

**NATIONAL INSTITUTE FOR HEALTH AND CARE  
EXCELLENCE**

**Appraisal consultation document**

**Canagliflozin, dapagliflozin and  
empagliflozin as monotherapies for treating  
type 2 diabetes**

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using canagliflozin, dapagliflozin and empagliflozin as monotherapies in the NHS in England. The Appraisal Committee has considered the evidence submitted 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 draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 9) and the public. This document should be read along with the evidence base (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 provisional 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 these technologies. 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 determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using canagliflozin, dapagliflozin and empagliflozin as monotherapies in the NHS in England.

For further details, see the Guides to the technology appraisal process.

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

Closing date for comments: Wednesday 27<sup>th</sup> January

Second Appraisal Committee meeting: Tuesday 16<sup>th</sup> February

Details of membership of the Appraisal Committee are given in section 8, and a list of the sources of evidence used in the preparation of this document is given in section 9.

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

## **1 Appraisal Committee's preliminary recommendations**

1.1 Canagliflozin, dapagliflozin and empagliflozin as monotherapies are recommended as options for treating type 2 diabetes in adults when diet and exercise alone do not provide adequate glycaemic control in patients and for whom metformin is contraindicated or not tolerated, only if:

- a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and
- a sulfonylurea or pioglitazone is not appropriate.

1.2 Adults whose treatment with canagliflozin, dapagliflozin or empagliflozin as monotherapy is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

## **2 Clinical need and practice**

2.1 Type 2 diabetes is a chronic metabolic disorder in which a lack of the hormone insulin or resistance to its action causes elevated blood glucose levels (hyperglycaemia). It is a progressive disease, gradually worsening over time. The UK Prospective Diabetes Study (UKPDS) estimated an increase in haemoglobin A1c (HbA1c), which identifies average plasma glucose concentration, of around 0.2% per year.

- 2.2 Approximately 2.7 million people in England of 17 and over had a diagnosis of diabetes in 2013, of whom 90% had type 2 diabetes. However, many people with type 2 diabetes are undiagnosed, and so the number of people with the condition may be higher than reported. The prevalence of type 2 diabetes in England is rising because of increased obesity, decreased physical activity and increased life expectancy after diagnosis because of better cardiovascular risk protection. Type 2 diabetes is particularly prevalent in people of African, South Asian and Caribbean family origin.
- 2.3 Type 2 diabetes is not easy to live with and has a big impact on the day-to-day lives of people with the condition, their families and their carers. People are often concerned about the disease developing further. They may have to inject insulin, or may develop complications such as deteriorating eye sight or neuropathy, which could make it difficult for them to take their medication, to manage their blood glucose levels or to stay active.
- 2.4 Lowering blood glucose levels and achieving good diabetes control minimises the risk of developing complications, reduces the likelihood that someone will need to inject insulin to manage their disease, and can help to reduce anxiety and depression caused by the stress of managing diabetes. Diabetes can sometimes be controlled by diet and exercise, otherwise, tablets or insulin are needed.

### **3 The technologies**

- 3.1 Canagliflozin (Invokana, Janssen), dapagliflozin (Forxiga, AstraZeneca) and empagliflozin (Jardiance, Boehringer Ingelheim and Lilly UK) are all selective sodium-glucose cotransporter 2 (SGLT-2) inhibitors, which block the reabsorption of glucose in the

kidneys and promote excretion of excess glucose in the urine. Through this mechanism these drugs may help control glycaemia independently of insulin pathways. They all have UK marketing authorisations for treating type 2 diabetes to improve glycaemic control in adults:

- as monotherapy: when diet and exercise alone do not provide adequate glycaemic control in people for whom the use of metformin is considered inappropriate due to intolerance or contraindications
- as add-on combination therapy: with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

### ***Canagliflozin***

3.2 The recommended starting dose of canagliflozin is 100 mg orally once daily. In people tolerating canagliflozin 100 mg once daily who have an estimated glomerular filtration rate (eGFR) of at least 60 ml/minute/1.73 m<sup>2</sup> or creatinine clearance of at least 60 ml/minute and who need tighter glycaemic control, the dose can be increased to 300 mg once daily. For people with renal impairment, the summary of product characteristics notes that canagliflozin should not be started in people with an eGFR of less than 60 ml/minute/1.73m<sup>2</sup> or creatinine clearance of less than 60 ml/minute. In people tolerating canagliflozin whose eGFR persistently falls below 60 ml/minute/1.73 m<sup>2</sup> or whose creatinine clearance persistently falls below 60 ml/minute, the dose of canagliflozin should be adjusted to or maintained at 100 mg once daily. Canagliflozin should be discontinued when eGFR is persistently below 45 ml/minute/1.73 m<sup>2</sup> or creatinine clearance is persistently below 45 ml/minute.

- 3.3 The summary of product characteristics lists the following adverse reactions for canagliflozin as the most commonly reported: vulvovaginal candidiasis, urinary tract infection, and polyuria. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 3.4 The price of canagliflozin is £39.20 for a 30-tablet pack of 100 mg or 300 mg tablets (excluding VAT; 'British national formulary' [BNF], accessed online September 2015). Costs may vary in different settings because of negotiated procurement discounts.

### ***Dapagliflozin***

- 3.5 The recommended dose is 10 mg dapagliflozin orally once daily for monotherapy and add-on combination therapy with other glucose-lowering medicinal products including insulin.
- 3.6 The summary of product characteristics lists the following adverse reactions for dapagliflozin: urinary tract and genital infection, back pain, dysuria, polyuria, dyslipidaemia and elevated haematocrit. Dapagliflozin is not recommended for people with moderate to severe renal impairment (people with a creatinine clearance rate of less than 60 ml/min or an eGFR of less than 60 ml/min/1.73 m<sup>2</sup>) because its efficacy depends on renal function. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 3.7 The list price of dapagliflozin is £36.59 for a 28-tablet pack of 5 mg or 10 mg tablets (excluding VAT; 'British national formulary' [BNF], accessed online September 2015). Costs may vary in different settings because of negotiated procurement discounts.

## ***Empagliflozin***

- 3.8 The recommended starting dose is 10 mg orally once daily for monotherapy. According to the summary of product characteristics, the dose can be increased to a maximum of 25 mg daily for people who tolerate empagliflozin well and need tighter glycaemic control, if they have an eGFR of 60 ml/min/1.73 m<sup>2</sup> or more.
- 3.9 The summary of product characteristics includes the following adverse reactions for empagliflozin: urinary tract infection and polyuria. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 3.10 The list price of empagliflozin is £36.59 for a 28-tablet pack of 10 mg or 25 mg tablets (excluding VAT; 'British national formulary' [BNF], accessed online September 2015). Costs may vary in different settings because of negotiated procurement discounts.

## **4 Evidence and interpretation**

The Appraisal Committee (section 8) considered evidence from a number of sources (section 9).

### ***Clinical effectiveness***

- 4.1 The Assessment Group (AG) did a systematic review of the literature to identify studies evaluating the clinical effectiveness and safety of canagliflozin, dapagliflozin and empagliflozin as monotherapies for adults with type 2 diabetes not controlled by diet and exercise alone. The AG noted that the target population as defined in the scope was also people with type 2 diabetes who were unable to take metformin, but because this was not a distinction made in the trials, this could not form part of the search criteria. The AG identified 7 relevant double-blind randomised controlled trials (2 each for canagliflozin and empagliflozin

[including both licensed doses], and 3 for dapagliflozin). Four of the trials were international, 2 were solely based in Japan, and 3 were based in 'Asian' countries (including Japan and China). The canagliflozin and dapagliflozin trials compared treatments with placebo, and the empagliflozin trials included comparisons with DPP4-inhibitors. The AG did not identify any additional trials relevant to the scope that were not identified in the companies' submissions.

4.2 The AG stated that most people in the trials:

- had diabetes for less than 5 years
- had an HbA1c of approximately 7.5–8.4% (in the main comparison groups) and 10.6–11.5% (in the high HbA1c subgroups)
- had a BMI of 25–34 kg/m<sup>2</sup>
- were women (34–59% in the main comparison groups).

The mean age was 50–60 years. The clinical trials also reported subgroups based on baseline HbA1c and weight.

4.3 The primary outcome in all trials was change in HbA1c from baseline to the end of the main intervention period (24 to 26 weeks). For the primary outcome, all active treatments reduced HbA1c by between –0.39% and –1.17% more than with placebo. The reductions for empagliflozin were also greater than those for sitagliptin (statistical significance was not presented).

