NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Canagliflozin in combination therapy for treating type 2 diabetes

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

1.1 Canagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if:

- a sulfonylurea is contraindicated or not tolerated **or**
- the person is at significant risk of hypoglycaemia or its consequences.

1.2 Canagliflozin in a triple therapy regimen is recommended as an option for treating type 2 diabetes in combination with:

- metformin and a sulfonylurea **or**
- metformin and a thiazolidinedione.

1.3 Canagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.

1.4 People currently receiving treatment initiated within the NHS with canagliflozin that is not recommended for them by NICE in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 The technology

2.1 Canagliflozin (Invokana, Janssen-Cilag) is an orally administered selective sodium–glucose cotransporter-2 (SGLT-2) inhibitor. It lowers blood glucose in people with type 2 diabetes by blocking the reabsorption of glucose in the kidneys and promoting excretion of excess glucose in the urine.

2.2 Canagliflozin has a European marketing authorisation for treating type 2 diabetes in adults aged 18 years and older to improve glycaemic control as:

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

The recommended starting dosage of canagliflozin is 100 mg once daily. In patients tolerating canagliflozin 100 mg once daily who have an estimated glomerular filtration rate (eGFR) of at least 60 ml/min/1.73 m^2 or creatinine clearance (CrCl) of at least 60 ml/min and need tighter glycaemic control, the dosage can be increased to 300 mg once daily. For patients with renal impairment, the summary of product characteristics notes that canagliflozin should not be initiated in patients with an eGFR of less than 60 ml/min/1.73m^2 or CrCl of less than 60 ml/min. In patients tolerating canagliflozin whose eGFR falls persistently below 60 ml/min/1.73 m^2 or whose CrCl persistently falls below 60 ml/min, 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/min/1.73 m^2 or CrCl is persistently below 45 ml/min.

2.3 The summary of product characteristics states the following adverse reactions for canagliflozin as the most commonly reported: hypoglycaemia in combination with insulin or a sulfonylurea, vulvovaginal candidiasis, urinary tract infection, and polyuria or pollakiuria (that is, urinary frequency). For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.4 According to the British national formulary (April 2014), the drug's price (excluding VAT) is £39.20 for canagliflozin 100 mg (30 tablets) and £49.99 for canagliflozin 300 mg (30 tablets). The expected annual cost of canagliflozin is £476.93 for the 100 mg daily dosage and £608.21 for the 300 mg daily dosage. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee (section 8) considered evidence submitted by the manufacturer of canagliflozin and a review of this submission by the Evidence Review Group (ERG; section 9).

Clinical effectiveness

3.1 The manufacturer's literature search identified 85 citations for use in the systematic literature review. It identified 11 clinical trials that evaluated canagliflozin in combination therapy for treating type 2 diabetes. The manufacturer indicated that 5 of these trials would not provide useful information for approaching the decision problem. No non-randomised clinical trials were included in the manufacturer's submission.

3.2 Of the 6 randomised controlled trials in the manufacturer's submission, 2 evaluated canagliflozin as part of dual therapy in combination with metformin (DIA3006 and DIA3009), 3 as part of triple therapy in combination with metformin and either a sulfonylurea or pioglitazone (DIA3012, DIA3002, DIA3015) and 1 with insulin with or without other antidiabetic treatments (DIA3008 insulin sub-study). All studies except DIA3015 evaluated 2 doses of canagliflozin (100 mg and 300 mg). DIA3015 used the higher dose only.

- DIA3009 compared canagliflozin 100 mg (n=483) and canagliflozin 300 mg (n=485) with glimepiride (n=484) as part of dual therapy in combination with metformin for 104 weeks (52-week core double blind and 52-week extension double blind).
- DIA3006 compared canagliflozin 100 mg (n=368) and canagliflozin 300 mg (n=367) with sitagliptin 100 mg (n=366) and with placebo/sitagliptin (n=183) as part of dual therapy in combination with metformin for 52 weeks (26-week core double blind and 26-week extension double blind).
- DIA3015 compared canagliflozin 300 mg (n=378) with sitagliptin 100 mg (n=378) as part of triple therapy in combination with metformin and a sulfonylurea for 52 weeks.
- DIA3002 compared canagliflozin 100 mg (n=157) and canagliflozin 300 mg (n=156) with placebo (n=156) as part of triple therapy in combination with metformin and a sulfonylurea for 52 weeks (26-week core double blind and 26-week extension double blind).
- DIA3012 compared canagliflozin 100 mg (n=115) and canagliflozin 300 mg (n=114) with placebo (n=115; crossover to sitagliptin at 26 weeks) as part of triple therapy in combination

with metformin and pioglitazone for 52 weeks (26-week core double blind and 26-week extension double blind).

- The DIA3008 insulin sub-study compared canagliflozin 100 mg (n=566) and canagliflozin 300 mg (n=587) with placebo (n=565) as an add-on treatment to insulin with or without other antidiabetic drugs for 18 weeks. It was part of the ongoing CANVAS safety study in 4330 patients with high risk or history of cardiovascular disease, which will report in 2017.

3.3 Patients were eligible for these trials if they had type 2 diabetes and inadequate glycaemic control on existing treatment (1 or 2 background therapies for all studies except the DIA3008 insulin sub-study, for which the maximum number of add-on treatments was not stated). Inadequate glycaemic control was defined as an HbA_{1c} level of 7.0–10.5%, except for DIA3009 in which the range was 7.0–9.5%. All patients enrolled into CANVAS had a history of, or were at high risk of, cardiovascular disease; those enrolled in the DIA3008 insulin sub-study were on insulin alone or in combination with standard of care. The trials enrolled 12–28% patients in Europe, of whom 27 were in the UK.

3.4 The primary outcome for all studies was change in HbA_{1c} from baseline to the end of the double-blind treatment period. Secondary outcomes included change in body weight, change in systolic blood pressure, and incidence of hypoglycaemia. Results for all trials reported in the manufacturer's submission were for the modified intention-to-treat populations (defined as randomised patients who received at least 1 dose of study drug using a last observation carried forward approach).

Manufacturer's results for dual therapy

3.5 In DIA3009, mean change in HbA_{1c} (minus glimepiride) at week 52 was −0.01% (95% confidence interval [CI] −0.109 to 0.085) for

canagliflozin 100 mg plus metformin compared with glimepiride and metformin. At week 52, canagliflozin 300 mg and metformin produced a statistically superior mean reduction in HbA_{1c} compared with glimepiride plus metformin, with a mean change (minus glimepiride) of −0.12% (95% CI −0.217 to −0.023, p<0.001). In DIA3006, mean change in HbA_{1c} (minus placebo) was −0.627% (95% CI −0.758 to −0.481) for canagliflozin 100 mg plus metformin and −0.77% for canagliflozin 300 mg plus metformin (95% CI −0.914 to −0.636), compared with −0.66% (95% CI −0.795 to −0.516) for sitagliptin plus metformin (p<0.001 compared with placebo for the canagliflozin arms).

3.6 In DIA3009, there was a greater improvement in systolic blood pressure at 52 weeks with both doses of canagliflozin compared with glimepiride (mean difference in systolic blood pressure reduction [minus glimepiride] −3.5 mmHg [95% CI −4.9 to −2.1] with canagliflozin 100 mg and −4.8 mmHg [95% CI −6.2 to −3.40 with canagliflozin 300 mg). In DIA3006, canagliflozin 100 mg and 300 mg decreased systolic blood pressure from baseline at 26 weeks with a difference in mean systolic blood pressure (minus placebo) of −5.36 mmHg (95% CI −7.280 to −3.439) and −6.58 mmHg (95% CI −8.504 to −4.653) respectively compared with −3.54 mmHg (95% CI −5.273 to −1.413) in the sitagliptin arm (p<0.001 for both canagliflozin doses compared with placebo).

3.7 In DIA3009 at week 52, both doses of canagliflozin were associated with a statistically greater change in body weight compared with glimepiride. Weight loss was −4.2 kg (standard error 0.2) for canagliflozin 100 mg and −4.7 kg (standard error 0.2) for canagliflozin 300 mg compared with a slight increase in weight with glimepiride of +1.0 kg (standard error 0.2). In DIA3006 at week 26, a weight loss of −3.7 kg (standard error 0.2) was observed with canagliflozin 100 mg and −4.2 kg (standard error: 0.2) with

canagliflozin 300 mg compared with −1.2 kg (standard error 0.2) with sitagliptin. Both doses of canagliflozin demonstrated statistical superiority to sitagliptin up to week 52 with a difference in mean weight reduction (minus sitagliptin) of −2.1 kg for canagliflozin 100 mg and −2.5 kg for canagliflozin 300 mg (p<0.001 for both doses).

Manufacturer's results for triple therapy

3.8 In DIA3015 at week 52, canagliflozin 300 mg produced a statistically superior reduction in HbA_{1c} compared with sitagliptin, with a difference in mean change in HbA_{1c} for canagliflozin 300 mg (minus sitagliptin) of −0.37% (95% CI −0.50 to −0.25). DIA3002 and DIA3012 showed a statistically significant reduction in HbA_{1c} at 26 weeks for both doses of canagliflozin compared with placebo. Mean reduction in HbA_{1c} at week 26 with canagliflozin 100 mg (minus placebo) was −0.71% (95% CI −0.904 to −0.524, p<0.001) in DIA3002 and −0.62% (95% CI −0.811 to −0.437, p<0.001) in DIA3012. Mean reduction with canagliflozin 300 mg was −0.92% (95% CI −1.114 to −0.732, p<0.001) in DIA3012 and −0.76% (95% CI −0.951 to −0.575, p<0.001) in DIA3002.

3.9 Both doses of canagliflozin, when used in triple therapy, resulted in a statistically significant greater reduction in systolic blood pressure compared with sitagliptin or placebo in DIA3015 and DIA3012 but not DIA3002. In DIA3015, canagliflozin 300 mg statistically significantly decreased systolic blood pressure compared with sitagliptin with a difference in mean change (minus sitagliptin) in systolic blood pressure at week 52 of −5.9 mmHg (95% CI −7.642 to −4.175, p<0.001). Similarly, a statistically significant difference was seen in DIA3012 at 26 weeks, with a mean difference in systolic blood pressure (minus placebo) of −4.07 (95% CI −6.879 to −1.251, p=0.005) with canagliflozin 100 mg and −3.46 (95% CI −6.281 to −0.643, p=0.016) with canagliflozin 300 mg. No

statistically significant difference in mean systolic blood pressure (minus placebo) was seen at 26 weeks in DIA3002 with canagliflozin 100 mg (−2.24 [95% CI −4.719 to 0.241, p=0.077]) or canagliflozin 300 mg (−1.62 [95% CI −4.111 to 0.866, p=0.201]).

