Empagliflozin in combination therapy for treating type 2 diabetes

Technology appraisal guidance
Published: 25 March 2015

www.nice.org.uk/guidance/ta336

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces ESNM35.

1 Recommendations

1.1 Empagliflozin 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 Empagliflozin 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 Empagliflozin 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 empagliflozin 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   Empagliflozin (Jardiance, Boehringer Ingelheim) is an orally administered selective sodium-glucose cotransporter-2 (SGLT-2) inhibitor, which 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   Empagliflozin has a European marketing authorisation for the treatment of type 2 diabetes to improve glycaemic control in adults as:

- 'Monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.

- Add-on combination therapy with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control'.

2.3   The recommended starting dosage is 10 mg once daily for both monotherapy and as an add-on combination therapy with other glucose-lowering medicinal products including insulin. According to the summary of product characteristics, the dosage can be increased to a maximum of 25 mg daily for people who tolerate empagliflozin well and need tighter glycaemic control, if they have an estimated glomerular filtration rate (eGFR) of 60 ml/min/1.73 m2 or more.

2.4   The summary of product characteristics states the following adverse reactions for empagliflozin 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.

2.5   The cost of empagliflozin is £36.59 (excluding VAT) per pack of 28 tablets for both 10 mg and 25 mg doses (MIMS December 2014). The annual cost of empagliflozin is estimated to be £477.30. Costs may vary in different settings because of negotiated procurement discounts.

3 The company's submission

The [Appraisal Committee](#) considered evidence submitted by the company and a review of this submission by the [Evidence Review Group](#) (ERG).

Clinical effectiveness

3.1　　The company identified 11 studies that evaluated empagliflozin for treating type 2 diabetes. The company's submission included details of 8 of these 11 studies: 7 randomised controlled trials and 1 long-term extension study (1245.31). The 3 studies excluded were 1 that evaluated empagliflozin as monotherapy (1245.20), EMPA-REG OUTCOM (1245.25) and EMPA-REG-JAPAN (1245.52). The company did not explain why these studies were excluded. One of the included studies (1245.48) compared empagliflozin with placebo as monotherapy and therefore is not relevant to this appraisal.

3.2　　The long-term extension study (1245.31) recruited patients from 3 trials: 2 in which empagliflozin was evaluated as a combination therapy (1245.19 and 1245.23) and 1 monotherapy trial (1245.20). The results were presented separately for the patients from each trial.

3.3　　Study 1245.23 comprised 2 separate sub-studies: EMPA-REG-MET, evaluating empagliflozin plus metformin, and EMPA-REG-METSU, evaluating empagliflozin plus metformin and a sulfonylurea. Another study, 1254.19, evaluated empagliflozin plus pioglitazone or pioglitazone plus metformin. Two studies, 1245.33 and 1245.49, evaluated empagliflozin as an add-on to basal insulin and multiple daily injections of insulin respectively, with or without other oral antidiabetic agents.

3.4　　Study 1245.36 (in patients with renal impairment) included some patients with moderate to severe renal impairment. Because the summary of product characteristics states that empagliflozin 10 mg and 25 mg should not be initiated in patients with an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m2, only the subgroup of patients with mild renal impairment (eGFR of 60 to 90 ml/min/1.73 m2) is relevant for this appraisal.

3.5   All but 1 of the relevant studies had 3 treatment arms: empagliflozin 10 mg, empagliflozin 25 mg and placebo. Study 1245.28 instead compared empagliflozin 25 mg with glimepiride (a sulfonylurea) as a dual therapy on a background of metformin. Also, study 1245.23 included an open-label treatment arm comprising patients with very poor glycaemic control whose baseline glycated haemoglobin (HbA$_{1c}$) was more than 10%. The patients in this arm had empagliflozin 25 mg.

3.6   The duration of the relevant studies varied from 24 weeks (1245.19 and 1245.23) to 2 years (1245.28). The efficacy and safety results at 76 weeks for patients enrolled in the 1245.19 and 1245.23 trials were available in study 1245.31. The studies evaluating empagliflozin as an add-on to insulin therapy lasted for 78 weeks (1245.33) and 52 weeks (1245.49).

3.7   The primary outcome measure in the trials was change in the levels of HbA$_{1c}$ from baseline. The results showed that empagliflozin at both doses (10 mg or 25 mg) was associated with a statistically significant reduction in mean HbA$_{1c}$ compared with placebo in patients on different background therapies, including insulin. These reductions were maintained throughout the duration of treatment in the long-term extension study (1245.31). The glycaemic control achieved with empagliflozin 25 mg in patients with metformin background therapy was statistically non-inferior compared with glimepiride at week 104 in trial 1245.28. Empagliflozin also showed a statistically significantly better reduction in HbA$_{1c}$ compared with placebo in patients with mild renal impairment (1245.36). The adjusted change from baseline in mean HbA$_{1c}$ level from the relevant studies is summarised in tables 1a to e.

