycaemic control and an increased risk of adverse events.

**Risk equations for macrovascular complications derived from the DCCT/EDIC data are preferred**

3.13 The committee noted that DCCT/EDIC also provided data on cardiovascular disease and queried why the company had not used the original trial-based data in preference to the Swedish registry data. The company explained that the Swedish registry provided risk equations but acknowledged that bespoke risk equations could have been developed with the DCCT/EDIC data. However, it added that the Swedish registry data were more recent than the DCCT/EDIC data and may better reflect the current background risk of events. The committee concluded that it would have preferred to see whether the model was sensitive to the choice of the risk equations for macrovascular complications. It also requested that the company provide a clear presentation of the risk equations that drive the incidence of diabetic complications over a patient's lifetime.

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

3.14 The committee noted that the statistically significant improvement in HbA1c seen in DCCT/EDIC was substantially bigger (2% reduction) and sustained for substantially longer (over 10 years) than the statistically significant improvement in HbA1c seen in the pooled DEPICT trials (0.26% reduction over 1 year). 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 seen in DCCT/EDIC in terms of fewer complications. The company also explained that changes in HbA1c in its model immediately lowered the risk of developing microvascular and

macrovascular complications, which the committee questioned. The committee highlighted 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. The committee therefore would prefer to see a range of scenario analyses in which the company has varied the benefit associated with the degree and duration of improvement in HbA1c seen in the pooled DEPICT trials (that is, has not assumed a proportional relationship). These scenarios would include an analysis in which there are no ongoing benefits associated with improved glycaemic control and body weight beyond the 52-week trial period. This would allow the committee to understand how sensitive the model is to assuming all, some and none of benefits seen in DCCT/EDIC accrued to people having dapagliflozin. In addition, the committee would prefer to see scenario analyses in which the risk of developing diabetes-related complications does not change immediately when HbA1c changes.

### ***Assumptions in the economic model***

#### **The modelled population should reflect the people with type 1 diabetes seen in NHS likely to be offered dapagliflozin**

3.15 The company used the baseline characteristics derived from the pooled DEPICT data for the 'indicated' subgroup in the model. The committee recalled that it did not consider that the population in the trials reflected patients seen in the NHS likely to be offered dapagliflozin (see section 3.8). In the NHS, it is likely that there are more people who smoke, a higher prevalence of complications, higher use of cardiovascular medications and lower rates of insulin-pump use. In addition, the committee was concerned that the model did not reflect the summary of product characteristics for dapagliflozin, which recommends that it should not be used in people with low insulin needs (see section 3.3), defined by the clinical experts as 0.5 units/kg of body weight. It concluded that the modelled population should reflect people in England with type 1 diabetes.

It also concluded that the company should provide analyses that restricts the population to include patients needing insulin at a dose of more than 0.5 units/kg of body weight.

### **The company should include a progressive increase in HbA1c and body weight in the model**

- 3.16 The company explained that it did not model a progressive increase in HbA1c and body weight. One clinical expert explained that HbA1c is likely to increase over time. One committee member noted that a publication of the Cardiff type 1 diabetes model ([McEwan et al. 2016](#)) included a progressive increase in HbA1c of 0.045%, and considered that this should also be included in this appraisal. The clinical experts explained that it is likely that body weight would increase over time, as it does in people without diabetes, but for people on dapagliflozin, body weight might increase at a slower rate than for people with type 1 diabetes not on dapagliflozin. The committee concluded that the company should include a progressive increase in HbA1c and body weight over the course of patients' lifetimes in both arms of its model.