3.10 Both doses of canagliflozin, when used in triple therapy, lowered body weight. In DIA3015 at week 52, canagliflozin 300 mg treatment resulted in statistically significant reductions in body weight relative to sitagliptin (−2.8 kg [95% CI −3.3 to −2], p<0.001). In DIA3002 at week 26, canagliflozin 100 mg and 300 mg (in combination with metformin and a sulfonylurea) resulted in a reduction in weight of −2.1 kg (standard error 0.3) and −2.6 kg (standard error 0.3) respectively compared with a weight change of −0.7 kg (standard error 0.3) in the placebo group. Changes in body weight were also evident at week 52 with a difference in mean weight change (minus placebo) of −1.0 kg (95% CI −1.8 to −1.2) for canagliflozin 100 mg and −2.1 kg (95% CI −2.9 to −1.2) for canagliflozin 300 mg. In DIA3012 at week 26, a change in weight of −2.7 kg (standard error 0.3) and −3.8 kg (standard error 0.3) was observed for canagliflozin 100 mg and 300 mg respectively (in combination with metformin and a thiazolidinedione).

Manufacturer's results for add-on treatment to insulin

3.11 At week 18 in the DIA3008 insulin sub-study, the difference in mean change in HbA_{1c} compared with placebo was −0.65% (95% CI −0.73 to −0.56) in the canagliflozin 100 mg group and −0.73% (95% CI −0.82 to −0.65) in canagliflozin 300 mg arm (p<0.001 both comparisons). Both doses of canagliflozin resulted in a significant reduction in systolic blood pressure (p<0.001) compared with placebo. The difference in mean systolic blood pressure change (minus placebo) at week 18 was −2.58 mmHg (95% CI −4.060 to 1.091; p<0.001) with canagliflozin 100 mg and −4.38 mmHg (95% CI −5.850 to −2.903; p<0.001) with canagliflozin 300 mg.

Change in body weight (minus placebo) at week 18 was −1.8 kg (95% CI −2.2 to −1.6) in the canagliflozin 100 mg group and −2.3 kg (95% CI −2.7 to −2.1) in the canagliflozin 300 mg group ($p<0.001$ for both comparisons).

Manufacturer's meta-analyses

3.12 The manufacturer conducted a systematic literature review to identify randomised controlled trials that evaluated treatments relevant to the NICE scope for this appraisal in patients with type 2 diabetes. The manufacturer's base-case network meta-analyses included 38 studies comparing treatments given in combination with metformin (metformin background), 10 studies comparing treatments given in combination with metformin and a sulfonylurea (metformin and sulfonylurea background), 2 studies comparing treatments given in combination with metformin and pioglitazone (metformin and pioglitazone background) and 14 studies comparing treatments given in combination with insulin (insulin background). The manufacturer used a Bayesian hierarchical model for the network meta-analyses. After assessing relative goodness of fit of fixed-effects and random-effects models using the deviance information criterion, the model associated with the lowest score was selected (with a difference of at least 3 points). All analyses were conducted by background therapy. The manufacturer conducted sensitivity analyses to determine the robustness of results. The manufacturer's submission reported outcomes that were relevant to its economic model including change in HbA_{1c}, weight, BMI, systolic blood pressure and incidence of hypoglycaemia.

Dual therapy with a metformin background

3.13 The manufacturer presented differences in HbA_{1c} change at 52 weeks from its meta-analysis (complete with 95% credible

intervals [95% CrI]) for canagliflozin 100 mg and 300 mg compared with the different comparators as dual therapy with a metformin background. Canagliflozin 100 mg produced a numerically greater reduction in HbA_{1c} than sitagliptin 100 mg (−0.01%, 95% CrI −0.48 to 0.44) and dapagliflozin 10 mg (−0.14%, 95% CrI −0.81 to 0.47), but not liraglutide 1.2 mg (0.40%, 95% CrI −0.33 to 1.11), canagliflozin 300 mg (0.13%, 95% CrI −0.25 to 0.52), pioglitazone 30 mg (0.11%, 95% CrI −0.44 to 0.84), exenatide 10 micrograms (0.02%, 95% CrI −0.65 to 0.55) or glimepiride (0.00%, 95% CrI −0.45 to 0.46). Canagliflozin 300 mg was associated with a numerically greater reduction in HbA_{1c} than pioglitazone 30 mg (−0.02%, 95% CrI −0.57 to 0.72), exenatide 10 micrograms (−0.11%, 95% CrI −0.78 to 0.42), glimepiride (−0.13%, 95% CrI −0.58 to 0.33), canagliflozin 100 mg (−0.13%, 95% CrI −0.52 to 0.25), sitagliptin 100 mg (−0.14%, 95% CrI −0.61 to 0.31) and dapagliflozin 10 mg (−0.27%, 95% CrI −0.94 to 0.34). However, it was not associated with a numerically greater reduction in HbA_{1c} compared with liraglutide 1.2 mg (0.27%, 95% CrI −0.46 to 0.98).

3.14 When given as part of dual therapy with a metformin background, canagliflozin 100 mg and 300 mg were associated with greater weight reductions at 52 weeks compared with sitagliptin 100 mg (differences of −2.12 kg [95% CrI −2.66 to −1.57] and −2.48 kg [95% CrI 3.03 to −1.93] respectively), glimepiride (differences of −3.97 kg [95% CrI −5.54 to −2.48] and −4.33 kg [95% CrI −5.89 to −2.85] respectively) and pioglitazone 30 mg (differences of −4.57 kg [95% CrI −6.28 to −2.93] and −4.93 kg [95% CrI −6.64 to −3.29] respectively). The reduction in weight was at least similar for canagliflozin 100 mg and 300 mg compared with dapagliflozin 10 mg (differences of −0.11 kg [95% CrI −1.10 to 0.89] and −0.48 kg [95% CrI −1.47 to 0.53] respectively). When comparing canagliflozin with the glucagon-like peptide-1 (GLP-1) analogues,

canagliflozin 100 mg and 300 mg gave a lesser weight reduction than exenatide 10 micrograms (differences of 1.47 kg [95% CrI −1.48 to 4.41] and 1.11 kg [95% CrI −1.84 to 4.05] respectively) but a greater weight reduction than liraglutide 1.2 mg (−0.49 [95% CrI −1.37 to 0.38] and −0.85 kg [−1.73 to 0.02] respectively).

3.15 The manufacturer reported that canagliflozin 100 mg and 300 mg were associated with greater reductions in systolic blood pressure compared with glimepiride (differences of −3.52 mmHg [95% CrI −5.02 to −2.05] and −4.73 mmHg [95% CrI −6.22 to −3.26] respectively), liraglutide 1.2 mg (differences of −3.50 mmHg [95% CrI −6.55 to −0.43] and −4.71 mmHg [95% CrI −7.73 to −1.66] respectively) and sitagliptin 100 mg (differences of −2.84 mmHg [95% CrI −4.44 to −1.22] and −4.04 mmHg [95% CrI −5.64 to −2.44] respectively), and smaller reductions in systolic blood pressure than pioglitazone 30 mg (differences of 2.05 mmHg [95% CrI −3.22 to 7.37] and 0.83 mmHg [95% CrI −4.44 to 6.15] respectively).

3.16 The manufacturer reported that canagliflozin 100 mg and 300 mg were associated with a lower risk of hypoglycaemia compared with glimepiride (odds ratios 0.11 [95% CrI 0.07 to 0.16] and 0.10 [95% CrI 0.07 to 0.15] respectively). It described a higher risk of hypoglycaemia for canagliflozin 100 mg and 300 mg compared with dapagliflozin 10 mg (odds ratios 3.65 [95% CrI 1.44 to 9.93] and 3.43 [95% CrI 1.34 to 9.23] respectively) and sitagliptin (odds ratios 1.77 [95% CrI 0.97 to 3.44) and 1.66 [95% CrI 0.90 to 3.23] respectively). The manufacturer advised that the difference in risk of hypoglycaemia compared with dapagliflozin in this network meta-analysis was likely to be because of differences in how hypoglycaemic events were reported in the clinical trials, but did not provide any further explanation for this.

Triple therapy with a metformin plus sulfonylurea background

3.17 Comparisons for canagliflozin and comparators with a metformin and sulfonylurea background were provided by the manufacturer. Compared with sitagliptin 100 mg, canagliflozin 100 mg produced a similar reduction in HbA_{1c} (0.07%, 95% CrI −1.48 to 1.64), whereas canagliflozin 300 mg was associated with a slightly greater HbA_{1c} reduction (−0.17%, 95% CrI −1.30 to 0.97). Canagliflozin 100 mg gave a similar HbA_{1c} reduction (difference of 0.03%, 95% CrI −1.78 to 1.79) compared with exenatide 10 micrograms, and canagliflozin 300 mg gave a higher HbA_{1c} reduction (difference of −0.21%, 95% CrI −1.87 to 1.42). Canagliflozin 100 mg and 300 mg were associated with greater weight reductions than sitagliptin 100 mg (differences of −2.03 kg [95% CrI −7.78 to 3.76] and −2.64 kg [95% CrI −6.83 to 1.56] respectively) and similar weight reductions to exenatide 10 micrograms (differences of 0.47 kg [95% CrI −6.09 to 7.24] and −0.14 kg [95% CrI −6.15 to 6.08] respectively). Canagliflozin 100 mg and 300 mg were associated with a higher reduction in systolic blood pressure than sitagliptin 100 mg (differences of −5.76 mmHg [95% CrI −9.02 to −2.53] and −5.16 mmHg [95% CrI −6.94 to −3.38] respectively). Canagliflozin 100 mg and 300 mg were associated with a similar risk of hypoglycaemia as sitagliptin 100 mg (odds ratios of 0.75 [95% CrI 0.43 to 1.29] and 0.96 [95% CrI 0.72 to 1.29]) respectively) and exenatide 10 micrograms (odds ratios of 0.96 [95% CrI 0.46 to 2.00] and 1.23 [95% CrI 0.62 to 2.48] respectively).

Triple therapy with a metformin plus thiazolidinedione background

3.18 The manufacturer's submission presented comparisons for canagliflozin and comparators with a metformin and thiazolidinedione background. Compared with sitagliptin 100 mg, canagliflozin 100 mg was associated with a smaller reduction in HbA_{1c} at 26 weeks (difference of 0.07%, 95% CrI −0.19 to 0.33)

and canagliflozin 300 mg was associated with a greater reduction (difference of −0.07%, 95% CrI −0.33 to 0.19). Canagliflozin 100 mg and 300 mg were associated with weight reductions compared with sitagliptin 100 mg (differences of −2.70 kg [95% CrI −10.10 to 4.62] and −3.65 kg [−11.07 to 3.67] respectively). No statistical analysis was conducted for changes in systolic blood pressure because of limitations in the evidence base. Canagliflozin 100 mg was associated with a similar risk of hypoglycaemic events as sitagliptin 100 mg (odds ratio of 0.86, 95% CrI 0.10 to 7.09), whereas canagliflozin 300 mg was associated with a higher risk (odds ratio of 1.89, 95% CrI 0.30 to 13.72).

Add-on to insulin with or without an antihyperglycaemic background

3.19 When given as an add-on treatment to insulin, the reduction in HbA_{1c} at 26 weeks with canagliflozin 100 mg and 300 mg was greater than with sitagliptin 100 mg (differences of −0.01% [95% CrI −0.17 to 0.16] and −0.15% [95% CrI −0.31 to 0.02] respectively) and dapagliflozin 10 mg (differences of −0.01% [95% CrI −0.17 to 0.15] and −0.15% [95% CrI −0.31 to 0.01] respectively). The higher dose of canagliflozin gave a greater HbA_{1c} reduction than exenatide 10 micrograms (difference of −0.05%, 95% CrI −0.31 to 0.21) but the lower dose did not (difference of 0.09%, 95% CrI −0.17 to 0.35). A similar pattern was observed for the comparison of canagliflozin and pioglitazone 30 mg (difference of −0.10% [95% CrI −0.37 to 0.17] for canagliflozin 300 mg and 0.04% [95% CrI −0.23 to 0.30] for canagliflozin 100 mg). Pioglitazone 45 mg produced a greater HbA_{1c} reduction than either canagliflozin 100 mg or 300 mg.