Table 1a Adjusted mean change from baseline in mean HbA1c level (%) ±SE: Patients on baseline pioglitazone or pioglitazone plus metformin (dual or triple therapy)

Trial	Duration	Placebo/active comparator	Empagliflozin 10 mg	Empagliflozin 25 mg
1245.19	At week 24	−0.11±0.07	−0.59±0.07	−0.72±0.07
1245.19	P value	–	<0.0001	<0.0001
1245.31 (patients from study 1245.19)	At week 76	−0.01±0.07	−0.61±0.07	−0.70±0.07
1245.31 (patients from study 1245.19)	P value	–	<0.0001	<0.0001

Table 1b Adjusted mean change from baseline in mean HbA1c level (%) ±SE: Dual therapy: patients on baseline metformin

Trial	Duration	Placebo/active comparator	Empagliflozin 10 mg	Empagliflozin 25 mg
1245.23 (metformin only sub-study)	At week 24	−0.13±0.05	−0.70±0.05	−0.77±0.05
1245.23 (metformin only sub-study)	P value	–	<0.0001	<0.0001
1245.31 (patients from 1245.23 metformin only sub-study)	At week 76	−0.01±0.05	−0.62±0.05	−0.74±0.05
1245.31 (patients from 1245.23 metformin only sub-study)	P value	–	<0.0001	<0.0001
1245.28 (compared with glimepiride)	At week 104	−0.55±0.03	–	−0.66±0.03
1245.28 (compared with glimepiride)	P value (non-inferiority)	–	–	<0.0001

Table 1c Adjusted mean change from baseline in mean HbA1c level (%) ±SE: Triple therapy: patients on baseline metformin plus SU

Trial	Duration	Placebo/active comparator	Empagliflozin 10 mg	Empagliflozin 25 mg
1245.23 (metformin plus SU sub-study)	At week 24	−0.17±0.05	−0.82±0.05	−0.77±0.05
1245.23 (metformin plus SU sub-study)	P value	–	<0.001	<0.001
1245.31 (patients from 1245.23 metformin plus SU sub-study)	At week 76	−0.03±0.06	−0.74+0.06	−0.72+0.06
1245.31 (patients from 1245.23 metformin plus SU sub-study)	P value	–	<0.0001	<0.0001

Table 1d Adjusted mean change from baseline in mean HbA1c level (%) ±SE: Add-on to insulin ± other anti-diabetics

Trial	Duration	Placebo/active comparator	Empagliflozin 10 mg	Empagliflozin 25 mg
1245.33	At week 18	−0.01±0.07	−0.57±0.07	−0.71±0.07

Trial	Duration	Placebo/active comparator	Empagliflozin 10 mg	Empagliflozin 25 mg
1245.33	P value	–	<0.0001	<0.0001
1245.33	At week 78	−0.02±0.09	−0.48±0.08	−0.64±0.09
1245.33	P value	–	<0.0001	<0.0001
1245.49	At week 18	−0.50±0.06	−0.94±0.06	−1.02±0.06
1245.49	P value	–	<0.0001	<0.0001
1245.49	At week 52	−0.81±0.08	−1.18±0.08	−1.27±0.08
1245.49	P value (non-inferiority)	–	<0.0001	<0.0001

Table 1e Adjusted mean change from baseline in mean HbA1c level (%) ±SE: Empagliflozin in patients with mild renal impairments

Trial	Duration	Placebo/active comparator	Empagliflozin 10 mg	Empagliflozin 25 mg
1245.36 (subgroup with mild renal impairment)	At week 24	0.06±0.07	−0.46±0.07	−0.63±0.07
1245.36 (subgroup with mild renal impairment)	P value	–	<0.0001	<0.0001
1245.36 (subgroup with mild renal impairment)	At week 52	0.06±0.08	−0.57±0.08	−0.60±0.08
1245.36 (subgroup with mild renal impairment)	P value	–	<0.0001	<0.0001

Abbreviations: HbA1c, glycated haemoglobin; SE, standard error; SU, sulfonylurea.

