

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

Technology appraisal guidance

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1 Recommendations

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

2.1 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

2.2 The recommended starting dosage 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 m² 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/1.73 m² or creatinine clearance of less than 60 ml/minute. In people tolerating canagliflozin whose eGFR persistently falls below 60 ml/minute/1.73 m² 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 m² or creatinine clearance is persistently below 45 ml/minute.

2.3 The summary of product characteristics lists the following adverse reactions for canagliflozin as the most commonly reported: balanitis, constipation, dyslipidaemia, haematocrit increase, nausea, polyuria, thirst, urinary tract infection and vulvovaginal candidiasis. For full details of adverse reactions and contraindications, see the summary of product characteristics.

- 2.4 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

- 2.5 The recommended dosage is 10 mg dapagliflozin orally once daily for monotherapy and add-on combination therapy with other glucose-lowering medicinal products including insulin.
- 2.6 The summary of product characteristics lists the following adverse reactions for dapagliflozin: back pain, balanitis, creatinine renal clearance decrease, dizziness, dysuria, dyslipidaemia, elevated haematocrit, polyuria, urinary tract infection and vulvovaginitis. 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 m²). For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 2.7 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

- 2.8 The recommended starting dosage 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 m² or more.
- 2.9 The summary of product characteristics includes the following adverse reactions for empagliflozin: balanitis, increased urination, pruritus, urinary tract infection, vaginal moniliasis and vulvovaginitis. For full details of adverse reactions and contraindications, see the summary of product characteristics.

- 2.10 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.

3 Evidence

The appraisal committee ([section 6](#)) considered evidence from a number of sources. See the [committee](#) papers for full details of the evidence.

Clinical need and practice

- 3.1 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.
- 3.2 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.
- 3.3 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.
- 3.4 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.

Clinical effectiveness

3.5 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 (described as 'exploratory') with DPP4-inhibitors. The AG did not identify any additional trials relevant to the scope that were not identified in the companies' submissions.

3.6 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/m²
- 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.

3.7 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 reduction for empagliflozin 25 mg was also greater than sitagliptin 100 mg in exploratory analyses, but there was no difference when sitagliptin 100 mg was compared with empagliflozin 10 mg.

3.8 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. 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

3.9 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.

3.10 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

3.11 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, sulfonylureas, pioglitazone and repaglinide for people with type 2 diabetes not controlled by diet and exercise 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.

- 3.12 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

- 3.13 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); sulfonylureas (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.
- 3.14 Results for canagliflozin 100 mg were as follows:
- compared with SGLT-2 inhibitors, dapagliflozin, and empagliflozin 10 mg it resulted in a greater reduction in weight, and there were no differences for HbA1c and systolic blood pressure
 - compared with SGLT-2 inhibitors, canagliflozin 300 mg, and empagliflozin 25 mg there were no differences (other than weight change, where canagliflozin 300 mg was associated with a greater weight loss)
 - compared with DPP-4 inhibitors, it resulted in a greater reduction in HbA1c, weight and systolic blood pressure (other than when compared with sitagliptin for HbA1c, where there was no difference)
 - compared with sulfonylureas, only results for the HbA1c outcome were presented; there were no differences
 - compared with pioglitazone (all doses) it was more effective for change in weight and systolic blood pressure, and there was no difference for HbA1c
 - in all comparisons, there were no differences for hypoglycaemia.

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

AstraZeneca network meta-analysis

- 3.16 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, sulfonylureas, 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 sulfonylureas, 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.
- 3.17 The company presented results for sensitivity analyses. It stated that there were only small differences between the base case and sensitivity analyses.
- 3.18 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 trials for other SGLT-2 inhibitors. The company 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

- 3.19 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),

sulfonylureas (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.

3.20 For change in HbA1c, all results including empagliflozin 10 mg and 25 mg and other SGLT-2 inhibitors showed greater reductions in HbA1c compared with placebo at 24 weeks and 52 weeks. For hypoglycaemia and urinary tract infection outcomes, the company found no 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, 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, sulfonylureas and DPP-4 inhibitors had increases in weight. For systolic blood pressure, all SGLT-2 inhibitors showed decreases compared with placebo.