3.20 When given as an add-on treatment to insulin, canagliflozin 100 mg and 300 mg were associated with greater weight reduction than sitagliptin 100 mg (differences of −2.10 kg [95% CrI −2.67 to −1.53] and −2.67 kg [95% CrI −3.24 to −2.11] respectively), pioglitazone

30 mg (differences of −3.28 kg [95% CrI −11.72 to 5.14] and −3.85 kg [95% CrI −12.31 to 4.57] respectively) and dapagliflozin 10 mg (differences of −0.41 kg [95% CI −1.01 to 0.20] and −0.98 kg [95% CrI −1.59 to −0.38] respectively) but not exenatide 10 micrograms (differences of 0.64 kg [95% CrI −0.44 to 1.71] and 0.07 kg [95% CrI −1.01 to 1.14] respectively). Canagliflozin 100 mg and 300 mg were associated with higher reductions in systolic blood pressure compared with dapagliflozin 10 mg (differences of −0.92 mmHg [95% CrI −3.93 to 2.08] and −2.62 mmHg [95% CrI −5.64 to 0.40] respectively). When comparing canagliflozin and exenatide 10 micrograms, canagliflozin 300 mg was associated with a lower reduction in systolic blood pressure (difference of −1.33 mmHg, 95% CrI −5.19 to 2.52) but canagliflozin 100 mg was not (0.38 mmHg, 95% CrI −3.46 to 4.23). No analysis of BMI results or all hypoglycaemic events was conducted because of lack of data at 26 weeks for the canagliflozin trial.

Adverse events

3.21 The canagliflozin clinical trials included in the submission evaluated the safety of canagliflozin in 10,285 people with type 2 diabetes. The manufacturer provided data from 3 pre-specified pooled safety datasets, focusing on a broad dataset that included data for canagliflozin 100 mg (n=3092), canagliflozin 300 mg (n=3085) and all non-canagliflozin arms (placebo, glimepiride and sitagliptin [n=3262]).

3.22 In the broad dataset, the incidence of any adverse event was similar across groups (76.6% for canagliflozin 100 mg, 77.0% for canagliflozin 300 mg and 75.8% in the non-canagliflozin group). The incidence of adverse events leading to discontinuation in the broad dataset was higher in the canagliflozin 300 mg group (7.3%) than the canagliflozin 100 mg (5.6%) and non-canagliflozin (5.0%) groups. Adverse events that led to discontinuation of more than

0.2% of patients in the canagliflozin 300 mg group were decreased glomerular filtration rate, renal impairment and increased blood creatinine. The incidence of adverse events considered related to the study drug by the investigator was slightly higher in the canagliflozin 100 mg and 300 mg groups (33.6% and 29.4% respectively) than the non-canagliflozin group (21.8%). The incidence of serious adverse events and deaths was similar in the canagliflozin and non-canagliflozin groups. Adverse events occurring in at least 5% of subjects in a canagliflozin group were nasopharyngitis, hypoglycaemia, upper respiratory tract infection, urinary tract infection, diarrhoea, arthralgia, back pain and headache.

3.23 The manufacturer noted that sodium–glucose cotransporter-2 (SGLT-2) inhibitors are associated with a higher incidence of genital mycotic infections because of urinary glucose excretion. In the broad dataset, the incidence of genital mycotic infection adverse events in women was higher in those receiving canagliflozin 100 mg (14.7%) and canagliflozin 300 mg (13.9%) than in those taking placebo (3.1%). In men, the incidence was 7.3% in the canagliflozin 100 mg group and 9.3% in the canagliflozin 300 mg groups, compared with 1.6% of men in the non-canagliflozin group.

Evidence Review Group's comments on the manufacturer's clinical-effectiveness evidence

3.24 The ERG considered that only the trials with active comparator arms were relevant to the NICE scope (DIA3009 and DIA3006 [dual therapy] and DIA3015 [triple therapy]) and judged all 3 to be of generally good methodological quality. The ERG considered the manufacturer's submission to provide a generally unbiased estimate of canagliflozin's treatment effect within the stated scope

of the decision problem, and that the manufacturer's interpretation of the evidence was largely appropriate and justified.

3.25 However, the ERG identified some exceptions and uncertainties:

- A lack of direct evidence for comparisons with treatments other than sitagliptin and glimepiride.
- No discussion of the implications of differences in results between the modified intention-to-treat analyses (reported in the manufacturer's submission) and per protocol analyses (reported in the trial journal publications and clinical study reports).
- A low volume of direct evidence for some of the loops in the network meta-analyses, which led the ERG to conclude that the results should be interpreted with caution.
- It was not convinced by the manufacturer's justification for network meta-analysis for triple therapy assessing effects at 26 weeks, rather than at 52 weeks.
- The exclusion of background treatments that did not include metformin (because including these would better reflect all the potential uses of canagliflozin within its European marketing authorisation).
- Lack of evidence for the longer-term efficacy and safety of canagliflozin (because most outcomes were measured up to 52 weeks in the clinical trials).
- It did not have confidence in the manufacturer's favourable interpretation of adverse events related to canagliflozin compared with other treatments, and the discontinuation rates compared with sitagliptin and glimepiride.

Cost effectiveness

3.26 The manufacturer's submission included de novo economic analyses of canagliflozin in combination therapy for type 2 diabetes using the following regimens:

- dual therapy in combination with metformin
- triple therapy in combination with metformin and a sulfonylurea
- triple therapy in combination with metformin and a thiazolidinedione
- add-on treatment to insulin (with or without other antihyperglycaemic agents).

3.27 The manufacturer advised that these populations reflected the licensed indications for canagliflozin combination treatment and patients in the clinical trials, and it considered these patients to be representative of the population most likely to receive canagliflozin in clinical practice in England. The 100 mg and 300 mg doses of canagliflozin were considered separately in the base-case analyses (increasing the dose from 100 mg to 300 mg according to the summary of product characteristics [see section 2.2] was explored in a scenario analysis). Comparator treatments used at the different points in the treatment pathway were sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, GLP-1 analogues, dapagliflozin and insulin. The manufacturer selected a comparator to represent each treatment class in its economic model (based on frequency of use in clinical practice, comparators in the canagliflozin clinical trials and available data).

3.28 The manufacturer's systematic literature review of potentially relevant published cost-effectiveness evidence identified 52 analyses, and a similar systematic literature review found 21 economic evaluation models of type 2 diabetes. The manufacturer chose the ECHO-T2DM model, which was a stochastic micro-simulation model in which cohorts of individual hypothetical patients were created and simulated over time using Monte Carlo (first-order uncertainty) techniques. Second-order (parameter) uncertainty was captured by hypothetical cohorts of 1000 patients defined by baseline characteristics sourced from the

canagliflozin clinical trials including demographics (for example, age and sex), biomarker values (for example, HbA_{1c}, systolic blood pressure and BMI, which are short-term outcomes used to predict the likelihood of longer-term events in the model) and disease indicators (for example, disease duration and history of complications). Individual patient outcomes were simulated over time through health states capturing micro- and macrovascular complications and death. There were 1000 cohorts of 1000 patients for each model run for the base-case comparisons, and patient cohorts were simulated until death or the end of the designated follow-up period. Results of key parameter values (including treatment effects, risk equation coefficients, and quality-adjusted life year [QALY] disutility weights) were then aggregated. The model used a lifetime time horizon (40 years), the cycle length was 1 year, health benefits and costs were each discounted at 3.5% and the analysis was from an NHS perspective.

3.29 The manufacturer's model included 3 parallel sets of microvascular complications (to reflect increasing severity of retinopathy, chronic kidney disease and neuropathy) and 4 types of macrovascular complications (ischaemic heart disease, myocardial infarction, stroke and congestive heart failure; because of interdependence with neuropathic outcomes, peripheral vascular disease was classified as a microvascular neuropathy complication). These were represented by Markov health states and were associated with costs, utility values and, in some cases, a possible treatment contraindication (for example, end-stage renal disease for pioglitazone) or excess risk of death (for example, myocardial infarction or stroke). Annual probabilities of experiencing worsening microvascular complications were derived primarily from the Wisconsin Epidemiologic Study of Diabetic Retinopathy, the Rochester Epidemiology Project, and the Centers for Disease

Control model of chronic kidney disease. Risk equations from the original UK Prospective Diabetes Study (UKPDS) Outcomes Model were used to simulate macrovascular complications in the base case. The manufacturer mainly used published utility values derived from CODE-2, which was a non-interventional, observational study. Utility decrements were applied to the baseline quality-of-life value (estimated at 1.027 using multivariate regression techniques) for patient characteristics (for example, age and duration of disease), microvascular and macrovascular complications, hypoglycaemic events, obesity and adverse events.

3.30 The manufacturer explained that diabetes treatments have an initial effect followed by annual 'drift', where the effect lessens over time. Biomarker values after the first cycle were estimated using annual drift values for each treatment. Based on published values, HbA_{1c} drift was assumed to be 0.14% for canagliflozin, dapagliflozin, DPP-4 inhibitors and GLP-1 analogues, 0.07% for thiazolidinediones, 0.24% for sulfonylureas and 0.15% for insulin. The drift values for systolic blood pressure, lipids, weight and eGFR were assumed to be the same for all treatments. The manufacturer's model allowed patients to take anti-dyslipidaemia and anti-hypertension medications, and applied rescue treatments when biomarker thresholds for dyslipidaemia and hypertension were exceeded.

Manufacturer's cost-effectiveness results

3.31 The manufacturer presented pairwise comparisons using cohorts of simulated patients from the probability distribution of patient characteristics for canagliflozin 100 mg and 300 mg in dual therapy, triple therapy and as an add-on to insulin. At the clarification stage, the manufacturer provided some updated cost-effectiveness results after identifying that, where BMI was not available in the network meta-analysis, the change in actual BMI had been used instead of

being calculated using a weighted average of height in the UK general population. The updated incremental cost-effectiveness ratios (ICERs) were generally more favourable for canagliflozin than the ones they replaced.

Manufacturer's base case – dual therapy

3.32 Canagliflozin 100 mg as part of a dual therapy regimen showed QALY gains and increased costs compared with a sulfonylurea (ICER of £1537 per QALY gained [incremental costs £288; incremental QALYs 0.188]), a DPP-4 inhibitor (ICER of £97 per QALY gained [incremental costs £1; incremental QALYs 0.013]), and dapagliflozin (£8674 per QALY gained [incremental costs £63; incremental QALYs 0.007]). The ICER provided by the manufacturer at the clarification stage for the comparison with dapagliflozin was £2993 per QALY gained (incremental costs £33; incremental QALYs 0.011). Compared with a GLP-1 analogue, canagliflozin 100 mg was less effective and less costly (incremental costs −£2424; incremental QALYs −0.048). Canagliflozin 100 mg continued to be less effective and less costly than a GLP-1 analogue after correcting the BMI data (incremental costs −£2,414; incremental QALYs −0.034). Canagliflozin 100 mg was dominated by pioglitazone (that is, canagliflozin was more costly and less effective [incremental costs £2833; incremental QALYs −0.159]).