### **Dapagliflozin treatment effects are likely to wane after 1 year**

- 3.17 In its base case, the company assumed that the treatment effects on HbA1c and body weight seen at 52 weeks for the subgroup representing the limited marketing authorisation from the pooled DEPICT trials were maintained for the remainder of the 79-year time horizon of the model so long as patients stayed on treatment. The committee questioned the plausibility of the company's assumption given that the treatment effect had already waned between 24 weeks and 52 weeks in the trials. Also, it had not seen any evidence that the decline in effects had plateaued by 52 weeks. The committee concluded that the treatment effect of dapagliflozin is likely to wane further beyond year 1. The committee noted that, in response to the technical engagement, the company provided various scenarios reflecting waning. These included a scenario in which the effect of dapagliflozin on HbA1c waned to baseline between year 1



and year 2 and in which everyone stopped treatment at year 2. The committee considered that waning should be incorporated into the model, with the rate informed by other trial data (for example, DCCT). It also concluded that the company should provide a scenario in which the treatment effect wanes at the same rate over time as seen in the trial between 24 weeks and 52 weeks, and a scenario in which the treatment effect ceases at 52 weeks.

**The company should model a range of rules on when to stop treatment after assessing response to dapagliflozin**

3.18 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 the trials did not include stopping rules, but also recognised that they were too short to do this. It considered that it was reasonable that dapagliflozin would be stopped if it did not result in improved glycaemic control. The committee recognised that, in practice, it might be difficult to stop treatment for people who had lost weight only but that dapagliflozin does not have a marketing authorisation for weight loss. It agreed that it would have preferred to see different scenarios using a range of treatment stopping rules based on HbA1c at different timepoints.

**The company should base a stopping rate for dapagliflozin on the stopping rate seen for any reason at 52 weeks from DEPICT**

3.19 The company assumed that the probability that patients would stop dapagliflozin or standard care at 1 year equalled the probability of stopping treatment because of adverse events seen in the pooled 52-week DEPICT data. In its base case, the company applied the probability of stopping treatment only in the first year, after which it assumed that HbA1c and body weight returned to baseline values. The committee noted that patients stopped for reasons other than adverse events in DEPICT, and agreed that the stopping rate for any reason should be applied in the model at 1 year. It noted that feedback during the

technical engagement from clinical experts suggested that people would also stop treatment in subsequent years, but that the rate is likely to decrease because most adverse events occur in the first year. One clinical expert suggested stopping rates of 15% in first year, 10% in second year, and thereafter 5% per year. The committee concluded that the company should model the stopping rate for dapagliflozin based on the stopping rate for any reason, and apply a reduced rate in subsequent years. The committee noted that, in practice, the standard of care arm would not stop insulin therapy and concluded that the probability of stopping treatment in this arm should be 0, as provided in a company scenario in response to the technical engagement.

### ***Modelling adverse events***

#### **The company should include Fournier's gangrene and deaths from severe hypoglycaemia and diabetic ketoacidosis in the model**

3.20 In its base case, the company did not include life-threatening urogenital infections, such as Fournier's gangrene, as an adverse event in the model because it is rare. The company stated that no one in the DEPICT trials developed Fournier's gangrene. The committee was aware that small trials are unlikely to detect rare events, and that a [drug safety update](#) from the Medicines and Healthcare products Regulatory Agency emphasises the association between sodium-glucose co-transporter-2 inhibitors and Fournier's gangrene. The company also did not include deaths from severe hypoglycaemia or diabetic ketoacidosis in its base case. The committee acknowledged that deaths from these events are rare but do occur, so should be captured in the model. In response to the technical engagement, the company provided scenarios in which it modelled deaths from severe hypoglycaemia and diabetic ketoacidosis, but not Fournier's gangrene. The committee concluded that it would have also preferred to see Fournier's gangrene included in the model.

### ***Utility values in the economic model***

#### **The company should provide scenarios using both additive and multiplicative approach to disutilities**

3.21 Type 1 diabetes is associated with many complications that independently lower health-related quality of life. In its base case, for people with more than 1 complication, the company added together the values representing the decrements in quality of life, but also provided a scenario analysis in which it multiplied the values together. The committee noted that a third approach, which was used in the NICE guideline on [type 1 diabetes](#), involved applying only the value associated with the complication that has the largest impact on quality of life. The committee agreed that the additive and multiplicative approach were more appropriate than the minimum approach. It concluded that the company should present scenarios using both approaches to provide a range of cost-effectiveness estimates.