Assessment Group network meta-analysis

3.21 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), sulfonylureas, 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 more effective than placebo for HbA1c and weight change.
- Compared with sitagliptin, SGLT-2 inhibitors were either more effective for HbA1c (canagliflozin 100 mg and 300 mg, and dapagliflozin) or there was no difference (empagliflozin 10 mg and 25 mg), and all SGLT-2 inhibitors were more effective for weight change.

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

3.22 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.

3.23 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 sulfonylureas 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 sulfonylureas (that is, the initial response was followed by a relatively rapid deterioration). In 1 trial the AG noted that 34% of people taking sulfonylureas needed additional treatment within 5 years compared with 15% of those taking rosiglitazone.

Evidence from patient and clinical experts

- 3.24 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.
- 3.25 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

- 3.26 The AG carried out a systematic review of the literature to identify studies of the cost effectiveness of SGLT-2 inhibitor monotherapy compared with sulfonylureas, 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.

3.27 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

3.28 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.

3.29 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).

3.30 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 (or 'drift') in HbA1c over time. AstraZeneca, Boehringer Ingelheim and the AG all used the UKPDS68, whereas Janssen assumed a treatment-specific drift in HbA1c that it described as 'linear in segment but inherently non-linear'; that is, Janssen had assumed a linear drift in HbA1c, but downward pressure from rescue medication led to concave mean-HbA1c curves over time. All the 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

- 3.31 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.
- 3.32 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.
- 3.33 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 (at either the first or second intensification). 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	+gliclazide (other than gliclazide ^a or repaglinide ^b)	Switch to NPH insulin	+Sulfonylurea; or +DPP-4 inhibitor	+gliclazide (other than gliclazide ^a or repaglinide ^b)
2nd	Switch to NPH insulin	Intensify NPH insulin	Switch to NPH insulin	+NPH insulin
3rd	+Insulin aspart	None	None	-gliclazide, +bolus

Abbreviations: DPP-4, dipeptidyl peptidase-4; NPH, isophane insulin.
^aGliclazide intensified to sitagliptin (Janssen) or pioglitazone (AG).
^bRepaglinide switched to pioglitazone (Janssen) or pioglitazone and gliclazide (AG).
 Note: Janssen repaglinide intensifications differed and are not described in detail for 2nd intensification onwards.

Company economic model (Janssen, canagliflozin)

3.34 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.

3.35 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. In response to the appraisal consultation document, the company provided updated cost-effectiveness results which corrected 2 errors found in the model (the updated results used a corrected reduction in HbA1c for sulfonylurea and pioglitazone, and a corrected stopping rule associated with eGFR for empagliflozin 10 mg) and used the updated lower price of canagliflozin 300 mg. This document only presents the updated base case results, however all sensitivity and scenario analyses were based on the original base-case. ICERs compared with pioglitazone and sulfonylureas are presented in table 2. Compared with pioglitazone, sulfonylureas and DPP-4 inhibitors were dominated. The ICER for canagliflozin 300 mg compared with pioglitazone was £42,782 per quality-adjusted life year (QALY) gained, and canagliflozin 300 mg dominated all other treatments. In pairwise analyses canagliflozin 100 mg had ICERs of £1,987 per QALY gained compared with DPP-4 inhibitors and £7,875 per QALY gained compared with a sulfonylurea, and it dominated (that is, was cheaper and more effective than) dapagliflozin and empagliflozin 10 mg.

Table 2 Janssen base case cost-effectiveness results

	Cost	QALY	ICER (£/QALY) vs pioglitazone	ICER (£/QALY) vs sulfonylurea
Pioglitazone	£20,211	9.960	-	Not considered as a comparator
SU	£22,756	9.912	Pioglitazone dominates	Lowest cost
Cana 300 mg	£23,284	10.032	£42,782	£4,401
DPP-4	£23,317	9.937	Canagliflozin 300 mg dominates	Ccanagliflozin 300 mg dominates
Empa 25 mg	£23,410	9.975		
Cana incr.	£23,421	10.006		
Cana 100 mg	£23,441	9.999		

Dapa 10 mg	£23,495	9.958		
Empa 10 mg	£23,513	9.967		
Abbreviations: Cana, canagliflozin; dapa, dapagliflozin; DPP-4, dipeptidyl peptidase-4 inhibitor; empa, empagliflozin; ICER, incremental cost-effectiveness ratio; incr: canagliflozin 100 mg dose titrated to 300 mg dose; QALY: quality-adjusted life year; SU, sulfonylurea; vs, versus.				