4.4 Secondary outcomes included change in weight, systolic blood pressure, hypoglycaemia, and cholesterol (total cholesterol, high-density lipoprotein [HDL] cholesterol and low-density lipoprotein [LDL] cholesterol). All selective sodium-glucose cotransporter 2 (SGLT-2) inhibitors reduced weight, by between 0.97 kg and 3.9 kg more than placebo. Compared with placebo, all SGLT-2 inhibitors



reduced systolic blood pressure, however no results were statistically significant. The AG stated that given the infrequency of reported hypoglycaemia, the similar outcomes between active and placebo arms, and the cut-off level used, it was reasonable to assume that the SGLT-2 inhibitors did not cause hypoglycaemia. For cholesterol, not all trials reported all outcomes. Generally, the SGLT-2 inhibitors led to increases in all types of cholesterol.

### **Adverse effects of treatment**

- 4.5 The AG reviewed outcomes related to adverse effects of treatment in the clinical trials. The SGLT-2 inhibitors were generally associated with a higher incidence of urinary tract infections and genital tract infections, both of which were more common in women. Most of these infections were mild to moderate in severity and responded to standard treatment. No evidence of a dose-response relationship was found with any treatment.
- 4.6 The companies reported that canagliflozin, dapagliflozin and empagliflozin were well tolerated. The AG noted that rates of stopping treatment across the studies ranged from 7–20%, with rates balanced across groups. It noted that in the study by Inagaki et al. (2014), the rate of stopping was 7% in the canagliflozin group and 20% in the placebo group.

### **Meta-analysis**

- 4.7 Because there was no direct evidence to compare the SGLT-2 inhibitors with all the comparators in the scope, the companies and the AG did network meta-analyses comparing SGLT-2 inhibitors with dipeptidyl peptidase-4 (DPP-4) inhibitors, sulphonylureas, pioglitazone and repaglinide for people with type 2 diabetes not controlled by diet and exercise and alone. Not all network meta-analyses included repaglinide; submissions noted a lack of

evidence and infrequent use in clinical practice. The AG noted that the eligibility criteria for the trials did not include metformin contraindication or intolerance, therefore not all of the patients in the trials were in line with the scope for this appraisal.

- 4.8 All companies and the AG presented network meta-analysis results for outcomes including mean change in HbA1c, mean change in weight or BMI, mean change in systolic blood pressure, and hypoglycaemia incidence.

***Janssen network meta-analysis***

- 4.9 In its network meta-analyses Janssen presented outcomes for: SGLT-2 inhibitors (canagliflozin 100 mg and 300 mg; dapagliflozin 5 mg and 10 mg; empagliflozin 10 mg and 25 mg), DPP-4 inhibitors (linagliptin, saxagliptin, sitagliptin, vildagliptin); pioglitazone (15 mg, 30 mg and 45 mg); sulphonylureas (glibenclamide, gliclazide, glimepiride, glipizide). The company presented both fixed-effects and random-effects models and did analyses at 26 weeks (plus or minus 4 weeks) to match the assessment times in its trials. Trials reporting results at 16–21 weeks and 31–36 weeks, trials published in conference abstracts only, and trials assessing repaglinide were included in sensitivity analyses. The company also did sensitivity analyses excluding non-double-blind trials.

- 4.10 The company presented comparisons between all SGLT-2 inhibitors (all doses), several types of DPP-4 inhibitors and sulphonylureas, and 3 doses of pioglitazone. For canagliflozin 100 mg:

- compared with SGLT-2 inhibitors dapagliflozin and empagliflozin 10mg, it resulted in a greater reduction in weight, and there were no statistically significant differences for HbA1c and systolic blood pressure.

- compared with SGLT-2 inhibitors canagliflozin 300mg and empagliflozin 25mg, there were no statistically significant differences
- compared with DPP-4 inhibitors, it resulted in a greater reduction in HbA1c, weight and systolic blood pressure (all results statistically significant, other than compared with sitagliptin for HbA1c, where there was no difference)
- compared with sulphonylureas, only results for the HbA1c outcome were presented; there were no statistically significant differences
- compared with pioglitazone (all doses), it was statistically significantly more effective for change in weight and systolic blood pressure, and there was no statistically significant difference for HbA1c
- in all comparisons, there were no statistically significant differences for hypoglycaemia.

4.11 The company stated that most sensitivity analyses had a minor effect on the results.

### ***AstraZeneca network meta-analysis***

4.12 AstraZeneca presented outcomes for interventions as classes of treatment, rather than for specific drugs. The company stated this approach was relatively common in meta-analyses of antidiabetic agents because of the large number of drugs and similar levels of effectiveness within most drug classes. Classes of drug considered were SGLT-2 inhibitors, DPP-4 inhibitors, sulphonylureas, and pioglitazone. The company only included trials reporting data at 24 weeks (plus or minus 6 weeks). It did sensitivity analyses using the alternative model to that presented in the base case (fixed- or random-effects); adjustment of HbA1c using a meta-regression;

and exclusion of 9 trials including only people described as 'Asian'.  
For SGLT-2 inhibitors:

- compared with DPP-4 inhibitors and pioglitazone, there were no statistically significant differences for HbA1c and hypoglycaemia, and SGLT-2 inhibitors were statistically significantly more effective for weight and systolic blood pressure reduction
- compared with sulphonylureas, there were no statistically significant differences for HbA1c or systolic blood pressure; and SGLT-2 inhibitors demonstrated statistically significantly greater weight loss and fewer hypoglycaemic events

4.13 The company presented results for sensitivity analyses. It stated that there were only small differences between the base case and sensitivity analyses.

4.14 The company and the AG noted that some people in some of the dapagliflozin trials had a response to treatment with placebo, which was not seen in other dapagliflozin trials, or in trials for other SGLT-2 inhibitors. The AG stated this may have been because of the short duration of the trials, and a motivated placebo group having diet and exercise interventions for the first time.

### ***Boehringer Ingelheim network meta-analysis***

4.15 Boehringer Ingelheim presented outcomes for the following interventions in its network meta-analyses: SGLT-2 inhibitors (canagliflozin 100 mg and 300 mg, dapagliflozin 5 mg and 10 mg, and empagliflozin 10 mg and 25 mg), sulphonylureas (as a class), DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin), pioglitazone and repaglinide. The company noted that its economic model only considered sitagliptin 100 mg as a proxy for all DPP-4 inhibitors. The company considered 3 time points in its network meta-analysis: 24 weeks, 52 weeks and more than

52 weeks (only the results for 24 and 52 weeks are included here because these are the results used in the economic model). The company also presented results for a meta-regression analysis, in which results were adjusted for baseline HbA1c.

- 4.16 For change in HbA1c, all results including empagliflozin 10 mg and 25 mg and other SGLT-2 inhibitors showed statistically significantly greater reductions in HbA1c compared with placebo at 24 weeks and 52 weeks. For hypoglycaemia and urinary tract infection outcomes, the company found no statistically significant differences for any treatment compared with placebo at any time point. However it noted that studies reported low numbers or zero events, therefore results were unreliable with wide credible intervals. For weight change, statistically significantly greater reductions in weight were seen with all SGLT-2 inhibitors compared with placebo at 24 weeks. The company noted this was maintained for empagliflozin at 52 weeks (results at 52 weeks were not presented for other SGLT-2 inhibitors). People taking pioglitazone, sulphonylureas and DPP-4 inhibitors had increases in weight. For systolic blood pressure, all SGLT-2 inhibitors showed statistically significant decreases compared with placebo.

***Assessment Group network meta-analysis***

- 4.17 The AG considered the following interventions in its network meta-analysis: canagliflozin (100 mg and 300 mg), dapagliflozin (10 mg), empagliflozin (10 mg and 25 mg), sulphonylureas, DPP-4 inhibitors (linagliptin, sitagliptin and vildagliptin) and pioglitazone. It used trials of 24–26 weeks in which placebo was the comparator.

- All SGLT-2 inhibitors were statistically significantly more effective than placebo for HbA1c and weight change.
- Compared with sitagliptin, SGLT-2 inhibitors were more effective for HbA1c (in some instances this reached statistical

significance) and all SGLT-2 inhibitors were more effective for weight change.

- Compared with sulphonylureas, there were no statistically significant differences for HbA1c, and SGLT-2 inhibitors were more effective for weight change.
- Compared with pioglitazone, dapagliflozin and empagliflozin 10mg were statistically significantly less effective for HbA1c (no differences compared with other SGLT-2 inhibitors), and SGLT-2 inhibitors were more effective for weight change.

4.18 The AG considered the effectiveness of the SGLT-2 inhibitors compared with each other. It noted that both doses of canagliflozin lowered HbA1c more than dapagliflozin and both doses of empagliflozin. It stated that some of this reduction may be because studies suggested that canagliflozin, unlike other SGLT-2 inhibitors, may also have an effect on the SGLT-1 receptor (which reduces absorption of glucose in the gut). However, it could not be certain whether this dual mechanism of action was clinically significant.