3.33 Canagliflozin 300 mg as part of a dual therapy regimen, when compared with a sulfonylurea, produced higher costs and greater QALY gains (ICER of £4899 per QALY gained [incremental costs £976; incremental QALYs 0.199]), a DPP-4 inhibitor (ICER of £18,349 per QALY gained [incremental costs £576; incremental QALYs 0.031]), and dapagliflozin (ICER of £27,419 per QALY gained [incremental costs £625; incremental QALYs 0.023]. The ICER provided at the clarification stage for the comparison with dapagliflozin was £21,626 per QALY gained (incremental costs

£616; incremental QALYs 0.029). Similar to the 100 mg dose, canagliflozin 300 mg was less costly and less effective than a GLP-1 analogue, giving an ICER of £76,214 per QALY gained for a GLP-1 analogue to replace canagliflozin 300 mg (incremental costs −£1892; incremental QALYs −0.025). Canagliflozin 300 mg continued to be less effective and less costly than a GLP-1 analogue after correcting the BMI data (incremental costs −£1879; incremental QALYs −0.018). Like the 100 mg dose, canagliflozin 300 mg was also dominated by pioglitazone (incremental costs £3353; incremental QALYs −0.141).

Manufacturer's base case – triple therapy

3.34 The manufacturer also presented cost-effectiveness results for triple therapy regimens containing canagliflozin 100 mg and 300 mg. In a triple therapy combination with metformin and a sulfonylurea, canagliflozin 100 mg dominated a DPP-4 inhibitor (incremental costs −£42; incremental QALYs 0.016), and also dominated a GLP-1 analogue (incremental costs −£1297; incremental QALYs 0.001). Adjusting the change in BMI at the clarification stage caused canagliflozin to become less costly and less effective than a GLP-1 analogue, giving an updated ICER of £265,928 per QALY gained for a GLP-1 analogue to replace canagliflozin 100 mg. Canagliflozin 100 mg was associated with greater costs and QALYs than long-acting insulin, with an ICER of £263 per QALY gained (incremental costs £135; incremental QALYs 0.514). An updated ICER provided at the clarification stage was £183 per QALY gained. In a triple therapy combination with metformin and a thiazolidinedione, canagliflozin 100 mg had higher costs and QALY gains than a DPP-4 inhibitor, producing an ICER of £1095 per QALY gained (incremental costs £7; incremental QALYs 0.007).

3.35 In combination with metformin and a sulfonylurea, canagliflozin 300 mg compared with a DPP-4 inhibitor had an ICER of £13,287 per QALY gained (incremental costs £461; incremental QALYs 0.035) and dominated a GLP-1 analogue (incremental costs −£685; incremental QALYs 0.004). Canagliflozin 300 mg continued to dominate a GLP-1 analogue after updating the BMI data at the clarification stage. In combination with metformin and a thiazolidinedione, the ICER for canagliflozin 300 mg compared with a DPP-4 inhibitor was £21,430 per QALY gained (incremental costs £691; incremental QALYs 0.032). Canagliflozin 300 mg compared with long-acting insulin gave an ICER of £607 per QALY gained (incremental costs £379; incremental QALYs 0.624). After updating the BMI data at the clarification stage, the ICER increased slightly to £671 per QALY gained.

Manufacturer's base case – add-on to insulin

3.36 Canagliflozin 100 mg as an add-on treatment to insulin dominated dapagliflozin (incremental costs −£72; incremental QALYs 0.003). Canagliflozin 100 mg was associated with lower costs and lower QALY gains compared with a DPP-4 inhibitor (incremental costs −£13; incremental QALYs −0.010), with an ICER of £1340 per QALY gained for canagliflozin 100 mg to be replaced by a DPP-4 inhibitor. Compared with a GLP-1 analogue, canagliflozin 100 mg was also associated with lower costs and lower QALY gains (incremental costs −£836; incremental QALYs −0.065) with an ICER of £12,915 per QALY gained for canagliflozin 100 mg to be replaced by a GLP-1 analogue.

3.37 Canagliflozin 300 mg as an add-on treatment to insulin produced greater costs and QALY gains compared with a DPP-4 inhibitor (ICER of £7975 per QALY gained [incremental costs £322; incremental QALYs 0.040]), and dapagliflozin (ICER of £5992 per QALY gained [incremental costs £327; incremental QALYs 0.055]).

Compared with a GLP-1 analogue, canagliflozin 300 mg was associated with lower costs and lower QALY gains (incremental costs −£526; incremental QALYs −0.015), with an ICER of £35,575 per QALY gained for canagliflozin to be replaced by a GLP-1 analogue.

Manufacturer's sensitivity analyses

3.38 The manufacturer conducted deterministic and probabilistic sensitivity analyses for canagliflozin compared with a DPP-4 inhibitor (in dual therapy, triple therapy and as an add-on to insulin therapy) and with a sulfonylurea in dual therapy, because it perceived these to be the key comparators for canagliflozin. The manufacturer did not report results for other comparators used in its base case, including dapagliflozin.

3.39 The manufacturer's deterministic sensitivity analyses showed that the results from the model were most sensitive to varying the metabolic drift of HbA_{1c} associated with canagliflozin and its comparators. The manufacturer commented that, except for HbA_{1c} drift, the ICERs for the comparisons of both doses of canagliflozin with a sulfonylurea in dual therapy were largely insensitive to parameter changes. However, the manufacturer noted the ICERs for canagliflozin compared with a DPP-4 inhibitor were generally less stable.

3.40 The manufacturer presented results of probabilistic sensitivity analyses for canagliflozin compared with some of the comparators used in its base case and commented that there was greater uncertainty where the incremental changes in costs and QALYs were small. It noted that, at a maximum acceptable ICER of £20,000 per QALY gained, the probability of canagliflozin being cost effective compared with a DPP-4 inhibitor for the different comparisons was 45–56% for the 100 mg dose and 52–61% for the

300 mg dose. The manufacturer stated that there was less uncertainty in the dual therapy comparisons of canagliflozin (100 mg and 300 mg) with a sulfonylurea, with the probability of cost effectiveness being around 90% for both doses (at maximum acceptable ICERs of £20,000 or £30,000 per QALY gained).

3.41 The manufacturer undertook scenario analyses that explored dose escalation from the recommended starting dose of 100 mg to 300 mg (see section 2.2). Modelling techniques were used because this had not been studied in clinical trials. If patients in the simulated cohort had tolerated the 100 mg dose of canagliflozin but had not reached an HbA_{1c} of less than 7.5% at 6 months, then the canagliflozin dose was increased to 300 mg in cycle 2. The manufacturer based this assumption on clinical specialist opinion. Switching to the higher dose was only permitted at the end of the first cycle: patients who tolerated treatment and had satisfactory glycaemic control continued the 100 mg dose and switched to standard rescue therapy when needed. It was assumed that patients who switched to the higher dose experienced the same treatment effects as patients treated with 300 mg for the full 12 months. The manufacturer stated that the dose escalation scenario improved the cost effectiveness of canagliflozin for 11 out of 12 comparisons made. Only the ICER comparing canagliflozin with a sulfonylurea in dual therapy increased (from £1537 per QALY gained to £1721 per QALY gained) and canagliflozin was dominant in 7 of the scenarios.

Evidence Review Group's comments on the manufacturer's cost-effectiveness analyses

3.42 The ERG concluded that the methods and inputs in the manufacturer's economic evaluation were generally in line with the NICE reference case, but noted:

- Not all comparators in the NICE scope had been included in the manufacturer's decision problem.
- Comparators used were not always the most widely prescribed.
- The NICE reference case states that data from head-to-head trials should be presented in the reference-case analysis if possible, but the manufacturer had instead sometimes used results from the meta-analyses. The ERG indicated that although the manufacturer had stated this was for consistency, this was not properly justified because the manufacturer had not provided a fully incremental cost-effectiveness analysis (that is, only pairwise comparisons had been generated).
- It was not clear if the preference data for utility values wholly represented the population of England because they were derived from a European study (CODE-2).

The ERG considered the model to be internally consistent and well validated.

3.43 Overall, the ERG considered the clinical-effectiveness data in the model to be appropriate (although sometimes network meta-analysis estimates were used instead of head-to-head trial data). It found the equations used for the extrapolation of biomarker outcomes to be well-established and appropriate for the patient population in England, and the drift assumptions for the biomarkers to be reasonable. However, the ERG was concerned that using only 1000 patients per cohort in the base case might not robustly capture the ICERs.

3.44 The ERG commented that health benefits had been measured and evaluated in line with the NICE reference case and that utility values had been appropriately incorporated into the manufacturer's model. The ERG generally agreed with the costs used by the manufacturer for drugs, adverse events and health states

(complications and comorbidities), although there was some uncertainty in the costs used for insulin.

3.45 Although the ERG agreed with the manufacturer's conclusions from the results of the deterministic analyses as presented, the ERG considered that the uncertainty in the decision problem had not been fully explored, and that the manufacturer did not present the results in the most informative way. The ERG was unclear why second-order uncertainty was not switched off in the deterministic sensitivity analyses (that is, by specifying only 1 patient cohort). Consequently, the ERG believed that the manufacturer's results were partly confounded by stochasticity in other parameters (that is, they included uncertainty from more than 1 source and did not truly reflect the uncertainty associated with varying 1 parameter).

3.46 The ERG reviewed the manufacturer's scenario analyses, focusing on the dose escalation scenario. It noted that, like the deterministic sensitivity analyses, second-order uncertainty was not switched off in the scenario analyses, meaning that the results were again partly confounded by parameter stochasticity. The ERG noted that the manufacturer's submission concluded from the dose escalation scenario analysis that the dose escalation schedule from 100 mg to 300 mg was cost effective, but the ERG did not consider that this conclusion applied to all treatment comparisons, noting that:

- Canagliflozin 100 mg compared with a thiazolidinedione in dual therapy remained dominated in the scenario analyses as well as in the base case.
- Canagliflozin 100 mg as an add-on to insulin was cheaper and less effective than a DPP-4 inhibitor in the base case, but associated with an ICER of £503 per QALY gained in the scenario analysis.

- Canagliflozin 100 mg as an add-on to insulin was cheaper and less effective than a GLP-1 analogue in the base case and remained so in the scenario analysis.

3.47 The ERG concluded that although all relevant variables appeared to have been included in the manufacturer's probabilistic sensitivity analyses, it was unclear if uncertainty in the decision problem had been sufficiently explored because the distributional assumptions were not well described in the manufacturer's submission and were not transparent in the model. The ERG also commented that standard errors used for the HbA_{1c} treatment effect parameters were too small and that cost-effectiveness acceptability data had not been presented for all base-case comparisons.

Evidence Review Group's exploratory analyses

3.48 The ERG did exploratory work to:

- examine the variation in base-case ICERs by re-running some of the manufacturer's analyses
- examine the variation in final ICERs for dual therapy with no parameter uncertainty and 100,000 patients
- produce incremental analyses for dual therapy
- calculate the probability that canagliflozin is cost effective compared with dapagliflozin
- determine the effect of varying the efficacy estimates for glimepiride and exenatide.