- 3.36 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.
- 3.37 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 in segment' assumption of progression used in the base case; see section 3.30), 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 sulfonylureas.
- 3.38 The company presented probabilistic analyses for canagliflozin 100 mg compared with all comparators. Pioglitazone had the highest probability of being cost effective at ICERs of £20,000 and £30,000 per QALY gained, with probabilities of approximately 70% and 40% respectively. The probabilities for all other treatments were less than 20%.
- 3.39 The AG reviewed the model submitted by Janssen. It noted that the modelling was 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
- sulfonylureas: £593 and £8,751 per QALY gained
- DPP-4 inhibitors: canagliflozin dominant and £8,528 per QALY gained.

3.40 The AG stated that when comparing canagliflozin with dapagliflozin and empagliflozin, the main scenario analyses of interest were: using patient characteristics from the same database that was used in the NICE's guideline update on [type 2 diabetes](#) (but collected from a separate analysis conducted by Janssen); 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 scenarios changed the ICERs to between £5,000 to £10,000 per QALY gained.

Company model (AstraZeneca)

3.41 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.

3.42 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 £6,125 per QALY gained compared with DPP-4 inhibitors, £20,639 per QALY gained compared with pioglitazone and £59,013 per QALY gained compared with sulfonylureas.

3.43 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 sulfonylureas, the company noted that the ICER was sensitive to uncertainty about the relative efficacy of SGLT-2 inhibitors and sulfonylureas 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 (£4,434 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 sulfonylureas.

3.44 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 sulfonylureas, the ICER remained above £40,000 per QALY gained. The company stated that the base-case ICER and scenario analyses compared with sulfonylureas were likely to be overestimates because sulfonylureas had an initially high clinical-effectiveness estimate, but with a faster Hb1Ac progression than other treatments.

3.45 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 sulfonylureas the probabilities were 51% and 13% respectively.

3.46 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 who 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)

- 3.47 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.
- 3.48 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 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 sulfonylureas, pioglitazone and repaglinide respectively. When using 24-week data, empagliflozin 10 mg had an ICER of £9,834 per QALY gained compared with dapagliflozin; was cheaper but less effective than canagliflozin 300 mg (when using the outdated higher price of canagliflozin 300 mg, see section 3.33); 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)
Model B results – 52-week ICERs (vs pio)			
Empa 25 mg od	£2,834	0.06	£46,480

Empa 10 mg od	£2,837	0.06	£50,892
Pio 45 mg od	Baseline	Baseline	Baseline
Repa 1 mg od	£635	0.03	£25,349
Sita 100 mg od	£2,504	0.02	£163,917
Sulfonylureas	£1,527	0.01	£121,660
Model B results - 24-week ICERs (vs dapa 10)			
Empa 25 mg od	£46	0.02	£2,172
Empa 10 mg od	£68	0.01	£9,834
Cana 300 mg od	£970	0.06	£17,363
Cana 100 mg od	£1	0.03	£39
Dapa 10 mg od	Baseline	Baseline	Baseline
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.			

- 3.49 The company did not present any sensitivity or scenario analyses for model B. In response to the appraisal consultation document, the company provided a summary of one-way sensitivity analyses not previously presented, which showed that results were most sensitive to the incidence of hypoglycaemic events, weight loss and the incidence of urinary tract infection. Other variables, including cost and utility decrements associated with adverse events, had less impact.
- 3.50 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.

Assessment Group's economic model

- 3.51 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.

- 3.52 Table 4 presents the results of the model. 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).
- 3.53 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.
- 3.54 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/m² (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).

3.55 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
Sulfonylureas	£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.

3.56 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, sulfonylureas, and pioglitazone (see tables 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
Sulfonylureas	-	-	-	-	-	-
Repaglinide	Dom	£3,388	£3,388	£3,388	£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

Treatment	ICERs (£/QALY)					
	No BMI	BMI-1	BMI-2	BMI-3	BMI-4	BMI-5
Cana 300 mg	£12,034	£2,467	£8,494	£5,820	£9,777	£6,312
Empa 25 mg	£17,278	£4,471	£13,917	£10,294	£14,864	£10,724
Dapa 10 mg	£37,871	£6,542	£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 sulfonylureas

Treatment	ICERs (£/QALY)					
	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

Treatment	ICERs (£/QALY)					
	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.