4.19 The AG stated that there were several issues to consider when interpreting the results of the network meta-analyses:

- the higher doses of canagliflozin and empagliflozin were more effective than the starting doses. However in the clinical trials, people were randomised to the larger dose, rather than have to titrate up to it if the starting dose was insufficiently effective. Therefore it was not clear if the results seen for people starting on larger doses would be seen in clinical practice
- in the dapagliflozin clinical trials in the network, people in the placebo arm had a reduction in their HbA1c levels. This could be because of better access to lifestyle advice, but this was unlikely

- many trials included in the network provided data on only some of the variables that are used in the UK Prospective Diabetes Study (UKPDS) outcomes model
- there was a lack of data in the trials to calculate the cholesterol ratio (ratio of total cholesterol to HDL cholesterol, [TC: HDL ratio]) for use in the economic models, and when it was reported, it was often high. These high results were not likely to reflect clinical practice because of the use of statins
- some of the trial evidence included the intervention given as combination therapy. For example, most available evidence for sulphonylureas for HbA1c and weight gain was from studies in which it was given with metformin. This may not represent their effectiveness when used as monotherapy
- several trials noted issues with the durability of the effect of sulphonylureas (that is, the initial response was followed by a relatively rapid deterioration). In 1 trial the AG noted that 34% of people taking sulphonylureas needed additional treatment within 5 years compared with 15% of those taking rosiglitazone.

### **Evidence from patient and clinical experts**

4.20 Comments from the patient organisation were that people with diabetes reported advantages of taking dapagliflozin (when used as combination therapy, as currently recommended by NICE). These were lowered blood glucose levels leading to increased self-confidence in overall diabetes management, ease of administration, and no need to take the tablets with food. A concern about the treatment was the risk of genital fungal infection. It was noted that dapagliflozin has been shown to have positive effects on weight management, so may be of increased benefit to people with type 2 diabetes who are overweight.

4.21 The clinical experts stated that the SGLT-2 inhibitors have an insulin independent mode of action, unlike other oral diabetes treatments used when metformin cannot be tolerated. This makes the risk of hypoglycaemia extremely low. They stated that the SGLT-2 inhibitors were effective in improving HbA1c, and also had additional benefits of reducing weight and blood pressure. The clinical experts stated there were no data to confirm whether any SGLT-2 inhibitor was most effective. For adverse events, the clinical experts stated that genital fungal infection was a concern, but this was usually mild and not repeated. There were no data to suggest an increase in more serious adverse events such as malignancies, but more long-term data would be needed to confirm this. The patient expert stated that she had not had any adverse events while taking SGLT-2 inhibitors.

### ***Cost effectiveness***

4.22 The AG carried out a systematic review of the literature to identify studies of the cost effectiveness of SGLT-2 inhibitor monotherapy compared with sulphonylureas, DPP-4 inhibitors, pioglitazone and repaglinide for people with type 2 diabetes for whom metformin was not appropriate. No studies were found to be relevant to all SGLT-2 inhibitors, and the AG and all the companies used existing economic models for diabetes to consider the cost effectiveness of SGLT-2 inhibitor monotherapy.

4.23 The AG noted that the UKPDS had been used for many assumptions in the cost-effectiveness analyses. It explained that UKPDS68 included a number of equations for estimating the progression of HbA1c, systolic blood pressure, ratio of total cholesterol to HDL cholesterol and smoking status over time, and the annual risk of micro- and macrovascular events associated with diabetes, for example stroke and blindness. It also predicts the



annual risk of death and provides costs associated with adverse events. UKPDS68 was used by Oxford University to derive the OM1 cost-effectiveness model. It has recently been updated by UKPDS82, which provides an alternative set of equations based on longer follow-up data to those used in UKPDS68. The latest version is UKPDS84.

### **Overview – all models**

- 4.24 In all the models, people entered having had 1 of the scope interventions. The intervention determined the initial change from baseline in outcomes HbA1c, systolic blood pressure, weight change, and cholesterol levels. These outcomes progressed over time, with HbA1c worsening until it rose above 7.5%, triggering the start of another treatment (which improved outcomes, followed by another progressive worsening of HbA1c). Throughout the model, people received a pre-specified treatment sequence depending on their initial treatment.
- 4.25 All models included micro- and macrovascular health states for morbidities and increased mortality associated with diabetes. Microvascular health states included retinopathy (including macular oedema and blindness), chronic kidney disease (ranging from stage 1 to end-stage renal disease), and neuropathy (including peripheral vascular disease and amputation). Macrovascular health states included ischaemic heart disease, myocardial infarction, stroke, and congestive heart failure. The models also accounted for weight change, hypoglycaemia, urinary tract infections, genital tract infections, peripheral oedema, and stopping treatment. In addition, they included a health state in which modelled patients were free from complications. Health states were associated with costs, utility values, and in some cases a possible treatment contraindication or

with excess risk of death (for example, through stroke or myocardial infarction).

- 4.26 The AG stated that the assumptions used in the Janssen model differed from those of the other 2 submissions. The main difference was the assumption used to model the change in the outcomes HbA1c, systolic blood pressure and cholesterol over time. AstraZeneca, Boehringer Ingelheim and the AG all used the UKPDS68, whereas Janssen assumed a linear change in these outcomes, and for HbA1c this was treatment specific. For weight outcomes, all models assumed linear evolution. All models submitted were done from the perspective of the NHS and Personal Social Services, discounted costs and health effects at 3.5% annually, and had a time horizon of 40 years. The cycle length was either 6 months (AstraZeneca) or 12 months (all other models).

**Key clinical effectiveness, quality of life and cost data for all models**

- 4.27 The companies and the AG took most of their clinical effectiveness values from their own network meta-analyses. Some data were also taken from the literature or trial data, and in some instances assumptions were used for missing values.
- 4.28 The AG, AstraZeneca and Boehringer Ingelheim all based their quality-of-life values on data from the UKPDS, and Janssen used the CODE-2 study (an observational study of 4000 people with type 2 diabetes in Europe, including the UK, based on the EQ-5D health survey and using a UK tariff) dataset as its main source of quality-of-life values. The AG stated that all sources used to derive quality-of-life values by the companies were appropriate.
- 4.29 For costs, the AG stated there was variation in the models:

- Direct drug costs in the models were similar (based on list prices), but the AG added additional costs of £72.26 for brain natriuretic peptide (BNP) monitoring (£26.26 for the test and £46.00 for a dedicated GP appointment) to the costs of pioglitazone in its model.
- At treatment intensification (see table 1), the AG model assumed that people stayed on their initial monotherapy, whereas all the companies assumed that people switched treatments. This increased the total costs for all treatments, and also increased any initial cost variation between the starting monotherapy.
- The price of canagliflozin 300 mg reduced after the company submissions were received (from approximately £608 to the same price as the 100 mg dose, approximately £477). All the companies used the higher price of canagliflozin 300 mg, whereas the AG was able to use the lower price.
- The first year costs in the Janssen model were similar to the AG model, but costs for those with a history of adverse events were lower. The AG stated that this may be because the costs in the Janssen model did not include outpatient costs.
- The costs in the AstraZeneca model were higher than those assumed by the AG; the AG was not sure why there was a discrepancy.
- Boehringer Ingelheim applied the inpatient costs of the UKPDS84, but not the outpatient costs.

**Table 1 Treatment intensifications**

	Janssen	AstraZeneca	Boehringer Ingelheim	Assessment Group
1st	+Sulphonylurea (or + DPP-4 inhibitor if already on a sulphonylurea)	Switch to NPH insulin	+Sulphonylurea; or +DPP-4 inhibitor	+Sulphonylurea (other than sulphonylurea* or repaglinide†)
2nd	Switch to NPH insulin	Intensify NPH insulin	Switch to NPH insulin	+NPH insulin
3rd	+Insulin aspart	None	None	-Sulphonylurea, +bolus
Abbreviations: DPP-4, dipeptidyl peptidase-4; NPH, isophane insulin *Sulphonylurea intensified to pioglitazone †repaglinide switched to pioglitazone and sulphonylureas				

**Company economic model (Janssen, canagliflozin)**

4.30 Janssen used the ECHO-T2DM model, using data from the CODE-2 trial for most health-related quality of life values. It did not identify any sources to determine disutility rates associated with adverse events, therefore it did a time trade-off study of participants in the UK to determine the effect on quality of life from urinary tract and genital tract infections.