3.49 The ERG found there was minimal variation in the dual-therapy ICERs when it re-ran the manufacturer's base-case analyses. However, it was unsure if the manufacturer's use of 1000 cohorts of 1000 patients estimated the ICERs robustly, and how the base-case results might change if parameter uncertainty was removed. Its exploratory analyses with a single cohort of 100,000 patients

and no parameter uncertainty had a small impact on the different cost and QALY outcomes compared with the manufacturer's base-case analyses (typically hundreds of pounds or less, and thousandths of a QALY). The ERG noted, however, that the small differences in incremental QALYs could in some cases drive an apparently large variation in the ICER compared with the manufacturer's ICERs described in sections 3.32 and 3.33:

- Canagliflozin 100 mg was dominated by a thiazolidinedione (incremental costs £2929; incremental QALYs −0.166).
- Canagliflozin 100 mg compared with a sulfonylurea had an ICER of £1579 per QALY gained (incremental costs £274; incremental QALYs 0.174).
- Canagliflozin 100 mg compared with dapagliflozin had an ICER of £100,719 per QALY gained (incremental costs £193; incremental QALYs 0.002).
- Canagliflozin 100 mg compared with a DPP-4 inhibitor had an ICER of £12,938 per QALY gained (incremental costs £211; incremental QALYs 0.016).
- Canagliflozin 100 mg was less costly and less effective than a GLP-1 analogue, with an ICER of £67,414 per QALY lost (incremental costs −£2381; incremental QALYs −0.035).
- Canagliflozin 300 mg was dominated by a thiazolidinedione (incremental costs £3245; incremental QALYs −0.14).
- Canagliflozin 300 mg compared with a sulfonylurea had an ICER of £5368 per QALY gained (incremental costs £1121; incremental QALYs 0.21).
- Canagliflozin 300 mg compared with a DPP-4 inhibitor had an ICER of £9246 per QALY gained (incremental costs £412; incremental QALYs 0.04).

- Canagliflozin 300 mg compared with dapagliflozin had an ICER of £17,161 per QALY gained (incremental costs £751; incremental QALYs 0.04).
- Canagliflozin 300 mg was less costly and less effective than a GLP-1 analogue, with an ICER of £86,412 per QALY lost (incremental costs −£1867; incremental QALYs −0.0216).

3.50 The ERG did a fully incremental exploratory analysis for canagliflozin 100 mg in dual therapy in combination with metformin (excluding thiazolidinediones because their use in clinical practice in England is declining). In the ERG's exploratory analysis using the manufacturer's base-case inputs, canagliflozin 100 mg had an ICER of £507 per QALY gained (incremental costs £8; incremental QALYs 0.015) compared with the next best option, which was dapagliflozin. When using the ERG's preferred inputs (excluding parameter uncertainty and with 100,000 patients), canagliflozin 100 mg had an ICER of £84,800 per QALY gained (incremental costs £245; incremental QALYs 0.003) compared with the next best option, a DPP-4 inhibitor. The ERG noted that dapagliflozin, canagliflozin 100 mg and a DPP-4 inhibitor were associated with similar total costs and similar overall total QALYs.

3.51 The ERG did a fully incremental exploratory analysis (excluding thiazolidinediones) for canagliflozin 300 mg in dual therapy in combination with metformin. The ICER for canagliflozin 300 mg compared with the next best option, dapagliflozin, was £17,639 per QALY gained (incremental costs £587; incremental QALYs 0.033) for the manufacturer's base-case inputs of 1000 cohorts of 1000 patients, and £17,903 per QALY gained (incremental costs £585; incremental QALYs 0.033) compared with the next best option, a DPP-4 inhibitor, using data from the ERG's preferred input of a single cohort of 100,000 patients.

3.52 The ERG noted that the manufacturer's submission did not report the probability of canagliflozin being cost effective compared with dapagliflozin. The ERG's exploratory analyses for dual therapy with metformin and an SGLT-2 inhibitor showed that the probability of canagliflozin 100 mg being cost effective compared with dapagliflozin was 52.5% at maximum acceptable ICERs of £20,000 and £30,000 per QALY gained. For canagliflozin 300 mg, the probability of cost effectiveness was 46.7% at a maximum acceptable ICER of £20,000 per QALY gained and 50% at £30,000 per QALY gained.

3.53 The ERG was aware that the manufacturer had chosen a single comparator to be representative of each treatment class, but considered that there was variation in specific parameters between drugs within each treatment class that might not be fully captured by the manufacturer's deterministic sensitivity analyses. The ERG explored greater variation in hypoglycaemia event rate for sulfonylureas and agreed with the manufacturer that this parameter was not very influential. Similarly, the ERG found that using cost and efficacy data for liraglutide instead of exenatide 10 micrograms gave results that were consistent with the manufacturer's deterministic sensitivity analyses.

3.54 Full details of all the evidence are in the manufacturer's submission and the ERG report.

4 Consideration of the evidence

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

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

4.2 The Committee discussed the clinical treatment pathway for type 2 diabetes. It heard from the clinical specialists that although treatment for type 2 diabetes is individualised for each patient, current clinical practice in England broadly follows NICE guidance (see section 6). The Committee heard from the clinical specialists that all of the existing treatments have advantages and disadvantages, and that they do not enable everyone with type 2 diabetes to achieve target HbA_{1c} levels. It further heard that HbA_{1c} values tended to drift upwards over time (even after a good initial response to treatment), with sulfonylureas known to have a relatively high drift rate, and that a particular treatment aim is maintaining consistently tight glycaemic control to produce better long-term outcomes. The Committee heard from the clinical specialists that around 85% of people start treatment with metformin (with many of the remaining 15% starting treatment with a sulfonylurea) and that a sulfonylurea is often subsequently added to metformin for dual therapy. If patients are unable to take a sulfonylurea because of concerns about weight gain or hypoglycaemia, the clinical specialists stated that alternatives such as pioglitazone (a thiazolidinedione), sitagliptin (a dipeptidyl peptidase-4 [DPP-4] inhibitor) and dapagliflozin (a sodium–glucose cotransporter-2 [SGLT-2] inhibitor, like canagliflozin) may be used in combination with metformin. The Committee heard from the clinical specialists that the use of DPP-4 inhibitors was increasing and that the use of pioglitazone was decreasing because of concerns about weight gain and safety. The clinical specialists also said that the same treatments could be used in triple therapy and as add-on to insulin therapy. The Committee heard that when considering triple therapy options, many people prefer to take a

third oral agent rather than starting insulin (which is recommended in NICE clinical guideline 87) because of fear of hypoglycaemia, the need for injections, and the possible impact on their lifestyle (for example, concerns about keeping their driving licence, or employment). The Committee also noted that increased monitoring is needed with insulin, usually involving secondary care in addition to primary care. The Committee was aware that injectable GLP-1 analogues were also recommended in NICE guidance as part of dual therapy for a very small proportion of patients who were unable to take several other oral options. They are also recommended as part of triple therapy for a specific population (that is, a high BMI and associated problems, or if insulin treatment would have significant occupational implications, or if weight loss would be beneficial).

4.3 The Committee discussed the most likely place for canagliflozin in the treatment pathway, and which treatments in the NICE scope were the key comparators. The Committee heard from the clinical specialists that they would like to have the option of using canagliflozin as part of dual and triple therapy, and as add-on treatment to insulin. It was aware from the clinical specialists' input that evidence showed intensive early treatment of type 2 diabetes was associated with reduced macrovascular and microvascular complications, and therefore canagliflozin might be of most benefit early in the pathway. However, it also heard from the clinical specialists that there was extensive experience of using sulfonylureas, and that it was unlikely that healthcare professionals would imminently stop using them in favour of drugs with little or no long-term evidence of their efficacy and safety. However, the Committee further heard from the clinical specialists that this extensive experience with sulfonylureas has shown that they are not an appropriate treatment for all patients (for example, if weight

gain is a concern or in older people who are more at risk of injury from a fall secondary to hypoglycaemia). On the basis of the evidence from the clinical specialists, the Committee agreed that canagliflozin was most likely to be used in dual therapy in combination with metformin only for those people for whom a sulfonylurea was not appropriate. Consequently, the Committee concluded that the principal comparator to consider at this place in the pathway would be a DPP-4 inhibitor (such as sitagliptin). The Committee noted that dapagliflozin, which is an SGLT-2 inhibitor like canagliflozin, is recommended by NICE in technology appraisal guidance 288 for use in dual therapy in combination with metformin and that this was also a key comparator. The Committee heard that although pioglitazone is still prescribed, and is suitable for some patients, safety concerns have reduced the use of thiazolidinediones as a class in clinical practice. The Committee concluded that for dual therapy in combination with metformin, DPP-4 inhibitors and dapagliflozin were the key comparators.

4.4 The Committee heard from the clinical specialists that canagliflozin would also potentially be used as part of triple therapy, principally in combination with metformin and a sulfonylurea. It heard that the clinical specialists considered that the key comparator here would be a DDP-4 inhibitor. The Committee noted that dapagliflozin was not recommended in triple therapy by NICE in technology appraisal guidance 288 except as part of a clinical trial (that is, not in routine clinical practice) because there was no direct trial evidence for dapagliflozin in triple therapy at that time and dapagliflozin's manufacturers had highlighted limitations in the indirect comparison. The Committee also heard from the clinical specialists that canagliflozin had a place as an add-on treatment to insulin because of its different mechanism of action and the potential for an insulin-sparing effect, which could decrease the rate of

hypoglycaemic events. Taking all the evidence into account, including current clinical practice, the Committee concluded that a DPP-4 inhibitor was the key comparator in triple therapy, and a DPP-4 inhibitor and dapagliflozin were the key comparators as add-on treatment to insulin.

Clinical effectiveness

4.5 The Committee considered the evidence on the clinical effectiveness of canagliflozin compared with other antidiabetic treatments and noted that the manufacturer's submission contained the results from 3 head-to-head trials (DIA3006, DIA3009 and DIA3015) comparing canagliflozin with an active comparator: a DPP-4 inhibitor (sitagliptin) or a sulfonylurea (glimepiride) in dual therapy and a DPP-4 inhibitor (sitagliptin) in triple therapy. The Committee recalled that the Evidence Review Group (ERG) had considered these trials to be of generally good methodological quality. The Committee was aware, however, that most data came from the manufacturer's network meta-analyses. The Committee heard from the ERG that the manufacturer's searches had been well conducted and that it was generally satisfied with the manufacturer's approach to the network meta-analyses, although it was initially unclear why the triple therapy meta-analyses had been conducted with 26-week data instead of 52-week data. The manufacturer clarified that this was because there were more comparators with data available at 26 weeks than at 52 weeks. The Committee heard that the ERG agreed that using 52-week data for the triple therapy meta-analysis could make it difficult to construct a suitable network. The Committee also heard from the ERG that results for the 26-week and 52-week dual therapy meta-analyses were similar, and considered that this lessened the uncertainty around using the 26-week data for triple therapy. The Committee concluded that the results of the manufacturer's network meta-

analyses provided an appropriate basis for making decisions about the clinical effectiveness of canagliflozin compared with other antidiabetic therapies.