3.8   Important secondary outcomes included change in body weight and blood pressure from baseline. In a study of dual therapy (1245.23 EMPA-REG MET), at week 24 compared with placebo, empagliflozin 10 mg resulted in mean weight loss of 1.6 kg and empagliflozin 25 mg resulted in a loss of 2.0 kg. Similarly, at week 24 in triple therapy (in study 1245.23 EMP-REG METSU) compared with placebo empagliflozin 10 mg reduced weight by 1.8 kg and empagliflozin 25 mg reduced it by 2.0 kg. The long-term extension study (1245.31) confirmed that weight loss from baseline achieved at week 24 was largely maintained at week 76. Both doses of empagliflozin with basal insulin regimens (in study

1245.33) were associated with much greater weight loss compared with placebo at week 78: 3.6 kg for empagliflozin 10 mg and 3.1 kg for empagliflozin 25 mg. In combination with multiple daily injections of insulin (1245.49), compared with placebo empagliflozin reduced mean body weight by 2.39 kg (10 mg) and 2.48 kg (25 mg). Reductions in systolic blood pressure ranged from 1.4 mm Hg in the 1245.49 trial to 4.8 mm Hg in the metformin-only sub-study of trial 1245.23.

3.9 Health-related quality of life data were collected in 6 trials that compared empagliflozin with placebo (including a trial of empagliflozin as a monotherapy, 1245.20). The mean EQ-5D utility index score at baseline was comparable across the 6 trials and ranged between 0.791 and 0.813. Across all trials the addition of empagliflozin did not result in a clinically meaningful change in quality of life, with baseline EQ-5D utility index scores being maintained throughout the trials. The company's submission presents pooled data from the 6 trials at different time points (weeks 4, 6, 12, 18, 24, 40 and 52). The company also stated that no differences in EQ-5D score were evident in any subgroups based on age, sex, BMI, country, blood pressure, HbA$_{1c}$ level at baseline, eGFR at baseline, prior cardiovascular events, time since diagnosis, race or cardiovascular risk predictor. The trials also collected data using a visual analogue scale (EQ VAS), and the company reported that change from baseline EQ VAS was similar across all treatment groups at all time points.

3.10 The company's submission presented adverse events as reported in the individual studies. In general, the proportions of patients who experienced any adverse events, severe adverse events or adverse events leading to discontinuation of trial medication were similar between both empagliflozin groups and placebo across all trials. In most trials, adverse events leading to discontinuation were more frequent in the placebo group than in the empagliflozin groups. Adverse events in more than 5% of patients in any randomised group in the trials were: urinary tract infections, balanitis, upper respiratory tract infections, bronchitis, nasopharyngitis, influenza, cough, diarrhoea, hypoglycaemia, hyperglycaemia, dyslipidaemia, hypertension, arthralgia, back pain, pain in extremity, headache, dizziness and depression.

3.11 Hypoglycaemic events, urinary tract infection, genital infections, volume depletion and fractures were considered to be 'adverse events of special interest' and reported separately. The data showed that treatment with empagliflozin did

not lead to an increase in hypoglycaemic events, except when empagliflozin was administered with a sulfonylurea (the 1245.23 EMPA-REG-METSU sub-study and patients moving from the same sub-study in extension study 1245.31) or with insulin as background therapy (1245.33 and 1245.49). Across all trials, genital infections (generally of mild to moderate intensity) were consistently more frequent in the empagliflozin groups than with placebo. The incidence of urinary tract infections was similar across both empagliflozin groups and placebo, although it was reported that empagliflozin was associated with a greater frequency in women compared with placebo. In addition, both genital and urinary tract infections were more common in women than men. The frequency of volume depletion was low across all clinical studies and comparable between all treatment groups. The rates of fracture were very low and similar for all treatment groups across all empagliflozin trials.

3.12   The company's submission considered dipeptidyl peptidase-4 (DPP-4) inhibitors and other sodium-glucose cotransporter-2 (SGLT-2) inhibitors (dapagliflozin and canagliflozin) to be the comparators for empagliflozin. In the absence of any head-to head trial, the company performed indirect comparisons by means of network meta-analyses. The company conducted a systematic literature review to identify randomised controlled trials that evaluated the comparators. Five networks of randomised controlled trials were considered, each 1 including trials that compared the interventions for patients whose diabetes was no longer responding adequately to:

- metformin (for dual therapy)

- metformin plus sulfonylurea (for triple therapy)

- thiazolidinediones (for dual therapy)

- thiazolidinediones and metformin (for triple therapy)

- insulin therapy plus other oral antidiabetic drugs (as an add-on to insulin therapy).

3.13   The outcomes compared in the network meta-analyses in the company's submission included change from baseline in HbA_{1c}, systolic blood pressure, and body weight. Safety outcomes were hypoglycaemia (severe and non-severe), urinary tract infection and genital tract infection. For continuous outcomes,

Bayesian network meta-analysis was used to determine the mean differences in change from baseline and associated 95% credible intervals between all interventions. For binary outcomes, the proportions of events were modelled in a logistic regression framework, and relative risks and associated 95% credible intervals were estimated.