4.31 The company presented incremental cost-effectiveness results (ICERs) for all treatments. The results for canagliflozin were presented for 3 arms: 100 mg, 300 mg, and 100 mg increased to 300 mg. The company presented results with and without pioglitazone, because it stated that use of pioglitazone was declining in the UK. Compared with pioglitazone, sulphonylureas and DPP-4 inhibitors were dominated, and ICERs for the other comparators ranged from £47,546 (canagliflozin 300 mg) to £416,250 (dapagliflozin) per quality-adjusted life year (QALY) gained. Results for all comparators compared with sulphonylureas and DPP-4 inhibitors are presented in tTable 2. In other pairwise comparisons, canagliflozin 100 mg dominated dapagliflozin and

empagliflozin (10 mg and 25 mg), and was cheaper but less effective than both other canagliflozin doses (£12,070 saved per QALY lost compared with canagliflozin 100 mg increased to 300 mg, and £17,845 saved per QALY lost compared with canagliflozin 300 mg).

**Table 2 Janssen base case cost-effectiveness results**

	Cost	QALY	ICER vs pioglitazone (£/QALY)	ICER vs sulphonylureas (£/QALY)	ICER vs DPP-4 inhibitor (£/QALY)
Pioglitazone	£20,264	9.998			
Sulphonylurea	£23,220	9.949	Dom		
DPP-4 inhibitor	£23,443	9.981	Dom	£6969	
Cana 100 mg	£23,525	10.039	£79,537	£3377	£1414
Empa 25 mg	£23,528	10.024	£125,538	£4107	£1977
Empa 10 mg	£23,580	10.010	£276,333	£5902	£4724
Dapa	£23,594	10.006	£416,250	£6561	£6040
Cana 100/300 mg	£23,669	10.051	£64,245	£4402	£3229
Cana 300 mg	£24,302	10.083	£47,456	£8075	£8422

Note: Table subject to rounding errors.  
Abbreviations: Cana, canagliflozin; dapa, dapagliflozin; dom, dominated; DPP-4, dipeptidyl peptidase-4; empa, empagliflozin; ICER, incremental cost-effectiveness ratio; QALY: quality-adjusted life year; Vs, versus

4.32 The company did deterministic sensitivity analyses, all of which used canagliflozin 100 mg as the intervention arm. The company stated that canagliflozin 100 mg dominated dapagliflozin and empagliflozin in most analyses and results were relatively stable compared with all comparators.

4.33 The company did scenario analyses on 17 key drivers of cost effectiveness in the economic model. The assumption of HbA1c progression had the biggest impact on results. When HbA1c progression was based on equations taken from the UKPDS (instead of the linear assumption of progression used in the base case), the ICERs for canagliflozin 100 mg were:

- £71,395 per QALY gained compared with dapagliflozin
- £50,826 per QALY gained compared with empagliflozin 10 mg
- £133,274 per QALY gained compared with sulphonylureas.

4.34 The company presented probabilistic analyses for canagliflozin 100 mg compared with all comparators. The probability of canagliflozin 100 mg being cost effective at an ICER of £20,000 and £30,000 per QALY gained was approximately 70% and 40% respectively. The probabilities for all other treatments were less than 20%.

4.35 In response to the Assessment Report, the company stated that it had found an error in its network meta-analysis for the comparisons of canagliflozin 100 mg and 300 mg with pioglitazone and gliclazide. The base-case ICERs were updated based on the lower price of canagliflozin 300 mg:

- canagliflozin 100 mg compared with pioglitazone: £83,334 per QALY gained (£78,518 per QALY gained in the base case)
- canagliflozin 100 mg compared with sulphonylureas: £7875 per QALY gained (£3377 per QALY gained in the base case)
- canagliflozin 300 mg compared with pioglitazone: £37,019 per QALY gained (£38,156 per QALY gained in the base case)
- canagliflozin 300 mg compared with sulphonylureas: £3820 per QALY gained (£1360 per QALY gained in the base case).

4.36 The AG reviewed the model submitted by Janssen. It stated that it was not clear what happened to people who stopped treatment after adverse events. It noted that the modelling was very sensitive to the annual rate of HbA1c progression assumed for canagliflozin (changing the annual rate of drift in the base case from 0.14% to 0.112% [20% decrease] and to 0.168% [20% increase]). The AG stated that the changes are likely more because of the time spent

on therapy and its immediate effects on treatment cost, weight, adverse events and hypoglycaemia than because of any changes in the modelled complications of diabetes. The ICERs compared with canagliflozin 100 mg were presented for a decrease and increase in HbA1c drift for canagliflozin:

- pioglitazone: £45,862 and £211,446 per QALY gained
- sulphonylureas: £593 and £8751 per QALY gained
- DPP-4 inhibitors: canagliflozin dominant and £8528 per QALY gained.

4.37 The AG stated that for comparing canagliflozin with dapagliflozin and empagliflozin the main scenario analyses of interest were: using patient characteristics from the database used in the NICE's guideline update on [type 2 diabetes](#); using UKPDS68 HbA1c progression; and using UKPDS68 HbA1c progression and quality of life (while also assuming that people can intensify their treatment to NPH insulin but not to basal-bolus insulin). These change the ICERs from canagliflozin 100 mg dominating to between £5000 to £10,000 per QALY gained.

### ***Company model (AstraZeneca)***

4.38 AstraZeneca used the Cardiff diabetes model. The company did analyses for all drugs as a class, including the SGLT-2 inhibitors, because they have similar safety and effectiveness and there is a limited amount of evidence for the individual treatments as monotherapy. The company stated that its primary analyses compared SGLT-2 inhibitors with DPP-4 inhibitors, because it expects SGLT-2 inhibitors to displace DPP-4 inhibitors in clinical practice.

4.39 In response to the Assessment Report, the company stated that it had found an error in its network meta-analysis for the results for

hypoglycaemic events. The resulting base case ICERs were £6125 per QALY gained compared with DPP-4 inhibitors, £20,639 per QALY gained compared with pioglitazone and £59,013 per QALY gained compared with sulphonylureas.

4.40 The company presented results of one-way sensitivity analyses, including varying HbA1c and weight change outcomes using 95% credible intervals:

- Compared with DPP-4 inhibitors, the ICER was less than £10,000 per QALY gained in all sensitivity analyses.
- Compared with pioglitazone, the ICER was most sensitive to the disutility associated with BMI increase, with a range of £14,626 to £32,065 per QALY gained.
- Compared with sulphonylureas, the company noted that the ICER was sensitive to uncertainty about the relative efficacy of SGLT-2 inhibitors and sulphonylureas for HbA1c (£42,724 to £165,409 per QALY gained) and weight change (£28,422 to £68,366 per QALY gained); and in utility value for decrease in BMI (£4434 to £62,810 per QALY gained). The company stated these ICERs reflected the greater relative uncertainty in the network meta-analysis for the comparison of SGLT-2 inhibitors with sulphonylureas.

4.41 The company presented a range of scenario analyses for SGLT-2 inhibitors compared with the comparators, including varying the HbA1c values at baseline and varying the HbA1c thresholds for intensifying treatment, altering the assumptions around maintenance of weight effects and the drug costs that were applied:

- Compared with DPP-4 inhibitors, the ICER was most sensitive to using the lowest priced DPP-4 inhibitor (£22,756 per QALY gained).



- Compared with pioglitazone, assuming weight convergence between SGLT-2 inhibitors and DPP-4 inhibitors at the second treatment switch increased the ICER to £38,199 per QALY gained (although the company stated that weight convergence was unlikely to occur in reality).
- Compared with sulphonylureas, the ICER remained above £40,000 per QALY gained. The company stated that the base-case ICER and scenario analyses compared with sulphonylureas were likely to be overestimates because sulphonylureas had an initially high clinical effectiveness estimate, but with a faster Hb1Ac progression than other treatments.

4.42 The company did probabilistic sensitivity analyses. At an ICER of £20,000 per QALY gained the probability that the SGLT-2 inhibitors were cost effective compared with DPP-4 inhibitors was 66%. Compared with pioglitazone and sulphonylureas the probabilities were 51% and 13% respectively.

4.43 The AG stated that it had concerns about the calculation of costs in the company model. This was because it appeared that the model only included inpatient and outpatient costs for patients that experienced a complication; inpatient and outpatient costs appeared to be completely omitted if the patient did not experience a complication. It stated that if this was the case, it would be a serious omission, and would bias the analysis in favour of the more effective treatment. It also noted that the company had used the same source for the costs of complications of diabetes (blindness and amputation; UKPDS84) as the AG, but that the AG had derived lower values, and it could not identify why.