4.6 The Committee discussed the generalisability of the clinical trial populations to the NHS patient population in England that was potentially eligible for treatment with canagliflozin. The Committee was satisfied that the populations in the dual therapy and triple therapy trials were generalisable, but had concerns about the population in the DIA3008 insulin sub-study. This was because the sub-study was part of the CANVAS trial, which only included patients with a history of, or estimated, high risk of cardiovascular disease. The Committee heard from the clinical specialists that, in general, by the time patients have tried different oral treatments and progressed to insulin (around 8–10 years from diagnosis), they would be likely to have an increased risk of cardiovascular disease compared with the general population. The Committee was persuaded that patients on insulin for type 2 diabetes would be at increased risk of cardiovascular disease as a result of the condition, and concluded that the results of all the canagliflozin trials (including the DIA3008 insulin sub-study) were generalisable to the population likely to receive canagliflozin in clinical practice in England.

4.7 The Committee considered the clinical effectiveness of canagliflozin as dual therapy in combination with metformin. The Committee noted that the evidence came from 2 clinical trials and a network meta-analysis. It noted that head-to-head trials had compared canagliflozin at doses of 100 mg and 300 mg with glimepiride (a sulfonylurea) and with sitagliptin (a DPP-4 inhibitor). The Committee considered that, on the basis of current clinical guidelines and clinical practice, SGLT-2 inhibitors would only be considered for use as dual therapy in combination with metformin

when sulfonylureas were unsuitable, and that therefore sulfonylureas were not a relevant comparator. However, the comparison with sitagliptin was relevant to the decision problem. For sitagliptin, the Committee considered that the data suggested that canagliflozin has a broadly comparable efficacy to sitagliptin in reducing HbA_{1c}, and greater efficacy in reducing body weight and systolic blood pressure. The Committee concluded that, on the basis of the results of the clinical trials and network meta-analyses (see sections 3.13–3.16), canagliflozin as part of dual therapy in combination with metformin appeared to provide broadly comparable glycaemic control to the other antidiabetic drugs, including the key comparators DPP-4 inhibitors and dapagliflozin, and may result in greater weight loss and lowering of blood pressure than DPP-4 inhibitors.

4.8 The Committee discussed an alternative dual therapy combination that was specified in the NICE scope: canagliflozin in combination with a sulfonylurea. The Committee noted that the manufacturer had not made a case for canagliflozin in combination with sulfonylurea in its submission because most people with diabetes would initially use metformin. The Committee agreed that most patients would start on metformin monotherapy, but was aware that, if metformin was unsuitable, some patients would receive a sulfonylurea instead. However, the Committee concluded that it was unable to make a recommendation on the dual therapy combination of canagliflozin and a sulfonylurea because the manufacturer had not provided any clinical data.

4.9 The Committee discussed the clinical effectiveness of canagliflozin as part of triple therapy in combination with metformin and a sulfonylurea. The Committee noted that the evidence came from 2 clinical trials and a network meta-analysis. It acknowledged the availability of head-to-head trial results for canagliflozin compared

with a sitagliptin (a DPP-4 inhibitor), but was aware that DIA3015 only investigated the higher dose of canagliflozin. The Committee noted that DIA3015 showed that canagliflozin 300 mg statistically significantly reduced HbA_{1c}, systolic blood pressure and body weight compared with sitagliptin. The Committee was aware that in DIA3002, which compared canagliflozin with placebo in triple therapy, benefits were seen in reducing HbA_{1c} and body weight, but not systolic blood pressure. The Committee concluded that, on the basis of the clinical trials and the manufacturer's meta-analysis (see section 3.17), canagliflozin as part of triple therapy in combination with metformin and a sulfonylurea gave a comparable HbA_{1c} reduction compared with a DPP-4 inhibitor. It further concluded that reduction in weight and systolic blood pressure was greater with canagliflozin than a DPP-4 inhibitor.

4.10 The Committee discussed the clinical effectiveness of canagliflozin as part of triple therapy in combination with metformin and a thiazolidinedione. The Committee noted that the evidence came from 1 clinical trial and a network meta-analysis. The Committee noted that the clinical trial compared canagliflozin with placebo and not an active comparator, and that it was more effective than placebo in lowering HbA_{1c}, body weight and blood pressure. It heard from the clinical specialists that the use of thiazolidinediones was decreasing in clinical practice in England because of safety concerns about cardiac problems and bladder cancer, as well as its association with weight gain. The Committee noted that although few people would start taking pioglitazone these days, there would be some people who were still taking metformin and pioglitazone as dual therapy. Although the Committee considered that this was likely to be uncommon in clinical practice, it agreed that the population being small should not prevent the Committee considering canagliflozin as a possible treatment for this group of

patients. The Committee concluded that, on the basis of the clinical trials and the manufacturer's meta-analysis, the evidence for canagliflozin as part of triple therapy in combination with metformin and a thiazolidinedione was adequate to confirm that it is clinically effective in this combination.

4.11 The Committee considered the clinical effectiveness of canagliflozin as an add-on treatment to insulin, noting that the evidence came from 1 clinical trial (the DIA3008 insulin sub-study) and a network meta-analysis. The Committee noted that the trial was placebo controlled and only 18 weeks long, and that patients were taking a range of background treatments. The Committee agreed with the manufacturer's opinion that the differences between the patient population of the DIA3008 insulin sub-study and other studies, and the heterogeneity in background treatments across the studies, were limitations of the insulin meta-analysis. Nevertheless, it considered the patient population in the DIA3008 insulin sub-study to be generalisable to the patient population in England (see section 4.6) and the range of background treatments to be typical of clinical trials investigating treatments at this point in the treatment pathway. The Committee concluded that, despite the limitations associated with the methodology of the DIA3008 insulin sub-study and the network meta-analysis, their results showed that canagliflozin as add-on therapy to insulin appeared to be slightly more effective in reducing HbA_{1c} and body weight than DPP-4 inhibitors and dapagliflozin.

4.12 In light of the dosing options specified in canagliflozin's marketing authorisation, the Committee discussed how dose escalation with canagliflozin might be implemented in clinical practice in England, and how it might relate to its clinical effectiveness. It was aware that canagliflozin 100 mg and 300 mg had been studied separately in the clinical trials, and that there was no clinical trial evidence for

the clinical effectiveness of canagliflozin after dose escalation. It heard from the clinical specialists that there was no experience in escalating the drug dose, and that it was not clear how many people would need dose escalation, or when this might occur. The Committee noted the comments received from commentators in response to the appraisal consultation document that data from the USA suggested that 50% of people taking canagliflozin 100 mg escalated to the canagliflozin 300 mg dose. However, the Committee heard from the manufacturer that its observational data showed that 75% of people took 100 mg and 25% of people escalated to the 300 mg dose, and that if dose escalation occurred it would be soon after starting treatment (rather than after prolonged exposure). The Committee concluded that there was uncertainty about the proportion of patients taking canagliflozin 100 mg who would escalate to canagliflozin 300 mg, the timing of this, and the precise clinical effectiveness of canagliflozin when escalating the dose in clinical practice.

4.13 The Committee discussed the adverse events associated with canagliflozin. It heard from clinical specialists that the risk of hypoglycaemia and weight gain were relatively low compared with some other antihyperglycaemic treatments, which was important to people with type 2 diabetes and their healthcare professionals. Focusing on the adverse events that were typically associated with SGLT-2 inhibitors, the Committee heard from the clinical specialists that although rates of genital mycotic infections in the clinical trials were much higher than with placebo, these had generally been resolved by topical treatment and that recurrence rates were low. The Committee noted a comment received during consultation about a possible increase in low-trauma fracture rate associated with canagliflozin, but was aware that the European public assessment report described the increase as ‘questionable’. The

Committee also noted the consultation comments on canagliflozin's lipid profile and potential long-term cardiovascular adverse events, but was aware that the CANVAS safety trial was ongoing. The Committee concluded that the short-term adverse events for canagliflozin (100 mg and 300 mg doses) were manageable and that further data for longer-term outcomes are still needed, particularly for cardiovascular adverse events.

Cost effectiveness

4.14 The Committee discussed the manufacturer's ECHO-T2DM model, which had not been used in previous NICE technology appraisals of technologies used to treat type 2 diabetes. The Committee observed that the manufacturer's model followed the NICE reference case and methodology, noting that the utility values had mainly been derived from a large European dataset using EQ-5D. It noted the ERG's view that the model had been well validated, and heard from the ERG that ECHO-T2DM had been validated against the well-established CORE model as part of the Mount Hood challenge. The Committee was aware that the ERG had concerns about the stability of the incremental cost-effectiveness ratios (ICERs) generated using the model, especially when probabilistic uncertainty was included (as it was in the manufacturer's base case). The Committee heard from the manufacturer and the ERG that although the values may vary slightly in each model run, the incremental values were highly consistent. It further heard that the instability of the ICER was primarily because the differences in costs and quality-adjusted life year (QALY) benefits between treatments were very small, which meant that very slight changes in either of these could have a large effect on the calculated ratio. The Committee concluded that, despite some uncertainty about the stability of the results, the manufacturer's economic model was

suitable for assessing the cost effectiveness of canagliflozin in combination therapy for treating type 2 diabetes.

4.15 The Committee discussed the cost-effectiveness analyses presented by the manufacturer, noting that these did not include all the comparators in the NICE scope. The Committee was aware that more comparators had been included in the network meta-analyses but then subsequently excluded from the cost-effectiveness analysis because the manufacturer had chosen a single comparator to represent each class. On balance, the Committee concluded that the manufacturer had included an adequate range of comparators for the cost-effectiveness analysis of canagliflozin in dual therapy, triple therapy and as an add-on to insulin therapy.

4.16 The Committee reviewed the manufacturer's general approach to incorporating clinical data into its economic model using a mixture of data from its meta-analyses and clinical trials, where available. The Committee noted that there was a lack of data in certain loops of the network meta-analyses and that these sometimes indicated slightly more efficacious estimates in favour of canagliflozin compared with some of the direct trial evidence. However, the Committee heard from the ERG that the meta-analyses of clinical effectiveness of canagliflozin and its comparators were sufficiently robust and generally consistent with the direct trial evidence, and had been appropriately incorporated into the model. The Committee therefore concluded that the clinical data incorporated into the manufacturer's model were acceptable for informing the cost-effectiveness estimates.

4.17 The Committee discussed specific areas of uncertainty relating to data used for the 2 SGLT-2 inhibitors, canagliflozin and dapagliflozin, which had been identified by commentators during

consultation. It noted that the same values for changes in lipids had been used for the 2 drugs in the model, and was aware that the ERG considered the evidence to show that dapagliflozin had a more favourable profile than canagliflozin. However, it heard that the ERG had explored the effect of using different profiles for these 2 SGLT-2 inhibitors and that this had little impact on the ICER. The Committee also noted that that the manufacturer's sensitivity analyses showed that varying the lipid values did not strongly influence the ICER. The Committee was also aware that there was some uncertainty in the modelling of hypoglycaemia associated with the 2 SGLT-2 inhibitors, because of differences in the clinical trials with these drugs, and noted the absence of a tornado plot for canagliflozin compared with dapagliflozin in the manufacturer's sensitivity analyses. However, it heard from the ERG that hypoglycaemia was not a key driver of the cost-effectiveness estimates when comparing canagliflozin with the other treatments. The Committee concluded that although there was some uncertainty about how some clinical outcomes had been modelled, this was acceptable because it would not have a material effect on the decision about cost effectiveness.