#### **The most robust source of utility values should be used**

3.22 The company used a range of sources for utility values in its model. In response to the technical engagement, it provided a scenario in which all the utility values came from 1 source ([Peasgood et al. 2016](#)). The committee agreed that the company should use the most robust sources of utility values, including those measuring quality of life associated with complications in type 2 diabetes, in preference to utility values from only a single source. However, the committee noted that some disutilities used in the model lacked face validity, such as the same disutility applied for minor and major amputations. In addition, it recognised that it may be appropriate to use utility values sourced from the literature for modelling, but it would have also preferred to see a scenario analysis including EQ-5D data from DEPICT.

## ***Costs in the economic model***

### **Increased blood glucose testing, and additional ketone monitoring and visits to diabetes specialist teams for dapagliflozin should be in the model**

3.23 In its base case, the company assumed no additional cost for ketone monitoring despite the increased risk of diabetic ketoacidosis (see section 3.10), and did not include increased blood glucose testing or additional visits to diabetes specialist teams associated with starting dapagliflozin. The company provided scenarios in response to the technical engagement in which it included ketone monitoring for patients having dapagliflozin. The committee noted that the scenario in which patients on dapagliflozin tested for ketones 3 times more often than patients on insulin alone was appropriate. During the technical engagement, clinical experts highlighted that the increased risk of diabetic ketoacidosis continues as long as treatment with dapagliflozin continues. The committee also noted that the company did not include more visits to a specialist for patients on dapagliflozin than patients on insulin alone, or the possibility that patients on dapagliflozin would do more frequent self-blood glucose monitoring. The committee concluded that these should all be reflected in the model.

## ***Cost-effectiveness estimate***

### **No analyses included the committee's preferences**

3.24 The analyses considered by the committee used the list price for dapagliflozin. However, the committee noted that, because dapagliflozin would only be offered in specialist care, then it would be eligible for a patient access scheme discount. The committee recalled its concerns about the company's base-case analysis, which were that it:

- assumed that the degree and duration of HbA1c improvement seen in DEPICT (0.26% 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, 2%, sustained over 10 years (see section 3.14)

- assumed that the impact on the risk of developing diabetes-related complications was immediate when HbA1c changes (see section 3.14)
- used the baseline characteristics of the DEPICT 'indicated' population, which does not reflect people in England with type 1 diabetes likely to have dapagliflozin (see sections 3.8 and 3.15)
- did not include a progressive increase in HbA1c and weight over time in the model (see section 3.16)
- assumed no waning of treatment effect over time (see section 3.17)
- did not include any treatment stopping rules (see section 3.18)
- included a stopping rate for dapagliflozin at 1 year based on the probability of stopping because of adverse events only from the DEPICT trials (see section 3.19)
- did not include risk of disutility and death from Fournier's gangrene, severe hypoglycaemia and diabetic ketoacidosis (see section 3.20)
- included disutilities that lacked face validity such as the same disutility applied for both minor and major amputations (see section 3.22)
- did not include additional ketone monitoring, increased blood glucose testing and additional visits to diabetes specialist team for patients on dapagliflozin (see section 3.23)

did not provide the results of the probabilistic sensitivity analyses (see section **Error! Reference source not found.**).

In addition, the committee considered that it would have preferred the company to have provided the following scenarios:

- analyses using both the additive and multiplicative approach to disutilities (see section 3.21)
- analysis including EQ-5D data from DEPICT (see section 3.22)
- sensitivity analyses using values for utilities from different sources (see section 3.22).

### **Results from probabilistic sensitivity analysis should be provided**

3.25 The committee was aware that NICE's [guide to the methods of technology appraisal](#) states that probabilistic sensitivity analyses are preferred, and noted that none had been presented by the company during the technical engagement. The committee concluded that the company should present results from probabilistic sensitivity analyses.

### ***Other factors***

#### **No equality issues were identified**

3.26 No equality issues were raised by stakeholders.

#### **Dapagliflozin is an innovative treatment**

3.27 The committee recognised that there is an unmet need for people with type 1 diabetes inadequately controlled despite optimised insulin therapy. The committee 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). It did not hear that there were any additional gains in health-related quality of life over those already included in the QALY calculations.

## **4 Proposed date for review of guidance**

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. 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  
April 2019

## 5 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

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