***Company model (Boehringer Ingelheim)***

- 4.44 The company presented 2 economic models based on OM1, which used patient-level data from the UKPDS to extrapolate diabetes risk and predict long-term costs and outcomes. Both models were similar, with patients initially treated for 1 year. In model A, people then entered the OM1 model with these treatment effects (for hypoglycaemia, urinary tract infection and weight change). Progression of disease was informed by UKPDS, with no further direct treatment effects, discontinuations, switches or intensifications. In the first year, people in the model could not die, and costs, quality of life and adverse events not related to treatment were not considered. The company stated that this accounted for the short-term nature of treatment effectiveness evidence. In model B, the more complex model, people could stop treatment, switch and intensify treatment.
- 4.45 The company presented results for model B relative to the cheapest treatment (compared with pioglitazone in 52-week data, and dapagliflozin in 24-week data; see t
- 4.46 Table 3). In pairwise comparisons using 52-week data, empagliflozin 10 mg had ICERs of approximately £30,000, £50,000 and £70,000 per QALY gained compared with sulphonylureas, pioglitazone and repaglinide respectively. When using 24-week data, empagliflozin 10 mg had an ICER of £9834 per QALY gained compared with dapagliflozin; was cheaper but less effective than canagliflozin 300 mg; and was dominated by canagliflozin 100 mg and empagliflozin 25 mg.

**Table 3 Model B cost-effectiveness results**

Treatment	Incremental costs	Incremental QALYs	ICERs (£/QALY)
<b>Model B results – 52-week ICERs (vs pio)</b>			
Empa 25 mg od	£2834.03	0.06	£46,480
Empa 10 mg od	£2836.63	0.06	£50,892
Pio 45 mg od	Baseline	Baseline	Baseline
Repa 1 mg od	£634.77	0.03	£25,349
Sita 100 mg od	£2503.70	0.02	£163,917
Sulphonylureas	£1526.77	0.01	£121,660
<b>Model B results – 24-week ICERs (vs dapa 10)</b>			
Empa 25 mg od	£45.98	0.02	£2172
Empa 10 mg od	£67.89	0.01	£9834
Cana 300 mg od	£969.93	0.06	£17,363
Cana 100 mg od	£1.29	0.03	£39
Dapa 10 mg od	Baseline	Baseline	Baseline
Dapa 5 mg od	£42.88	0.00	£31,836
Abbreviations: cana, canagliflozin; dapa, dapagliflozin; empa, empagliflozin; ICER, incremental cost-effectiveness ratio; od, once daily; pio, pioglitazone; QALY, quality-adjusted life year; repa, repaglinide; sita, sitagliptin; vs, versus.			

- 4.47 The company did not present any sensitivity or scenario analyses for model B.
- 4.48 The AG stated that based on a comparison of the written submission with model B it appeared that the effects of placebo had not been included in the model (apart from hypoglycaemia and urinary tract infection rates), which could have underestimated the absolute treatment effects from baseline to 24 or 52 weeks. The AG also stated that it was concerned about why the reported UKPDS costs of model B were around half of those of model A, whereas the QALY values of model A and B were similar. It stated that the reason for the discrepancy was unclear.

**Assessment Group’s economic model**

- 4.49 The AG, in common with Boehringer Ingelheim, used the OM1 model for its submission. The AG assumed the use of the larger doses of canagliflozin and empagliflozin rather than the starting

doses because it assumed that people would be at the maximum tolerated dose of each monotherapy drug before moving to dual therapy.

4.50 Table 4 presents the results of the model. Please note that after consultation on the assessment report, the AG noted that the baseline assumption for ischaemic heart disease prevalence had been incorrectly set to zero. It therefore presented a revised base case (setting baseline ischaemic heart disease to 2.7%), which had a minor effect on the cost-effectiveness results. This document presents the revised base case figures only, however all sensitivity and scenario analyses are based on the original base case (the AG did not have time to update the sensitivity and scenario analyses).

4.51 The AG noted that the SGLT-2 inhibitors were of similar cost, but the canagliflozin overall costs were cheaper. This was because the greater effect of canagliflozin on HbA1c meant that treatment was intensified to the more expensive subsequent lines of treatment slightly later. The AG noted that because people remain on initial treatment for the duration of the model, the initial expense of the SGLT-2 inhibitors and the DPP-4 inhibitor sitagliptin compared with other treatments is maintained over the time horizon of the model. The AG noted that a key difference between the AG modelling and that of the companies was that the AG assumed that people remained on monotherapy and added treatments to it. Retaining the original monotherapy increased the total costs, and in particular increased the total cost for the SGLT-2 inhibitors, and also sitagliptin.

4.52 The AG assumed an increase in weight of 0.1 kg per year. However it stated that there was debate about the effects of treatment on weight, because initial weight loss may be transient, and weight gain more permanent. Therefore it modelled 5 different

scenarios for BMI, with a decrement of 0.0061 for each point above a BMI of 25 kg/m<sup>2</sup> (as well as a scenario which assumed that BMI has no impact on quality of life, 'No BMI'). Scenarios were presented in which:

- weight changes are maintained with no rebound to natural history (BMI-1)
- weight gains are maintained, and weight losses rebound to natural history after 1 year (BMI-2)
- weight gains are maintained, and weight losses rebound to natural history at intensification (BMI-3)
- weight changes rebound to natural history after 1 year (BMI-4)
- weight changes rebound to natural history at intensification (BMI-5).

4.53 QALY gains for SGLT-2 inhibitors were lowest when it was assumed that BMI had no impact on quality of life, with higher lifetime QALY gains for gliclazide, repaglinide and pioglitazone than SGLT-2 inhibitors. However, if QALY gains for BMI were taken into account, the lifetime QALY gain was highest for the SGLT-2 inhibitors. These gains were reduced if it was assumed that weight losses rebound after 1 year, and if it was assumed that weight losses rebound at treatment change.

**Table 4 Assessment Group lifetime costs and QALYs**

Treatment	Total costs	Total QALYs					
		No BMI	BMI-1	BMI-2	BMI-3	BMI-4	BMI-5
Sulphonylureas	£27,600	10.376	9.618	9.618	9.618	9.755	9.723
Repaglinide	£27,704	10.374	9.649	9.649	9.649	9.755	9.73
Pioglitazone	£27,827	10.367	9.596	9.596	9.596	9.746	9.712
Sita 100 mg	£32,631	10.337	9.641	9.638	9.639	9.723	9.702
Cana 300 mg	£32,933	10.362	9.763	9.674	9.691	9.753	9.75
Empa 25 mg	£33,031	10.36	9.73	9.667	9.678	9.749	9.739
Dapa 10 mg	£33,136	10.35	9.718	9.656	9.665	9.74	9.729

Abbreviations: cana, canagliflozin; dapa, dapagliflozin; empa, empagliflozin; QALY, quality-adjusted life year;

4.54 The AG presented their results relative to the next least costly treatment that was not dominated (see table 5), and also compared with DPP-4 inhibitors, sulphonylureas, and pioglitazone (see Table 6, 7 and 8 respectively). The AG stated that the SGLT-2 inhibitors and DPP-4 inhibitors were considerably more expensive than the other comparators, and if there were no direct quality-of-life effects from weight changes, the SGLT-2 inhibitors were estimated to be dominated.

**Table 5 Assessment Group cost-effectiveness results**

Treatment	ICERs (£/QALY)					
	No BMI	BMI-1	BMI-2	BMI-3	BMI-4	BMI-5
Sulphonylureas	–	–	–	–	–	–
Repaglinide	Dom	£3388	£3388	£3388	£434,000	£16,413
Pioglitazone	Dom	Dom	Dom	Dom	Dom	Dom
DPP-4 inhibitor	Dom	Dom	Dom	Dom	Dom	Dom
Cana 300 mg	Dom	£45,641	£207,000	£124,000	Dom	£259,000
Empa 25 mg	Dom	Dom	Dom	Dom	Dom	Dom
Dapa 10 mg	Dom	Dom	Dom	Dom	Dom	Dom

Abbreviations: cana, canagliflozin; dapa, dapagliflozin; dom: dominated (more costly and less effective than another treatment); empa, empagliflozin; ICER, incremental cost-effectiveness ratio

**Table 6 Assessment Group cost-effectiveness results for SGLT-2 inhibitors compared with DPP-4 inhibitors**

	ICERs (£/QALY)					
Treatment	No BMI	BMI-1	BMI-2	BMI-3	BMI-4	BMI-5
Cana 300 mg	£12,034	£2467	£8494	£5820	£9777	£6312
Empa 25 mg	£17,278	£4471	£13,917	£10,294	£14,864	£10,724
Dapa 10 mg	£37,871	£6542	£29,341	£19,172	£29,116	£19,062
Abbreviations: cana, canagliflozin; dapa, dapagliflozin; empagliflozin; ICER, incremental cost-effectiveness ratio						