3.14   Several trials were available in which metformin was background therapy and so an uninformed random-effects model was applied for that network. For the other 4 background therapies (metformin plus a sulfonylurea, thiazolidinedione, thiazolidinedione plus metformin and insulin), all comparisons were based on single trials (except empagliflozin compared with placebo for add-on to insulin). The company used a conventional fixed-effects model to account for heterogeneity in these networks.

3.15   Results of the original network meta-analyses are not presented here because the company submitted a new set of network meta-analyses in response to consultation on the appraisal consultation document.

Company's response to consultation

3.16   In response to consultation, the company provided new network meta-analyses. The new networks focused on trials of empagliflozin, canagliflozin, dapagliflozin and sitagliptin compared with placebo. Trials with metformin and a sulfonylurea were also included to complete the networks where needed. The population, primary outcomes and adverse events in the new network meta-analyses were the same as in the original network meta-analyses.

3.17   The results of the new network meta-analyses are presented in table 2a to d.

Table 2a New network meta-analysis results for mean change from baseline in HbA1c level (%): Dual therapy with metformin (52-week data)

Treatment	Versus placebo (95% credible intervals)	Versus empagliflozin 10 mg (95% CI)	Versus empagliflozin 25 mg (95% CI)
Sulfonylurea	−0.52 (−0.64, −0.40)	0.06 (−0.08, 0.21)	0.10 (0.02, 0.17)
Empa 10 mg	−0.58 (−0.72, −0.45)	–	0.03 (−0.10, 0.16)

Treatment	Versus placebo (95% credible intervals)	Versus empagliflozin 10 mg (95% CI)	Versus empagliflozin 25 mg (95% CI)
Empa 25 mg	−0.62 (−0.73, −0.50)	−0.03 (−0.16, 0.10)	–
Dapa 10 mg	−0.47 (−0.58, −0.36)	0.11 (−0.04, 0.27)	0.15 (0.03, 0.26)
Cana 100 mg	−0.52 (−0.68, −0.37)	0.06 (−0.11, 0.23)	0.09 (−0.03, 0.21)
Cana 300 mg	−0.65 (−0.80, −0.50)	−0.07 (−0.24, 0.10)	−0.03 (−0.15, 0.08)
Sita 100 mg	−0.52 (−0.67, −0.37)	0.07 (−0.10, 0.24)	0.10 (−0.02, 0.22)

Table 2b New network meta-analysis results for mean change from baseline in HbA1c level (%): Triple therapy with metformin and a sulfonylurea (52-week data)

Treatment	Versus placebo (95% credible intervals)	Versus empagliflozin 10 mg (95% CI)	Versus empagliflozin 25 mg (95% CI)
Empa 10 mg	−0.71 (−0.88, −0.54)	–	−0.02 (−0.19, 0.15)
Empa 25 mg	−0.69 (−0.86, −0.52)	0.02 (−0.15, 0.19)	–
Cana 100 mg	−0.75 (−0.96, −0.54)	−0.04 (−0.31, 0.23)	−0.06 (−0.33, 0.21)
Cana 300 mg	−0.97 (−1.18, −0.76)	−0.26 (−0.53, 0.01)	−0.28 (−0.55, −0.01)
Sita 100 mg	−0.60 (−0.85, −0.35)	0.11 (−0.19, 0.41)	0.09 (−0.21, 0.39)

Table 2c New network meta-analysis results for mean change from baseline in HbA1c level (%): Triple therapy with metformin and a thiazolidinedione (24-week data)

Treatment	Compared with control (metformin plus thiazolidinedione) rather than placebo	Versus empagliflozin 10 mg (95% CI)	Versus empagliflozin 25 mg (95% CI)
Empa 10 mg	−0.44 (−0.66, −0.22)	–	0.15 (0.06, 0.36)
Empa 25 mg	−0.59 (−0.80, −0.38)	−0.15 (−0.36, 0.06)	–

Treatment	Compared with control (metformin plus thiazolidinedione) rather than placebo	Versus empagliflozin 10 mg (95% CI)	Versus empagliflozin 25 mg (95% CI)
Cana 100 mg	−0.63 (−0.82, −0.44)	−0.19 (−0.49, 0.10)	−0.04 (−0.32, 0.24)
Cana 300 mg	−0.77 (−0.93, −0.61)	−0.33 (−0.61, −0.06)	−0.18 (−0.44, 0.08)
Sita 100 mg	−0.70 (−0.84, −0.56)	−0.26 (−0.52, 0.00)	−0.11 (−0.36, 0.14)

Table 2d New network meta-analysis results for mean change from baseline in HbA1c level (%): Add on to insulin (52-week data)