3.57 Following consultation on the appraisal consultation document, the AG identified an error in the calculation of systolic blood pressure reduction for canagliflozin 300 mg. This reduced the base case ICERs for canagliflozin 300 mg (see table 9), but had no impact on the ICERs for dapagliflozin or empagliflozin. The updated ICERs shown in table 9 are based on the AG's original base case, and do not include a correction for the previously-identified error for ischaemic heart disease (see section 3.52).

Table 9 Assessment Group revised cost-effectiveness results for canagliflozin 300 mg compared with DPP-4 inhibitors, sulfonylureas and pioglitazone

Treatment	ICERs (£/QALY)					
	No BMI	BMI-1	BMI-2	BMI-3	BMI-4	BMI-5
vs DPP-4	£4,401	£1,341	£3,586	£2,729	£3,929	£2,896
vs SU	£1.1mn	£32,015	£71,038	£57,865	£330,000	£118,000
vs pio	£385,000	£27,003	£52,432	£44,590	£201,000	£90,653

Abbreviations: cana, canagliflozin; dapa, dapagliflozin; dom, dominated (more costly and less effective than another treatment); empagliflozin; ICER, incremental cost-effectiveness ratio; mn: million; pio, pioglitazone; SU, sulfonylureas; vs, versus.

- 3.58 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.
- 3.59 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 sulfonylureas 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.

4 Committee discussion

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.

4.1 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.

4.2 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 sulfonylureas 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, sulfonylureas 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 type 2 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, sulfonylureas and pioglitazone, but that in clinical practice the most appropriate comparator would depend on individual patient circumstances.

Clinical effectiveness

- 4.3 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.
- 4.4 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.

4.5 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.

4.6 The committee considered if there was any evidence of differences in effectiveness between the SGLT-2 inhibitors. It heard from the clinical experts 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. In response to the appraisal consultation document, Janssen (the company for canagliflozin) stated that although it agreed there was no direct evidence available, the indirect evidence from the AG and company network meta-analyses (see [sections 3.11 to 3.23](#)) demonstrated that canagliflozin was the most effective treatment. The committee was aware that some results showed differences between 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 that had different baseline patient characteristics to the others, and when this was

removed results were similar to the other SGLT-2 inhibitors. The committee also noted that the differences in effectiveness between the SGLT-2 inhibitors in the network meta-analyses were most pronounced in people having the higher doses of canagliflozin and empagliflozin, which were not licensed starting doses. The committee agreed that the results demonstrated in the higher dose groups, which were derived from clinical trials where patients were able to start on the higher doses, may not be seen in clinical practice, where people eligible for and requiring a higher dose would be required to titrate up to it. Furthermore, the committee heard from Janssen that in clinical practice the majority of patients use the lower, 100 mg, starting dose of canagliflozin. 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.

- 4.7 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

- 4.8 The committee discussed the structure of the AG and company models, considering if any single model was most appropriate for decision making. 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. For example, the Janssen model assumed a 'linear in segment' (see [section 3.30](#)) progression of HbA1c whereas all other models based progression of disease on the UK Prospective Diabetes Study (UKPDS) equations. Furthermore, the AG model assumed that when people intensified treatment, treatments were added, rather than switched (as assumed in all

company models at either first or second 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. Furthermore, the committee noted that NICE's guideline on [diabetes](#) had used the same model used by the AG (OM1, see [section 3.27](#)), preferring it to other models because it was based on 1 trial only (the committee was aware this was unlike ECHO-T2DM which was based on multiple sources) and also because it matched the NICE reference case, was internally and externally validated, and allowed for modelling of additional short-term outcomes. The committee was aware that in response to the appraisal consultation document, Janssen had described several advantages of the ECHO-T2DM model over the other submitted models. For example, it stated that ECHO-T2DM does not double count the treatment effect associated with rescue medication, unlike other models. The committee acknowledged there were different advantages and disadvantages to the different modelling approaches, and it agreed with the AG that all models submitted were appropriate and of a reasonable quality. However it concluded that the AG model was most appropriate for decision-making, because of its more accurate reflection of treatment intensification.