**Table 7 Assessment Group cost-effectiveness results for SGLT-2 inhibitors compared with sulphonylureas**

	ICERs (£/QALY)					
Treatment	No BMI	BMI-1	BMI-2	BMI-3	BMI-4	BMI-5
Cana 300 mg	Dom	£36,491	£93,384	£72,315	Dom	£193,000
Empa 25 mg	Dom	£48,160	£109,024	£90,124	Dom	£326,664
Dapa 10 mg	Dom	£55,000	£144,814	£115,997	Dom	£975,174
Abbreviations: cana, canagliflozin; dapa, dapagliflozin; dom, dominated (more costly and less effective than another treatment); empagliflozin; ICER, incremental cost-effectiveness ratio						

**Table 8 Assessment Group revised cost-effectiveness results for SGLT-2 inhibitors compared with pioglitazone**

	ICERs (£/QALY)					
Treatment	No BMI	BMI-1	BMI-2	BMI-3	BMI-4	BMI-5
Cana 300 mg	Dom	£30,510	£65,465	£53,910	£666,891	£134,899
Empa 25 mg	Dom	£38,728	£73,110	£63,714	£1,400,000	£190,612
Dapa 10 mg	Dom	£43,452	£88,966	£76,727	Dom	£321,161
Abbreviations: cana, canagliflozin; dapa, dapagliflozin; dom, dominated (more costly and less effective than another treatment); empagliflozin; ICER, incremental cost-effectiveness ratio						

4.55 The AG presented several scenario analyses, including urinary and genital tract infection rate applied to all cycles and assuming linear progression of HbA1c. When compared with the cheaper treatments, most scenarios did not have a substantial effect on the results. When compared with sitagliptin and assuming weight changes were maintained with no rebound to natural history (best-

case scenario for SGLT-2 inhibitors), the ICERs remained under £10,000 per QALY gained.

4.56 The AG presented probabilistic ICERs, which were similar to the deterministic ICERs:

- In probabilistic analyses when assuming no utility gain from the impact of BMI:
  - Including all comparators, SGLT-2 inhibitors and sitagliptin had a 0% chance of cost effectiveness even at ICERs of £50,000 per QALY gained.
  - Compared with DPP-4 inhibitors only, the probability of being cost effective was canagliflozin 45%, dapagliflozin 4%, empagliflozin 26%, and sitagliptin 26%, assuming an ICER of £20,000 per QALY gained.
- In probabilistic analyses, assuming weight changes were maintained indefinitely:
  - Including all comparators, the probabilities were canagliflozin 6%, repaglinide 74%, and sulphonylureas 20%, when assuming an ICER of £30,000 per QALY gained.
  - Compared with DPP-4 inhibitors only, the probability of being cost effective was canagliflozin 93%, dapagliflozin 0%, empagliflozin 6%, and sitagliptin 0%, assuming an ICER of £20,000 per QALY gained.

### ***Consideration of the evidence***

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of canagliflozin, dapagliflozin and empagliflozin as monotherapies, having considered evidence on the nature of type 2 diabetes and the value placed on the benefits of canagliflozin, dapagliflozin and empagliflozin as monotherapies by people with the condition, those who



represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.57 The Committee considered the experience of people with diabetes. It heard from the patient expert that she felt there was a lack of understanding about diabetes in the general population and variable knowledge and understanding of the condition among healthcare professionals. She felt there was stigma associated with type 2 diabetes because lifestyle factors may contribute to its development. The patient expert described her experience of treatment. She explained how she felt she had been given mixed messages about the most appropriate treatment, and sometimes felt that she had more knowledge about her diabetes management than some of her clinicians. The clinical experts agreed with these concerns, stating that treatment options are complex. The patient expert went on to describe the benefits of treatment with sodium-glucose cotransporter 2 drugs (SGLT-2s; canagliflozin, dapagliflozin and empagliflozin). She felt that this treatment was effective, and easy and flexible to administer, leaving her less stressed, more positive, and better able to manage her own condition. As a result her family were less concerned about her. The Committee also noted that diabetes can be associated with many unpleasant complications, some of which could affect the person's ability to manage their condition, such as worsening eyesight or blindness. The Committee concluded that diabetes has a substantial effect on quality of life, and that people with diabetes and their clinicians would value having an additional treatment option to help manage the disease.

4.58 The Committee considered the current treatment pathway for people with diabetes who cannot tolerate metformin. It heard from the clinical experts that metformin can cause gastrointestinal

problems. Although it is estimated that approximately 5–15% of people cannot tolerate metformin, this may vary; people can develop metformin intolerance over time. Modified-release metformin can reduce some of the gastrointestinal symptoms but many people were reluctant to try metformin again if they had unpleasant gastrointestinal side effects before. For people who cannot tolerate metformin, there were several other treatment options available. The clinical experts agreed that dipeptidyl peptidase-4 (DPP-4) inhibitors and sulphonylureas were the most commonly used treatments, and sometimes pioglitazone was appropriate. However, they emphasised that individual care is critical, because there is no 'one size fits all' treatment. For example, sulphonylureas may be less appropriate if people drive for a living, and pioglitazone is usually not appropriate if people have heart failure. The Committee also heard from the clinical and patient experts that in clinical practice in primary care (where about 80% of diabetes is managed) there is variation in care, because of confusion about which treatments are most appropriate for individual people. There are around 8 classes of treatments, all with different contraindications, and when combined with individual patient factors, this makes it very difficult to know the best option for individuals. The Committee asked the clinical experts if repaglinide, a comparator in the scope for this appraisal, was used in clinical practice. The clinical experts all agreed that repaglinide is rarely used; of half a million recent prescriptions for diabetes in Wales, only 4 were for repaglinide. The Committee concluded that the most appropriate comparators for this appraisal were DPP-4 inhibitors, sulphonylureas and pioglitazone, but that in clinical practice the most appropriate comparator would depend on individual patient circumstances.

### ***Clinical effectiveness***

- 4.59 The Committee discussed the clinical trials identified in the Assessment Group (AG) report and the company submissions. It was aware that the AG had not identified any additional trials to those originally identified in the company submissions, and that the AG considered the trials to be generally of good quality. The Committee concluded that all relevant trials had been identified, and were of an appropriate quality for decision-making.
- 4.60 The Committee discussed the baseline patient characteristics in the clinical trials. It questioned whether the results were generalisable to UK clinical practice, because several of the trials were done in populations described as 'Asian' (for example, China and Japan). It heard from the clinical experts that baseline measurements such as BMI were likely to vary between these trial populations and the UK population (the UK population is likely to have a higher BMI). This was an important consideration when interpreting secondary outcomes such as weight. However, overall the clinical experts stated they had no concerns about generalisability because:
- there were still people in the clinical trials with high BMIs
  - the primary outcome, change in HbA1c, was based on a physiological response to the drug, which would not generally be affected by baseline measurements such as BMI and
  - patient outcomes seen in UK clinical practice reflected the positive results seen in the clinical trials.

The Committee concluded that the trials were relevant to UK practice and appropriate for decision-making.

- 4.61 The Committee discussed the results of the clinical trials, most of which had compared SGLT-2 inhibitors with placebo for outcomes such as change in HbA1c and weight. The Committee was aware

that the SGLT-2 inhibitors had shown statistically significant improvements compared with placebo for the primary outcome of change in HbA1c. The clinical experts stated that this is the main goal of treatment with medication for diabetes. People had also had reductions in weight compared with placebo, which the clinical experts described as a welcome additional benefit of the SGLT-2 inhibitors. The Committee concluded that the SGLT-2 inhibitors were a clinically effective treatment compared with placebo.

4.62 The Committee discussed the results of the AG and company network meta-analyses. The Committee noted that some of the network meta-analyses showed differences between the effectiveness of the SGLT-2 inhibitors. For example, some of the network meta-analyses suggested dapagliflozin had a lower HbA1c response than canagliflozin and empagliflozin. However, it heard from the AG and AstraZeneca (the company for dapagliflozin) that the results for dapagliflozin were sensitive to the inclusion of a trial by Kaku et al. (2014), and when this was removed, results were similar to the other SGLT-2 inhibitors. The Committee asked the clinical experts whether there was any evidence of meaningful differences in effectiveness between the SGLT-2 inhibitors. The clinical experts stated that although it could be advantageous to have the option to increase the dose (as was possible with canagliflozin and empagliflozin), there was no direct evidence available to determine if there are clinically meaningful differences among the SGLT-2 inhibitors. The Committee concluded that from the evidence available it was not possible to determine if there are any differences in effectiveness between the SGLT-2 inhibitors.