Treatment	Versus placebo (95% credible intervals)	Versus empagliflozin 10 mg (95% CI)	Versus empagliflozin 25 mg (95% CI)
Empa 10 mg	−0.48 (−0.64, −0.33)	–	0.16 (0.00, 0.32)
Empa 25 mg	−0.64 (−0.80, −0.49)	−0.16 (−0.32, 0.00)	–
Dapa 2.5 mg	−0.40 (−0.55, −0.25)	0.08 (−0.14, 0.30)	0.24 (0.02, 0.46)
Dapa 5 mg	−0.50 (−0.65, −0.35)	−0.01 (−0.23, 0.20)	0.14 (−0.07, 0.36)
Dapa 10 mg	−0.57 (−0.72, −0.42)	−0.08 (−0.30, 0.13)	0.07 (−0.14, 0.29)

Abbreviations: Cana, canagliflozin; CI, credible intervals; Dapa, dapagliflozin; Empa, empagliflozin; Sita, sitagliptin.

Table 3a New network meta-analysis results for mean change from baseline in weight (kg): Dual therapy with metformin (52-week data)

Treatment	Versus placebo (95% credible intervals)	Versus empagliflozin 10 mg (95% CI)	Versus empagliflozin 25 mg (95% CI)
Sulfonylurea	2.47 (1.91, 3.03)	4.22 (3.63, 4.80)	4.80 (4.50, 5.10)
Empa 10 mg	−1.75 (−2.27, −1.22)	–	0.58 (0.06, 1.10)
Empa 25 mg	−2.33 (−2.83, −1.83)	−0.58 (−1.10, −0.06)	–
Dapa 10 mg	−2.21 (−2.87, −1.55)	−0.47 (−1.17, 0.24)	0.12 (−0.41, 0.65)

Treatment	Versus placebo (95% credible intervals)	Versus empagliflozin 10 mg (95% CI)	Versus empagliflozin 25 mg (95% CI)
Cana 100 mg	−1.98 (−2.71, −1.25)	−0.24 (−0.99, 0.51)	0.35 (−0.21, 0.90)
Cana 300 mg	−2.33 (−3.06, −1.60)	−0.59 (−1.34, 0.17)	−0.00 (−0.56, 0.55)
Sita 100 mg	0.07 (−0.69, 0.83)	1.81 (1.03, 2.60)	2.40 (1.80, 2.99)

Table 3b New network meta-analysis results for mean change from baseline in weight (kg): Triple therapy with metformin and a sulfonylurea (52-week data)

Treatment	Versus placebo (95% credible intervals)	Versus empagliflozin 10 mg (95% CI)	Versus empagliflozin 25 mg (95% CI)
Empa 10 mg	−2.00 (−2.49, −1.51)	–	0.05 (−0.49, 0.59)
Empa 25 mg	−2.05 (−2.56, −1.55)	−0.05 (−0.59, 0.49)	–
Cana 100 mg	−1.28 (−2.11, −0.44)	0.72 (−0.23, 1.68)	0.77 (−0.19, 1.75)
Cana 300 mg	−2.28 (−3.11, −1.46)	−0.28 (−1.24, 0.68)	−0.22 (−1.20, 0.74)
Sita 100 mg	0.37 (−0.53, 1.27)	2.37 (1.35, 3.40)	2.42 (1.38, 3.45)

Table 3c New network meta-analysis results for mean change from baseline in weight (kg): Triple therapy with metformin and a thiazolidinedione (24-week data)

Treatment	Compared with control (metformin plus thiazolidinedione) rather than placebo	Versus empagliflozin 10 mg (95% CI)	Versus empagliflozin 25 mg (95% CI)
Empa 10 mg	−2.14 (−2.82, −1.45)	–	−0.15 (0.86, −0.54)
Empa 25 mg	−1.98 (−2.68, −1.28)	0.15 (−0.54, 0.86)	–
Cana 100 mg	−2.55 (−3.36, −1.74)	−0.41 (−1.48, 0.64)	−0.57 (−1.64, 0.49)
Cana 300 mg	−3.49 (−4.29, −2.69)	−1.35 (−2.41, −0.30)	−1.51 (−2.56, −0.45)

Treatment	Compared with control (metformin plus thiazolidinedione) rather than placebo	Versus empagliflozin 10 mg (95% CI)	Versus empagliflozin 25 mg (95% CI)
Sita 100 mg	0.20 (−0.40, 0.80)	2.33 (1.42, 3.24)	2.18 (1.26, 3.09)

Table 3d New network meta-analysis results for mean change from baseline in weight (kg): Add on to insulin (52-week data)

Treatment	Versus placebo (95% credible intervals)	Versus empagliflozin 10 mg (95% CI)	Versus empagliflozin 25 mg (95% CI)
Empa 10 mg	−1.41 (−1.82, −1.00)	–	0.40 (−0.06, 0.86)
Empa 25 mg	−1.81 (−2.26, −1.36)	−0.40 (−0.86, 0.06)	–
Dapa 2.5 mg	−1.35 (−1.90, −0.81)	0.06 (−0.62, 0.74)	0.46 (−0.25, 1.17)
Dapa 5 mg	−1.43 (−1.97, −0.90)	−0.02 (−0.70, 0.65)	0.38 (−0.33, 1.08)
Dapa 10 mg	−2.04 (−2.58, −1.49)	−0.63 (−1.31, 0.05)	−0.23 (−0.93, 0.48)

Abbreviations: Cana, canagliflozin; CI, credible intervals; Dapa, dapagliflozin; Empa, empagliflozin; Sita, sitagliptin.