4.18 The Committee discussed how the manufacturer had modelled changes in clinical effectiveness over time. It noted that the annual drift values for biochemical and other risk factors had been based on available data (see section 3.30), but that the same annual drift values for HbA_{1c} were used for the SGLT-2 inhibitors, DPP-4 inhibitors and GLP-1 analogues. The manufacturer clarified that although there were 4-year data for the DPP-4 inhibitors and GLP-1 analogues, only 104-week data were available for canagliflozin. The Committee considered this to have implications for the economic modelling, because the manufacturer's deterministic sensitivity analyses showed that results from the model were most

sensitive to varying HbA_{1c} drift. Following comments received during consultation, the Committee heard from the manufacturer that the assumption that canagliflozin had an annual HbA_{1c} drift value of 0.14% was supported by coefficient durability data from DIA3009, which showed the rate of HbA_{1c} increase was 0.16% for both canagliflozin 100 mg and 300 mg over 72 weeks. The Committee heard from the ERG that it had received clinical advice that the manufacturer's values were appropriate. Although the Committee was concerned that extrapolating short-term data over a lifetime time horizon contributed uncertainty to the cost-effectiveness estimates, it was persuaded that the clinical data from DIA3009 were not inconsistent with the manufacturer's drift values assumed in the model. The Committee also heard from clinical specialists that sulfonylureas were recognised to have a high drift rate, that the ADOPT study indicated lower drift rates for other treatments, and that that the assumption of broadly equivalent drift rates for other treatments was not unreasonable. In the absence of any long-term clinical data, the Committee concluded that the manufacturer's approach to modelling the long-term effectiveness of canagliflozin was acceptable.

4.19 The Committee discussed the manufacturer's scenario for dose escalation. It heard from the clinical specialists that it was impossible to predict with any certainty the number of patients who would be eligible for dose escalation, or when this would occur (see section 4.12). The Committee observed that the summary of product characteristics stated that the higher dose could be used if tighter glycaemic control was needed, but did not provide a definition of this, or specify a time when dose escalation should take place. In the absence of any other information, the Committee accepted that the manufacturer's assumptions for dose escalation in its scenario analysis were not unreasonable. However, it

considered that the results were associated with significant uncertainty and should be interpreted with caution, especially because the manufacturer had assumed that clinical effectiveness was the same in patients who had started on the 100 mg dose and escalated to 300 mg as those who had started and continued on the 300 mg dose. Given the absence of evidence to inform any alternative scenarios, the Committee concluded that the cost effectiveness of canagliflozin in combination therapy for treating type 2 diabetes should be informed by considering the cost-effectiveness estimates for the separate 100 mg and 300 mg doses for each treatment comparison.

4.20 The Committee discussed the level of uncertainty associated with the cost-effectiveness estimates from the manufacturer's economic model. It was aware of the ERG's opinion that the deterministic sensitivity analyses were incomplete and that the results were not clearly presented. It further noted that the ERG was unclear if the manufacturer's probabilistic sensitivity analyses had been sufficiently explored because the distributional assumptions were not transparent or well described. The Committee noted that the cost and QALY differences between canagliflozin and its comparators were generally stable, but also very small. It concluded that a level of uncertainty associated with the cost-effectiveness estimates generated using the manufacturer's model was inevitable with such small differences in the QALYs gained between canagliflozin and its comparators.

4.21 The Committee considered the most plausible ICERs for canagliflozin in combination with metformin as dual therapy. Based on clinical specialist opinion, the Committee decided that thiazolidinediones and sulfonylureas were not key comparators in this setting (see section 4.3). The Committee also believed that the GLP-1 analogues were not key comparators because they are

recommended only for a very small population (see sections 4.2–4.3). The Committee noted that the manufacturer's and ERG's analyses showed that canagliflozin was associated with higher costs and QALYs than DPP-4 inhibitors and dapagliflozin, but that these incremental differences were small (see sections 3.32–3.37 and 3.49–3.52).The Committee understood that these low incremental costs and health benefits meant the ICERs could vary dramatically in response to even small changes because of a pronounced effect on the cost-effectiveness ratio. The Committee noted that the ERG had carried out a fully incremental analysis including all dual therapy combinations. However, it noted that this included treatment options that would not be appropriate for all patients in clinical practice. The Committee therefore examined appropriate parts of the incremental analysis, together with relevant pairwise analyses, to evaluate the cost effectiveness of canagliflozin in dual therapy compared with the key comparators (DPP-4 inhibitors and dapagliflozin). The Committee saw that in some cases there was a very wide range of estimates of the ICER for the same drug comparison. After exploring the reasons for this, the Committee noted that the differences in costs over a 40-year time horizon were modest (from £1 to £751) and the differences in QALYs were extremely small (from 0.002 to 0.04). The Committee considered that it was important to take these small incremental differences into account when interpreting the ICERs. Overall, the Committee concluded that because of the very small differences in costs and QALYs between canagliflozin and DPP-4 inhibitors, and between canagliflozin and dapagliflozin, canagliflozin 100 mg and 300 mg in a dual therapy regimen in combination with metformin had been shown to be a cost-effective use of NHS resources. The Committee therefore recommended canagliflozin 100 mg and 300 mg as a treatment option when the alternative treatments would be a DPP-4 inhibitor or dapagliflozin in line with the

recommendations in NICE clinical guideline 87 and technology appraisal guidance 288 (that is, if they are at significant risk of hypoglycaemia or its consequences or if a sulfonylurea is not tolerated or contraindicated).

4.22 The Committee considered the most plausible ICERs for canagliflozin in combination with metformin and a sulfonylurea as triple therapy. Based on clinical specialist opinion, the Committee decided that the injectable therapies insulin and GLP-1 analogues were not key comparators because canagliflozin would be most suitable for people who prefer to add a third oral treatment rather than an injectable one, and also because GLP-1 analogues are only recommended for a specific patient population (see section 4.2). The Committee noted that the manufacturer's results showed that there were small incremental differences in costs and QALYs between canagliflozin and the DPP-4 inhibitors. Although there was considerable uncertainty around the precise ICERs (especially because only canagliflozin 300 mg was investigated in DIA3015), the Committee concluded that because of the small differences in costs and QALYs between canagliflozin and DPP-4 inhibitors, canagliflozin 100 mg and 300 mg in combination with metformin and a sulfonylurea in a triple therapy regimen had been shown to be a cost-effective use of NHS resources and should be recommended as a treatment option for people with type 2 diabetes.

4.23 The Committee considered the most plausible ICERs for canagliflozin in combination with metformin and a thiazolidinedione as triple therapy. It decided that the injectable therapies insulin and GLP-1 analogues were not key comparators (see section 4.22). The Committee recalled that canagliflozin had been shown to be more clinically effective than placebo in this setting, and observed that there were small increases in costs and QALYs for the addition

of canagliflozin compared with a DPP-4 inhibitor. The Committee considered that these cost-effectiveness estimates were subject to uncertainty and noted that the model had not incorporated disutilities for the possible long-term adverse effects of thiazolidinediones, such as fractures and bladder cancer. However, it did note that the manufacturer's deterministic ICERs for the 2 doses were within the range which could be considered cost effective. On balance, the Committee concluded that canagliflozin 100 mg and 300 mg in combination with metformin and a thiazolidinedione in a triple therapy regimen had been shown to be a cost-effective use of NHS resources and should be recommended as a treatment option for people with type 2 diabetes.

4.24 The Committee considered the most plausible ICERs for canagliflozin as an add-on treatment to insulin. It noted that the NICE scope specified that the comparators were oral agents, and so disregarded the cost-effectiveness estimates for a GLP-1 analogue. The Committee concluded that canagliflozin 100 mg and 300 mg had been shown to be a cost-effective use of NHS resources compared with DPP-4 inhibitors and dapagliflozin as an add-on treatment to insulin because of its very small incremental costs and incremental QALYs. The Committee recommended canagliflozin as a treatment option for people with diabetes that is inadequately controlled by insulin with or without other oral antidiabetic drugs.

4.25 The Committee discussed whether canagliflozin was an innovative treatment and if there were any additional QALYs that had not been included in the manufacturer's model. The manufacturer said that that there were no health benefits that had not been captured in the model. The Committee concluded that all substantial benefits

related to treatment with canagliflozin had been captured in the QALY calculation.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title: Canagliflozin in combination therapy for treating type 2 diabetes	Section
Key conclusion		
Canagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if a sulfonylurea is contraindicated or not tolerated, or the person is at significant risk of hypoglycaemia or its consequences. Canagliflozin in a triple therapy regimen is recommended as an option for treating type 2 diabetes in combination with metformin and either a sulfonylurea or a thiazolidinedione. Canagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes. The Committee concluded that the very small differences in costs and QALYs between canagliflozin (100 mg and 300 mg) and its key comparators showed that canagliflozin was a cost-effective use of NHS resources as dual therapy in combination with metformin, triple therapy in combination with metformin and either a sulfonylurea or a thiazolidinedione, and as an add-on treatment to insulin.		1.1, 1.2, 1.3, 4.21–4.24
Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee heard from the clinical specialists that treatment for type 2 diabetes is individualised for each patient and that all existing treatments had advantages and disadvantages. It further heard that current treatments do not enable everyone with type 2 diabetes to achieve and maintain target HbA_{1c} levels.	4.2
	The Committee noted that some people with type 2 diabetes are unable to take a sulfonylurea because of concerns about weight gain or hypoglycaemia, that the use of pioglitazone was decreasing because of concerns about weight gain and safety and that many people prefer to delay starting insulin in favour of other options because of fear of hypoglycaemia and its consequences, and the need for injections.	4.3