4.63 The Committee discussed the adverse events associated with SGLT-2 inhibitors. It heard from the clinical experts that genital fungal infections were a concern. However, there is debate about

whether this is a treatment or disease-related effect, and when infections did occur, they were typically one-off and were not serious. Furthermore, for more serious outcomes such as malignancy, the clinical experts stated that there were no data to suggest an increase in risk associated with SGLT-2 inhibitors (although long-term data are needed). The Committee also heard from the patient about her experience with SGLT-2 inhibitors. The patient expert had not had any adverse events. She noted that she had been advised to drink plenty of water, which had probably reduced her risk of having an adverse event, although this resulted in an increased need to pass water, which could be an inconvenience for some people. The Committee concluded that the SGLT-2 inhibitors had an acceptable adverse event profile.

### ***Cost effectiveness***

4.64 The Committee discussed the structure of the AG and company models. It was aware that the AG considered all the models to be of reasonable quality, and it noted that the structure of the models was generally similar, but there were some important differences. The Janssen model assumed a linear progression of HbA1c whereas all other models based progression of disease on the UK Prospective Diabetes Study (UKPDS) equations. The AG model assumed that when people intensified treatment, treatments were added, rather than switched (as assumed in all company models). For treatment intensification, the Committee heard from the clinical experts that the AG model was the most similar to NHS clinical practice, because clinicians typically retain oral therapies and add another treatment, to reduce the risk of losing control of the disease. The Committee concluded that all models submitted were appropriate and of a reasonable quality, but the AG model was most appropriate for decision-making, because of its more accurate reflection of treatment intensification.

- 4.65 The Committee discussed the quality-of-life assumptions in the AG and company models. It noted that there were generally very small quality-adjusted life year (QALY) differences between the various treatments. It also noted that the AG had presented a number of scenarios varying the assumptions about BMI. “No BMI” assumed BMI had no impact on quality of life (worst-case scenario for SGLT inhibitors), and BMI scenarios 1 to 5 varied the duration of treatment effect on weight loss (where BMI-1, with weight changes maintained with no rebound to natural history, was the best case scenario for SGLT2 inhibitors). The Committee agreed that weight loss does affect quality of life and agreed with the approach of a disutility of 0.0061 being applied per BMI point greater than 25. The Committee noted that the evidence had shown that SGLT-2 inhibitors do have a significant effect on weight loss, and felt that the AG’s BMI-2 scenario (in which weight gains were maintained and weight losses rebounded to natural history after 1 year) best reflected the treatment effect on weight loss. It was also aware that NICE’s guideline on [diabetes](#) used the same assumption as that used in scenario ‘BMI-2’. It therefore concluded that BMI-2 was the most plausible scenario, but noted that the small QALY differences between treatments made the ICERs unstable.
- 4.66 The Committee discussed the cost-effectiveness results presented in the AG and company models. It noted that the Janssen model had highly favourable ICERs of £4000 to £8000 per QALY gained for canagliflozin 100 mg or 300 mg compared with sulphonylureas, whereas ICERs in the other models were substantially higher (for example, £59,000 per QALY gained for the SGLT-2 inhibitors compared with the sulphonylureas in the AstraZeneca model, and at least £93,400 per QALY gained in the AG model). The Committee heard from the AG that there were important differences between the AG and Janssen models. For example, the Janssen

model had assumed a linear progression of disease (see section 4.26), whereas the AG and other companies had used equations from UKPDS. The Janssen model also allowed the effect of estimated glomerular filtration rate (eGFR) to be explored, whereas all the other models did not. However, the AG stated that neither of these sufficiently explained the variation, because the AG model was not sensitive to drift assumptions, and the Janssen model was not sensitive to removing assumptions about eGFR. The Committee heard from the company that its own model was sensitive to drift assumptions, but that it could not say for sure what caused the variation from the AG model because it had not explored this specific issue in detail. The Committee concluded that the favourable ICERs for canagliflozin compared with sulphonylureas in the Janssen model were anomalous, and it was not clear why they were not consistent with most other similar cost-effectiveness comparisons presented.

- 4.67 The Committee discussed whether it could determine the most plausible ICERs for the SGLT-2 inhibitors compared with the relevant comparators (compared with each other, pioglitazone, sulphonylureas and DPP-4 inhibitors), using its preferred model (AG model, see section 4.63) and its preferred assumptions about the effect of treatment on BMI (scenario BMI-2, see section 4.64).
- When the SGLT-2 inhibitors were compared with each other, the Committee agreed that the clinical and cost evidence submitted did not support any differences between them.
  - When compared with pioglitazone, ICERs for all the SGLT-2 inhibitors were more than £65,500 per QALY gained.
  - When compared with sulphonylureas, ICERs for the SGLT-2 inhibitors were all over £93,000 per QALY gained.

- When compared with DPP-4 inhibitors, the ICERs ranged from £8500 to £29,300 per QALY gained.

4.68 In summary, at ICERs of £20,000 to £30,000 per QALY gained, the SGLT-2 inhibitors were cost effective compared with DPP-4 inhibitors, but not cost effective compared with pioglitazone and sulphonylureas. Therefore the Committee concluded that canagliflozin, dapagliflozin and empagliflozin as monotherapy were a cost-effective use of NHS resources, but only when pioglitazone or sulphonylureas were not appropriate treatment options.

4.69 The Committee considered whether it should take into account the consequences of the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism, when appraising canagliflozin, dapagliflozin and empagliflozin as monotherapy. The Committee noted NICE’s position statement in this regard, and accepted the conclusion ‘that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines’. The Committee heard nothing to suggest that there is any basis for taking a different view with regard to the relevance of the PPRS to this appraisal of canagliflozin, dapagliflozin and empagliflozin as monotherapy. It therefore concluded that the PPRS payment mechanism was not relevant for its consideration of the cost effectiveness of canagliflozin, dapagliflozin and empagliflozin as monotherapy.

***Summary of Appraisal Committee’s key conclusions***

TAXXX	Appraisal title:	Section
<b>Key conclusion</b>		



<p>The Committee, using its preferred model from the Assessment Group (AG) and its preferred assumptions about the effect of treatment on BMI (scenario BMI-2), discussed the most plausible incremental cost-effectiveness ratios (ICERs) presented:</p> <ul style="list-style-type: none"> <li>• When the selective sodium-glucose cotransporter 2 (SGLT-2) inhibitors were compared with each other, the Committee agreed that the clinical and cost evidence did not support any differences between them.</li> <li>• When compared with pioglitazone, ICERs for all the SGLT-2 inhibitors were more than £65,500 per quality-adjusted life year (QALY) gained.</li> <li>• When compared with sulphonylureas, ICERs for the SGLT-2 inhibitors were all more than £93,000 per QALY gained.</li> <li>• When compared with dipeptidyl peptidase-4 (DPP-4) inhibitors, the ICERs ranged from £8500 to £29,300 per QALY gained.</li> </ul> <p>At ICERs of £20,000 to £30,000 per QALY gained, the SGLT-2 inhibitors were cost effective compared with DPP-4 inhibitors, but not cost effective compared with pioglitazone and sulphonylureas. Therefore the Committee concluded that canagliflozin, dapagliflozin and empagliflozin as monotherapy are a cost-effective use of NHS resources, but only when pioglitazone or sulphonylureas are not appropriate treatment options.</p>	<p>4.63</p> <p>4.64</p>
<p><b>Current practice</b></p>	

<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The Committee heard from the patient expert that she felt there was a lack of understanding about diabetes in the general population and a stigma associated with type 2 diabetes because it can be caused by lifestyle factors. The Committee also noted that diabetes can be associated with many unpleasant complications, some of which could affect the person’s ability to manage their condition, such as worsening eyesight or blindness.</p> <p>The patient expert felt that SGLT-2 inhibitors are effective and easy and flexible to administer, leaving her less stressed, more positive, and better able to manage her own disease.</p> <p>The Committee concluded that diabetes has a substantial effect on quality of life, and that people with diabetes and their clinicians would value having an additional treatment option to help manage the disease.</p>	<p>4.56</p>
<p><b>The technology</b></p>		

<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The Committee was aware that the SGLT-2 inhibitors had shown statistically significant improvements compared with placebo for the primary outcome of change in haemoglobin A1c (HbA1c), and that people had also had reductions in weight compared with placebo, which the clinical experts described as a welcome additional benefit of the SGLT-2 inhibitors.</p>	<p>4.60</p>
<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>Canagliflozin, dapagliflozin and empagliflozin all have UK marketing authorisations as monotherapy for treating type 2 diabetes to improve glycaemic control in adults when diet and exercise alone do not provide adequate glycaemic control, in people for whom the use of metformin is considered inappropriate due to intolerance or contraindications. The Committee was aware there are several other treatment options available. The clinical experts agreed that dipeptidyl peptidase-4 (DPP-4) inhibitors and sulphonylureas are the most commonly used treatments, and sometimes pioglitazone is appropriate. However, they emphasised that individual care is critical, because there is no 'one size fits all' treatment.</p>	<p>3.1</p> <p>4.57</p>