Table 4a New network meta-analysis results for mean change from baseline in systolic blood pressure: Dual therapy with metformin (52-week data)

Treatment	Versus placebo (95% credible intervals)	Versus empagliflozin 10 mg (95% CI)	Versus empagliflozin 25 mg (95% CI)
Sulfonylurea	1.31 (−1.06, 3.67)	4.20 (1.79, 6.58)	5.80 (4.41, 7.19)
Empa 10 mg	−2.89 (−4.84, −0.94)	–	1.60 (−0.34, 3.56)
Empa 25 mg	−4.49 (−6.44, −2.57)	−1.60 (−3.56, 0.34)	–
Dapa 10 mg	−3.80 (−6.65, −0.94)	−0.90 (−3.78, 1.91)	0.70 (−1.41, 2.78)
Cana 100 mg	−2.25 (−5.05, 0.51)	0.63 (−2.15, 3.42)	2.23 (0.23, 4.24)
Cana 300 mg	−3.42 (−6.20, −0.66)	−0.54 (−3.35, 2.26)	1.07 (−0.94, 3.07)

Treatment	Versus placebo (95% credible intervals)	Versus empagliflozin 10 mg (95% CI)	Versus empagliflozin 25 mg (95% CI)
Sita 100 mg	0.60 (−2.55, 3.74)	3.49 (0.34, 6.62)	5.09 (2.63, 7.56)

Table 4b New network meta-analysis results for mean change from baseline in systolic blood pressure: Triple therapy with metformin and a sulfonylurea (52-week data)

Treatment	Versus placebo (95% credible intervals)	Versus empagliflozin 10 mg (95% CI)	Versus empagliflozin 25 mg (95% CI)
Empa 10 mg	−2.80 (−4.89, −0.72)	–	−0.09 (−2.19, 1.98)
Empa 25 mg	−2.72 (−4.94, −0.48)	0.09 (−1.98, 2.19)	–
Cana 100 mg	−3.82 (−6.75, −0.85)	−1.00 (−4.59, 2.59)	−1.10 (−4.77, 2.60)
Cana 300 mg	−3.00 (−5.81, −0.21)	−0.20 (−3.69, 3.28)	−0.28 (−3.88, 3.27)
Sita 100 mg	2.99 (−0.35, 6.33)	5.79 (1.86, 9.74)	5.70 (1.68, 9.69)

Table 4c New network meta-analysis results for mean change from baseline in systolic blood pressure: Triple therapy with metformin and a thiazolidinedione (24-week data)

Treatment	Compared with control (metformin plus thiazolidinedione) rather than placebo	Versus empagliflozin 10 mg (95% CI)	Versus empagliflozin 25 mg (95% CI)
Empa 10 mg	−4.24 (−6.91, −1.54)	–	−0.18 (−2.82, 2.54)
Empa 25 mg	−4.06 (−6.72, −1.36)	0.18 (−2.54, 2.82)	–
Cana 100 mg	−4.11 (−6.98, −1.22)	0.10 (−3.87, 4.13)	−0.05 (−4.02, 3.93)
Cana 300 mg	−3.54 (−6.46, −0.54)	0.69 (−3.29, 4.68)	0.50 (−3.48, 4.53)

Table 4d New network meta-analysis results for mean change from baseline in systolic blood pressure: Add on to insulin (52-week data)

Treatment	Versus placebo (95% credible intervals)	Versus empagliflozin 10 mg (95% CI)	Versus empagliflozin 25 mg (95% CI)
Empa 10 mg	−2.45 (−4.03, −0.88)	–	0.05 (−1.52, 1.61)
Empa 25 mg	−2.51 (−4.07, −0.93)	−0.05 (−1.61, 1.52)	–
Dapa 2.5 mg	−0.66 (−3.32, 2.06)	1.79 (−1.28, 4.91)	1.84 (−1.22, 4.97)
Dapa 5 mg	−2.38 (−5.01, 0.27)	0.07 (−3.01, 3.16)	0.12 (−2.95, 3.21)
Dapa 10 mg	−3.11 (−5.76, −0.44)	−0.65 (−3.74, 2.42)	−0.60 (−3.70, 2.47)

Abbreviations: Cana, canagliflozin; CI, credible intervals; Dapa, dapagliflozin; Empa, empagliflozin; Sita, sitagliptin.