- 4.9 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-2 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 SGLT-2 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. The committee noted that in response to the appraisal consultation document, Janssen stated it considered the 'BMI-3' scenario (where weight gains were maintained, and weight losses rebound to natural history at

intensification) to be the most appropriate scenario based on expert clinical opinion, although it had noted a lack of evidence to support any assumptions about the duration of weight loss. The committee agreed there is a lack of long-term evidence to support firm conclusions about the duration of treatment-related weight change. However it noted that NICE's guideline on [diabetes](#) used the same assumption for the duration of weight gains and losses as that used in scenario BMI-2, because the clinical evidence on treatment-related weight-change was presented at follow-up of 1 year and 2 years, but was very limited at 2 years. The committee therefore concluded that BMI-2 was the most plausible scenario, but noted that the small QALY differences between treatments made the ICERs unstable.

- 4.10 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 £4,400 to £7,900 per QALY gained for canagliflozin 100 mg or 300 mg compared with sulfonylureas, whereas ICERs in the other models were substantially higher (for example, £59,000 per QALY gained for the SGLT-2 inhibitors compared with the sulfonylureas in the AstraZeneca model, and £71,000 per QALY gained in the AG model using the BMI-2 scenario). The committee heard from the AG that it considered the most probable driver of the differences between the AG and Janssen cost-effectiveness results to be the different modelling assumptions used for treatment intensification (see [section 3.33](#)). Discontinuing oral therapies when intensifying to insulin meant that patients received the relatively expensive oral therapies for a relatively short period of time in the Janssen model, contributing to lower incremental costs for canagliflozin relative to a sulfonylurea when compared with the AG model. The committee noted that the Janssen model showed total costs for canagliflozin 300 mg were around £500 more expensive than a sulfonylurea, whereas in the AG model total costs were around £5,000 more expensive. The committee concluded there was uncertainty about the reason for the favourable cost-effectiveness results for canagliflozin compared with a sulfonylurea in the Janssen model, but that the increased costs arising from retaining oral treatments in the AG model (a committee preferred assumption) was likely to be an important contributing factor.
- 4.11 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, sulfonylureas and DPP-4 inhibitors), using its

preferred model (AG model, see section 4.8) and its preferred assumptions about the effect of treatment on BMI (scenario BMI-2, see section 4.9).

- When compared with pioglitazone, ICERs for all the SGLT-2 inhibitors were more than £52,400 per QALY gained.
- When compared with sulfonylureas, ICERs for the SGLT-2 inhibitors were all over £71,000 per QALY gained.
- When compared with DPP-4 inhibitors, the ICERs for all SGLT-2 inhibitors were less than £29,300 per QALY gained.
- When the SGLT-2 inhibitors were compared with each other, the committee agreed that the clinical evidence (see section 4.6) and cost data (all tablets cost the same and had the same frequency of administration) did not support any differences between them.

4.12 The committee discussed the most plausible ICERs. For canagliflozin 300 mg, the committee noted that its preferred base case result from the AG had been updated following responses to the appraisal consultation document (to use a corrected value for systolic blood pressure for canagliflozin, see [section 3.57](#)). This had reduced the ICER when compared with sulfonylureas or pioglitazone to at least £52,400 per QALY gained, the lowest cost-effectiveness estimates of the SGLT-2 inhibitors, but still not within the range usually considered to be a cost-effective use of NHS resources. The committee also noted that even these ICERs were possibly optimistic, because the clinical-effectiveness assumptions were based on the more favourable results of the 300 mg dose, which was not the most commonly used dose in clinical practice (see section 4.6). 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 sulfonylureas. Therefore the committee concluded that canagliflozin, dapagliflozin and empagliflozin as monotherapy were a cost-effective use of NHS resources, but only when pioglitazone or sulfonylureas were not appropriate treatment options.