<p>Adverse reactions</p>	<p>The Committee heard from the clinical experts that genital fungal infections are a concern. However, there is debate about whether this is a treatment or disease-related effect, and when infections do occur, they are typically one-off and not serious.</p> <p>For more serious outcomes such as malignancy, the clinical experts stated that there are no data to suggest an increase in risk associated with SGLT-2 inhibitors (although long-term data are needed).</p> <p>The Committee also heard from the patient that she had not experienced any adverse events.</p> <p>The Committee concluded that the SGLT-2 inhibitors had an acceptable adverse event profile.</p>	<p>4.62</p>
<p><b>Evidence for clinical effectiveness</b></p>		
<p>Availability, nature and quality of evidence</p>	<p>The Committee concluded that all relevant trials had been identified, and were of an appropriate quality for decision-making.</p> <p>The Committee also discussed the results of the AG and company network meta-analyses. It concluded that from the evidence available it was not</p>	<p>4.58 4.61</p>

	possible to determine if there are any differences in effectiveness between the SGLT-2 inhibitors.	
Relevance to general clinical practice in the NHS	The Committee heard from the clinical experts that baseline measurements such as BMI would likely vary between the trial populations and the UK population, and this was an important consideration when interpreting secondary outcomes such as weight. However, overall the clinical experts stated they had no concerns about generalisability because there were people in the clinical trials with high BMIs; the primary outcome (change in HbA1c) was based on a physiological response to the drug, which would not generally be affected by baseline measurements such as BMI; and patient outcomes seen in UK clinical practice reflected the positive results seen in the clinical trials.	4.59
Uncertainties generated by the evidence	The Committee concluded that from the evidence available it was not possible to determine if there are any differences in effectiveness between the SGLT-2 inhibitors.	4.61

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	No specific Committee consideration.	
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The evidence included 7 clinical trials and company and assessment group network meta-analyses. The Committee concluded that the SGLT-2 inhibitors were a clinically effective treatment compared with placebo.	4.60
<b>Evidence for cost effectiveness</b>		
Availability and nature of evidence	The AG and all the companies used existing economic models for diabetes to consider the cost effectiveness of SGLT-2 inhibitor monotherapy.	4.22

<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The Committee noted that the Janssen model had highly favourable ICERs of £4000 to £8000 per QALY gained for canagliflozin 100 mg or 300 mg compared with sulphonylureas, whereas ICERs in the other models were substantially higher. The Committee heard from the AG that there were important differences between the AG and Janssen models, but the AG and Janssen were unable to explain the variation. The Committee concluded that the favourable ICERs for canagliflozin compared with sulphonylureas in the Janssen model were anomalous, and it was not clear why they were not consistent with the other cost-effectiveness comparisons presented.</p> <p>The Committee noted that the small QALY differences between treatments made the ICERs unstable.</p>	<p>4.65</p> <p>4.64</p>
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<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The Committee noted that there were generally very small QALY differences between the various treatments. It also noted that the AG had presented a number of scenarios varying the impact of BMI on quality of life. Overall the Committee agreed that weight loss does affect quality of life and that the evidence had shown that SGLT-2 inhibitors do have a significant effect on weight loss. It concluded that BMI-2 was the most plausible scenario, but noted that the small QALY differences between treatments made the ICERs unstable.</p>	<p>4.64</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>No specific Committee consideration.</p>	
<p>What are the key drivers of cost effectiveness?</p>	<p>The key driver of cost-effectiveness was the BMI scenario chosen. The Committee concluded that BMI-2 was the most plausible scenario, but noted that the small QALY differences between treatments made the ICERs unstable.</p>	<p>4.64</p>



<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>When the SGLT-2 inhibitors were compared with each other, the Committee agreed that the clinical and cost evidence did not support any differences between them.</p> <p>When compared with pioglitazone, ICERs for all the SGLT-2 inhibitors were more than £65,500 per QALY gained.</p> <p>When compared with sulphonylureas, ICERs for the SGLT-2 inhibitors were all more than £93,000 per QALY gained.</p> <p>When compared with DPP-4 inhibitors, the ICERs ranged from £8500 to £29,300 per QALY gained.</p>	<p align="center">4.66</p>
<p><b>Additional factors taken into account</b></p>		
<p>Patient access schemes (PPRS)</p>	<p>N/A</p>	
<p>End-of-life considerations</p>	<p>N/A</p>	
<p>Equalities considerations and social value judgements</p>	<p>N/A</p>	

## 5 Implementation

- 5.1 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.
- 5.2 The Welsh Assembly Minister for Health and Social Services has 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 3 months of the guidance being published.
- 5.3 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 person has type 2 diabetes and the doctor responsible for their care thinks that canagliflozin, dapagliflozin or empagliflozin as monotherapy is the right treatment, it should be available for use, in line with NICE's recommendations.

## 6 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the [NICE website](#).

- [Diabetic foot problems: prevention and management](#) (2015). NICE guideline NG19.

- [Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period](#) (2015). NICE guideline NG3.
- [Canagliflozin in combination therapy for treating type 2 diabetes](#) (2014). NICE technology appraisal guidance TA315.
- [Dapagliflozin in combination therapy for treating type 2 diabetes](#) (2013). NICE technology appraisal guidance TA288.
- [Type 2 diabetes in adults: management](#) (2015). NICE guideline NG28.

### NICE pathways

- There is a NICE pathway on diabetes, which is available from <http://pathways.nice.org.uk/pathways/diabetes>

## 7 Proposed date for review of guidance

- 7.1 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.

Iain Squire

Vice-Chair, Appraisal Committee

December 2015

## **8 Appraisal Committee members and NICE project team**

### ***Appraisal Committee members***

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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.

#### **Dr Jane Adam (Vice-Chair)**

Consultant Radiologist, Department of Diagnostic Radiology, St George's Hospital, London

#### **Professor Iain Squire (Chair)**

Consultant Physician, University Hospitals of Leicester

#### **Dr Graham Ash**

Consultant in General Adult Psychiatry, Lancashire Care NHS Foundation Trust

**Dr Jeremy Braybrooke**

Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

**Dr Gerardine Bryant**

General Practitioner, Swadlincote, Derbyshire

**Dr Justin Daniels**

Consultant Paediatrician, North Middlesex University Hospital

**Dr Andrew England**

Senior Lecturer, Directorate of Radiography, University of Salford

**Dr Anne McCune**

Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

**Ms Sarah Parry**

Clinical Nurse Specialist – Paediatric Pain Management, Bristol Royal Hospital for Children

**Ms Pamela Rees**

Lay Member

**Mr Stephen Sharp**

Senior Statistician, University of Cambridge MRC Epidemiology Unit

**Dr Eldon Spackman**

Research Fellow, Centre for Health Economics, University of York

**Mr David Thomson**

Lay member

### ***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.

#### **Carl Prescott**

Technical Lead

#### **Joanna Richardson**

Technical Adviser

#### **Bijal Joshi**

Project Manager

## **9 Sources of evidence considered by the Committee**

A. The assessment report for this appraisal was prepared by Warwick Evidence:

- Johnston R, Uthman O, Cummins E, et al. Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes: systematic review and economic evaluation. October 2015

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I, II and III were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I. Companies:

- AstraZeneca (dapagliflozin)

- Boehringer Ingelheim and Lilly UK (empagliflozin)
- Janssen (canagliflozin)

II. Professional/expert and patient/carer groups:

- Diabetes UK
- Royal College of Nursing
- Royal College of Physicians
- UK Clinical Pharmacy Association

III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

IV. Commentator organisations (without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Merck Sharp and Dohme (metformin, sitagliptin)
- Novo Nordisk (repaglinide)
- Servier Laboratories (gliclazide)

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on dapagliflozin, empagliflozin and canagliflozin by attending the initial Committee discussion and/or providing a written statement to the Committee. They are invited to comment on the ACD.

- Professor Stephen Bain, Professor of Medicine (Diabetes) & Honorary Consultant Physician, nominated by organisation representing AstraZeneca – clinical expert
- Dr Peter Winocour, Consultant Physician and Clinical Director , nominated by organisation representing Janssen – clinical expert
- Mrs Ruth Waxman, nominated by organisation representing Diabetes UK – patient expert

D. Representatives from the following companies attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- AstraZeneca
- Boehringer Ingelheim
- Janssen