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

3.18   The ERG considered the trials to be good quality but commented that the lack of head-to-head trials against the main comparators (DPP-4 inhibitors or other SGLT-2 inhibitors) was the main weakness of the evidence base. The demographic characteristics were well balanced across treatment groups except in study 1245.49, in which the proportion of men was much lower in the placebo arm than the empagliflozin arms (39.9% placebo, 52.2% empagliflozin 10 mg, 44.2% empagliflozin 25 mg).

3.19   The ERG noted that the company's submission did not report outcome data on change in lipid levels for any trial, but that change in lipid profiles for studies 1245.19 and 1245.23 had already been published. The results of study 1245.23 showed that in comparison with placebo, both doses of empagliflozin were associated with a statistically significant reduction in most of the components of serum lipids. Study 1245.19 also showed that both doses of empagliflozin reduced high-density lipoprotein cholesterol statistically

significantly compared with placebo. The changes in other fractions of lipids were not statistically significant.

3.20   The ERG identified many errors in the company's original network meta-analyses. The ERG commented that the systematic review process was inadequately described, lacking details on inclusion criteria for studies, justification for excluded studies, quality assessment and data extraction process for included studies. The ERG was also concerned that the company had not done any sensitivity analyses or statistical tests.

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

3.21   The ERG stated that the new network meta-analyses provided by the company were robust and successfully addressed the shortcomings of the original network meta-analyses.

Cost effectiveness

3.22   The company originally submitted a patient-level state transition model which had been developed for this appraisal. The ERG's critique of the model highlighted several errors which would invalidate any results and so the ERG concluded that the original model and its results were unreliable. As part of the consultation on the appraisal consultation document, the company were asked to provide further analyses, including revised estimations of the incremental cost-effectiveness ratios of empagliflozin using a validated economic model.

3.23   In response to consultation, the company provided a new cost-effectiveness model. The new model was an individual patient-level microsimulation model using IMS CORE. It modelled individual patients' transitions between health states using a fixed cycle length of 1 year over a lifetime horizon. An NHS and personal social services perspective was taken and costs and benefits were discounted at 3.5%.

3.24   The model simulated the incidence of the complications of diabetes based on baseline characteristics of the patient and the treatment's initial impact on HbA_{1c}, systolic blood pressure and BMI. Complications included in the model were: fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, angina, congestive heart failure, peripheral vascular disease, microalbuminuria, gross proteinuria, haemodialysis, diabetic retinopathy, cataract, macular oedema, severe vision loss, neuropathy, ulcer and amputation. Diabetes-related deaths and general mortality were also modelled.

3.25   Health-related quality of life values for the model were drawn from the UKPDS 62 and Sullivan et al. (2011). Quality of life decrements were applied to severe hypoglycaemic events, non-severe hypoglycaemic events, genital tract infections, urinary tract infections and post-urinary tract infection events. The IMS CORE model associated a quality of life change of 0.0038125 with each BMI point increase or decrease in people with a BMI of 25 kg/m2 or higher.

3.26   Data from the company's new network meta-analyses were used to model the clinical effectiveness of the drugs. If clinical effectiveness data were not available from the network meta-analyses, the clinical effectiveness of a comparator was assumed to be the same as empagliflozin 10 mg or empagliflozin 25 mg. Treatment-related adverse effects were hypoglycaemic events (severe and non-severe), urinary tract infections and genital tract infections. If a patient's HbA_{1c} exceeded 7.5%, they were switched to insulin, which was associated with a change in costs, an increase in BMI and an adverse event rate of zero.

3.27   The new cost-effectiveness model compared empagliflozin 10 mg and empagliflozin 25 mg with dapagliflozin 10 mg, sitagliptin 100 mg, canagliflozin 100 mg and canagliflozin 300 mg, each in dual therapy with metformin or as an add on to insulin therapy. It compared empagliflozin 10 mg and empagliflozin 25 mg with sitagliptin 100 mg, canagliflozin 100 mg and canagliflozin 300 mg, each in triple therapy with metformin and a sulfonylurea or metformin and a thiazolidinedione.

3.28   The company stated that only direct costs were included in its new model. The company sourced the relevant costs of managing complications from published studies, including UKPDS and previous NICE appraisals. Some costs were inflated to 2012 prices using the Personal Social Services Research Unit inflation rates.

The cost of insulin was a weighted average annual cost based on prescribing data and NHS list prices. Drug costs and the cost of testing strips were included in the cost of insulin, and the annual costs of needle and test strips were included in the cost of intravenous insulin.