The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	Canagliflozin (Invokana, Janssen-Cilag) is an orally administered selective sodium–glucose cotransporter-2 (SGLT-2) inhibitor. It lowers blood glucose in people with type 2 diabetes by blocking the reabsorption of glucose in the kidneys and promoting excretion of excess glucose in the urine.	2.1
What is the position of the treatment in the pathway of care for the condition?	On the basis of the evidence from the clinical specialists, the Committee agreed that canagliflozin in dual therapy in combination with metformin was likely to be used in people for whom a sulfonylurea was not appropriate. The Committee concluded that DPP-4 inhibitors and dapagliflozin were the key comparators. The Committee heard from the clinical specialists that canagliflozin would also potentially be used as part of triple therapy, principally in combination with metformin and a sulfonylurea, and concluded a DPP-4 inhibitor was the key comparator. The Committee also heard from the clinical specialists that canagliflozin had a place as an add-on treatment to insulin, and concluded that DPP-4 inhibitors and dapagliflozin were the key comparators.	4.3, 4.4
Adverse reactions	The summary of product characteristics states the following adverse reactions for canagliflozin as the most commonly reported: hypoglycaemia in combination with insulin or a sulfonylurea, vulvovaginal candidiasis, urinary tract infection, and polyuria or pollakiuria (that is, urinary frequency). The Committee noted that the CANVAS safety trial was ongoing. It concluded that the short-term adverse events for canagliflozin (100 mg and 300 mg doses) were manageable and that further data for longer-term outcomes are still required, particularly for cardiovascular adverse events.	2.3, 4.13
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee noted that the manufacturer's submission described the results from 6 randomised controlled trials, including 3 head-to-head trials (DIA3006, DIA3009 and DIA3015)	4.5, 4.8

	comparing canagliflozin with an active comparator: a DPP-4 inhibitor (sitagliptin) or a sulfonylurea (glimepiride) in dual therapy and a DPP-4 inhibitor (sitagliptin) in triple therapy. It concluded that the results of the manufacturer's network meta-analyses provided an appropriate basis for making decisions about the clinical effectiveness of canagliflozin compared with other antidiabetic therapies. However, the Committee concluded that it was unable to make a recommendation on the dual therapy combination of canagliflozin and a sulfonylurea because the manufacturer had not provided any clinical data.	
Relevance to general clinical practice in the NHS	The Committee was persuaded by the clinical specialists' opinion that patients on insulin for type 2 diabetes would be at increased risk of cardiovascular disease as a result of the condition, and concluded the results from the DIA3008 insulin sub-study, as well as those from the other trials, were generalisable to the population likely to receive canagliflozin in clinical practice in England.	4.6
Uncertainties generated by the evidence	The Committee was aware that there was no clinical trial evidence for the clinical effectiveness of canagliflozin after dose escalation, as described in canagliflozin's marketing authorisation, because canagliflozin 100 mg and 300 mg had been studied separately. The Committee concluded that there was uncertainty about the proportion of patients taking canagliflozin 100 mg who would escalate to canagliflozin 300 mg, the timing of this, and the precise clinical effectiveness of canagliflozin when escalating the dose in clinical practice.	4.12
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	Not applicable.	
Estimate of the size of the clinical effectiveness including strength of supporting evidence	For dual therapy in combination with metformin, the Committee concluded that, on the basis of the results of the clinical trials and network meta-analyses, canagliflozin appeared to provide broadly comparable glycaemic control to the other antidiabetic drugs, including the key comparators DPP-4 inhibitors and dapagliflozin, and may result in greater weight loss and lowering of blood pressure than DPP-4 inhibitors.	4.7

	The Committee concluded that, on the basis of the clinical trials and the manufacturer's meta-analysis, canagliflozin as part of triple therapy in combination with metformin and a sulfonylurea gave a comparable HbA_{1c} reduction compared with a DPP-4 inhibitor. It further concluded that reduction in weight and systolic blood pressure was greater with canagliflozin than a DPP-4 inhibitor.	4.9
	For triple therapy in combination with metformin and a thiazolidinedione, the Committee noted that canagliflozin was more effective than placebo in lowering HbA_{1c}, body weight and blood pressure. The Committee concluded that, on the basis of the clinical trials and the manufacturer's meta-analysis, the evidence for canagliflozin as part of triple therapy in combination with metformin and a thiazolidinedione was adequate to confirm that it is clinically effective in this combination .	4.10
	For add-on treatment to insulin, the Committee concluded that, despite the limitations associated with the methodology of the DIA3008 insulin sub-study and the network meta-analysis, their results showed that canagliflozin as add-on therapy to insulin appeared to be slightly more effective in reducing HbA_{1c} and body weight than DPP-4 inhibitors and dapagliflozin.	4.11
Evidence for cost effectiveness		
Availability and nature of evidence	The Committee observed that the manufacturer's ECHO-T2DM model followed the NICE reference case and methodology and noted the ERG's view that the model had been well validated. Despite some uncertainty about the stability of the results, the Committee concluded that the manufacturer's economic model was suitable for assessing the cost effectiveness of canagliflozin in combination therapy for treating type 2 diabetes.	4.14

Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee heard from the ERG that, despite some uncertainty, the manufacturer's meta-analyses were sufficiently robust and generally consistent with the direct trial evidence, and had been appropriately incorporated into the model. The Committee considered that although there was some uncertainty about how some clinical outcomes had been modelled, this was acceptable because it would not have a material effect on the decision about cost effectiveness. The Committee concluded that the clinical data incorporated into the manufacturer's model were acceptable for informing the cost-effectiveness estimates. The Committee had some concerns about how the manufacturer had modelled changes in clinical effectiveness over time (especially the annual drift values for HbA_{1c}, because this was a key driver of the model). However, in the absence of any long-term clinical data, the Committee concluded that the manufacturer's approach to modelling the long-term effectiveness of canagliflozin was acceptable. The Committee accepted the manufacturer's assumptions for dose escalation in its scenario analysis but concluded they were associated with significant uncertainty, and that the decision-making on cost effectiveness should instead be informed by considering the cost-effectiveness estimates for the separate 100 mg and 300 mg doses for each treatment comparison. The Committee concluded that a level of uncertainty associated with the cost-effectiveness estimates generated using the manufacturer's model was inevitable with such small differences in the QALYs gained between canagliflozin and its comparators.	4.16, 4.17 4.18 4.19 4.20
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and	The Committee observed that the utility values in the manufacturer's model had mainly been derived from a large European dataset using EQ-5D, in line with the NICE reference case.	4.14

substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The Committee concluded that all substantial benefits related to treatment with canagliflozin had been captured in the QALY calculation.	4.25
Are there specific groups of people for whom the technology is particularly cost effective?	Not applicable.	
What are the key drivers of cost effectiveness?	The Committee concluded that the manufacturer's deterministic sensitivity analyses showed that HbA_{1c} drift was a key driver of the model.	4.18
Most likely cost-effectiveness estimate (given as an ICER)	The Committee concluded that the very small differences in costs and QALYs between canagliflozin (100 mg and 300 mg) and its key comparators showed that canagliflozin was a cost-effective use of NHS resources as dual therapy in combination with metformin, triple therapy in combination with metformin and either a sulfonylurea or a thiazolidinedione, and as an add-on treatment to insulin.	4.21, 4.22, 4.23, 4.24
Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable.	
End-of-life considerations	Not applicable.	
Equalities considerations and social value judgements	No issues relating to equality considerations were raised in the submissions, during consultation or in the Committee meetings.	

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 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has type 2 diabetes and the doctor responsible for their care thinks that canagliflozin is the right treatment, it should be available for use, in line with NICE's recommendations.

5.3 NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Details are correct at the time of consultation. Further information is available on the NICE website.

Related NICE guidance

Published

- Dapagliflozin in combination therapy for treating type 2 diabetes. NICE technology appraisal guidance 288 (2013).

- Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes. NICE technology appraisal guidance 248 (2012).
- Liraglutide for the treatment of type 2 diabetes. NICE technology appraisal guidance 203 (2010).
- Type 2 diabetes: newer agents for blood glucose control in type 2 diabetes (partial update of CG66). NICE clinical guideline 87 (2009)
- Type 2 diabetes: the management of type 2 diabetes (partially updated by CG87). NICE clinical guideline 66 (2008).
- Diabetes in pregnancy: management of diabetes and its complications from pre-conception to the postnatal period. NICE clinical guideline 63 (2008).
- Continuous subcutaneous insulin infusion for the treatment of diabetes (review). NICE technology appraisal guidance 151 (2008).
- Type 2 diabetes: prevention and management of foot problems. NICE clinical guideline 10 (2004).

Under development

- Type 2 diabetes in adults: management of type 2 diabetes in adults. NICE clinical guideline, publication expected August 2015.

NICE pathways

- There is a NICE pathway on diabetes.

7 Review of guidance

7.1 The guidance on this technology will be considered for review in May 2017. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Jane Adam
Chair, Appraisal Committee
April 2014

8 Appraisal Committee members, guideline representatives 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 (Chair)
Department of Diagnostic Radiology, St George's Hospital, London

Professor Iain Squire (Vice-Chair)
Consultant Physician, University Hospitals of Leicester

Dr Graham Ash
Consultant in General Adult Psychiatry, Lancashire Care NHS Foundation Trust

Professor Thanos Athanasiou
Professor of Cardiovascular Sciences and Cardiac Surgery, Imperial College London; Consultant Cardiothoracic Surgeon, Imperial College Healthcare NHS Trust

Dr Jeremy Braybrooke

Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

Dr Simon Bond

Senior Statistician, Cambridge Clinical Trials Unit

Professor Aileen Clarke

Professor of Public Health & Health Services Research, University of Warwick

Dr Andrew England

Senior Lecturer, Directorate of Radiography, University of Salford

Dr Peter Heywood

Consultant Neurologist, Frenchay Hospital, Bristol

Dr Sharon Saint Lamont

Head of Quality and Innovation, North East Strategic Health Authority

Dr Ian Lewin

Consultant Endocrinologist, North Devon District Hospital

Dr Louise Longworth

Reader in Health Economics, HERG, Brunel University

Dr Anne McCune

Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

Professor John McMurray

Professor of Medical Cardiology, University of Glasgow

Dr Alec Miners

Lecturer in Health Economics, London School of Hygiene and Tropical Medicine

Dr Mohit Misra

GP, Queen Elizabeth Hospital, London

Ms Sarah Parry

CNS Paediatric Pain Management, Bristol Royal Hospital for Children

Ms Pamela Rees

Lay Member

Dr Ann Richardson

Lay Member

Ms Ellen Rule

Programme Director, NHS Bristol

Mr Stephen Sharp

Senior Statistician, MRC Epidemiology Unit, University of Cambridge

Dr Brian Shine

Consultant Chemical Pathologist, John Radcliffe Hospital

Dr Peter Sims

GP, Devon

Dr Eldon Spackman

Research Fellow, Centre for Health Economics, University of York

Mr David Thomson

Lay Member

Dr John Watkins

Clinical Senior Lecturer, Cardiff University; Consultant in Public Health Medicine, National Public Health Service Wales

Professor Olivia Wu

Professor in Health Economics, University of Glasgow

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.

Linda Landells

Technical Lead

Joanna Richardson

Technical Adviser

Bijal Joshi

Project Manager

9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Southampton Health Technology Assessments Centre (SHTAC), University of Southampton:

- Copley V, Pickett K, Shepherd J, et al. Canagliflozin in combination therapy for treating type 2 diabetes, December 2013

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, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Manufacturer/sponsor:

- Janssen

II. Professional/specialist and patient/carer groups:

- Association of British Clinical Diabetologists
- Diabetes UK
- National Diabetes Nurse Consultant Group
- Royal College of Nursing
- Royal College of Physicians

III. Other consultees:

- Department of Health
- NHS England

- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- AstraZeneca
- Boehringer Ingelheim
- Commissioning Support Appraisal Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Eli Lilly UK
- Healthcare Improvement Scotland
- Medicines and Healthcare Products Regulatory Agency (MHRA)
- Merck Sharp and Dohme
- National Clinical Guidelines Centre
- National Institute for Health Research Health Technology Assessment Programme
- Novo Nordisk
- Pfizer
- Sanofi
- Southampton Health Technology Assessments Centre (SHTAC), University of Southampton

C. The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They gave their expert personal view on canagliflozin by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Professor David Matthews, Professor of Diabetes Medicine, nominated by an organisation representing Janssen – clinical specialist
- Dr Thozhukat Sathyapalan, Reader/Honorary Consultant medical Consultant Endocrinologist, nominated by organisation representing Royal College of Physicians and Association of British Clinical Diabetologists – clinical specialist

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

- Janssen