4.13 The committee discussed the most appropriate wording of the final recommendation. It considered whether to recommend that the least costly SGLT-2 inhibitor should be used first. However, because all the SGLT-2 inhibitors cost the same per tablet and have the same dosing frequency, and the clinical data had not robustly demonstrated that any one SGLT-2 inhibitor was more

clinically effective than the others (see section 4.6), it could not determine a meaningful way to differentiate treatments by cost. It also noted concerns raised in response to the appraisal consultation document from Janssen (the company for canagliflozin) that the wording of the draft recommendation implied that a sulfonylurea or pioglitazone should be used before SGLT-2 inhibitors or DPP-4 inhibitors, which could affect individualisation of care. The committee discussed whether there was a need to reword the draft recommendation when the final guidance was published. It stated that the existing wording of the recommendation reflected the evidence base, and that the phrasing of the recommendation that SGLT-2 inhibitors are only recommended where 'a sulfonylurea or pioglitazone was not appropriate' still allowed for clinical choice and individualisation of care; the recommendation does not imply that any treatments have to be tried first if they are not appropriate. The committee agreed that the wording of the recommendation allowed clinicians the freedom to prescribe SGLT-2 inhibitors when they feel it is appropriate. It also agreed that there was no meaningful way to recommend a hierarchy of SGLT-2 inhibitors based on cost. It therefore concluded that the final wording of the recommendation should remain the same as the draft recommendation that was consulted on.

- 4.14 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

TA390	Appraisal title: Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes	Section
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Key conclusion	
<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"> • When compared with pioglitazone, ICERs for all the SGLT-2 inhibitors were more than £52,400 per quality-adjusted life year (QALY) gained. • When compared with sulfonylureas, ICERs for the SGLT-2 inhibitors were all over £71,000 per QALY gained. • When compared with DPP-4 inhibitors, the ICERs for all SGLT-2 inhibitors were less than £29,300 per QALY gained. • When the SGLT-2 inhibitors were compared with each other, the committee agreed that the clinical evidence and cost data (all tablets cost the same and had the same frequency of administration) did not support any differences between them. <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 sulfonylureas. Therefore the committee concluded that canagliflozin, dapagliflozin and empagliflozin as monotherapy are a cost-effective use of NHS resources for treating type 2 diabetes in adults for whom metformin is contraindicated or not tolerated, and when diet and exercise alone do not provide adequate glycaemic control, but only when pioglitazone or sulfonylureas are not appropriate treatment options.</p>	<p>1.1, 4.6, 4.11, 4.12</p>
Current practice	

<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. 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. 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>4.1</p>
<p>The technology</p>		
<p>Proposed benefits of the technology 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>4.5</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 sulfonylureas 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>2.1, 4.2</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>4.7</p>
<p>Evidence for clinical effectiveness</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 considered if there was any evidence of differences in effectiveness between the SGLT-2 inhibitors. It heard from the clinical experts that 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.</p>	<p>4.3, 4.6</p>

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.	4.4
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.	4.6
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.	4.5, 4.6
Evidence for cost effectiveness		
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.	3.26

<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 £4,400 to £7,900 per QALY gained for canagliflozin 100 mg or 300 mg compared with sulfonylureas, whereas ICERs in the other models were substantially higher. The committee concluded there was uncertainty about the reason for the favourable cost-effectiveness results for canagliflozin compared with a sulfonylurea in the Janssen model, but that the increased costs arising from retaining oral treatments (a committee preferred assumption) was likely to be an important contributing factor.</p> <p>The committee noted that the small QALY differences between treatments made the ICERs unstable.</p>	<p>4.10, 4.9</p>
<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 noted that NICE's guideline on diabetes used the same assumption for the duration of weight gains and losses as that used in scenario BMI-2. 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>4.9</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>No specific committee consideration.</p>	<p>–</p>

What are the key drivers of cost effectiveness?	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.	4.9
Most likely cost-effectiveness estimate (given as an ICER)	<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 £52,400 per QALY gained.</p> <p>When compared with sulfonylureas, ICERs for the SGLT-2 inhibitors were all more than £71,000 per QALY gained.</p> <p>When compared with DPP-4 inhibitors, the ICERs ranged from £3,600 to £29,300 per QALY gained.</p>	4.11, 4.12
Additional factors taken into account		
Patient access schemes (PPRS)	N/A	-
End-of-life considerations	N/A	-
Equalities considerations and social value judgements	N/A	-

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 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 A](#).

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.

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Accreditation