3.29   The base case results from the new cost-effectiveness model are presented in tables 5a to d. Where clinical-effectiveness data for particular parameters of the comparators were not available from the network meta-analyses, the corresponding data for empagliflozin 10 mg or empagliflozin 25 mg were used. The results in tables 5a to d are based on using the clinical effectiveness of empagliflozin 10 mg. There were slight differences in the results when the clinical effectiveness of empagliflozin 25 mg was used instead, but these did not have a substantial effect on the ICERs.

Table 5a Company's new base-case results: Dual therapy with metformin

Treatments	Costs	Net	QALYs	Net	ICER (£ per QALY)
Empagliflozin 25 mg	£61,535	–	7.995	–	–
Dapagliflozin 10 mg	£61,609	£74	7.964	−0.031	Dominated
Canagliflozin 100 mg	£61,719	£184	7.955	−0.040	Dominated
Empagliflozin 10 mg	£61,761	£226	7.963	−0.032	Dominated
Sitagliptin 100 mg	£61,778	£243	7.899	−0.096	Dominated
Canagliflozin 300 mg	£61,912	£377	7.990	−0.005	Dominated

Table 5b Company's new base-case results: Triple therapy with metformin plus a sulfonylurea

Treatments	Costs	Net	QALYs	Net	ICER (£ per QALY)
Empagliflozin 25 mg	£58,711	–	7.564	–	–
Empagliflozin 10 mg	£58,778	£67	7.571	0.007	£9,571
Canagliflozin 100 mg	£58,794	£16	7.569	−0.002	Dominated
Canagliflozin 300 mg	£59,000	£222	7.616	0.045	£4,933
Sitagliptin 100 mg	£59,390	£390	7.466	−0.150	Dominated

Table 5c Company's new base-case results: Triple therapy with metformin plus a thiazolidinedione

Treatments	Costs	Net	QALYs	Net	ICER (£ per QALY)
Sitagliptin 100 mg	£58,644	–	7.553	–	–
Canagliflozin 100 mg	£58,751	£107	7.579	0.026	£4,115
Empagliflozin 25 mg	£58,854	£103	7.561	−0.018	Dominated
Canagliflozin 300 mg	£59,106	£355	7.614	0.035	£10,143
Empagliflozin 10 mg	£59,166	£60	7.542	−0.072	Dominated

Table 5d Company's new base-case results: Add-on to insulin

Treatments	Costs	Net	QALYs	Net	ICER (£ per QALY)
Canagliflozin 100 mg	£60,235	–	7.545	–	–
Dapagliflozin 10 mg	£60,360	£125	7.545	0.000	Dominated
Empagliflozin 25 mg	£60,428	£193	7.534	−0.011	Dominated
Empagliflozin 10 mg	£60,539	£304	7.523	−0.022	Dominated
Sitagliptin 100 mg	£60,564	£329	7.511	−0.034	Dominated
Canagliflozin 300 mg	£60,599	£364	7.583	0.038	£9,579

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Note: comparator effectiveness was based on empagliflozin 10 mg where data were not available from the network meta-analyses. A treatment is 'dominated' when it is both less effective and more costly than its comparator.

Company's new sensitivity analyses

3.30 The company did 2 sensitivity analyses. One analysis modelled BMI converging over time, and the other assumed no change in systolic blood pressure with sitagliptin for pairwise comparisons of empagliflozin and sitagliptin only. The results of the sensitivity analyses were not substantially different from the results of the base-case analyses.

Evidence Review Group's critique of the company's new cost-effectiveness model

3.31 The ERG highlighted that the IMS CORE model used by the company in its new cost-effectiveness modelling has been validated and used in other NICE appraisals.

3.32 The ERG stated that rerunning the base case in IMS CORE gave different results from those reported in the company's response to consultation. However, the rerun results were qualitatively the same as the company's results. The ERG highlighted that the main cause of the differences in the ICERs was the very small difference in costs and QALYs when comparing treatments.

3.33 The ERG stated that it was not clear how the rates of non-severe hypoglycaemia used in the model were calculated, but highlighted that the relative rates between comparators were the same as those in the new network meta-analyses. They also highlighted that the changes to the IMS CORE default costs and utilities, and the source of the data for rates of genital tract infections, were not clear.

3.34 The ERG stated that second-order sampling was used for the company's deterministic analyses. As a consequence of using second-order sampling, the company's deterministic analyses provided probabilistic results. The ERG stated that the company did not present truly deterministic results.

Evidence Review Group's exploratory and sensitivity analyses using the new cost-effectiveness model

3.35 The ERG's new exploratory analyses revised the cost of complications using UKPDS 65 and the quality of life values using UKPDS 62. The ERG also revised the rates of urinary tract infections for canagliflozin 300 mg in the analyses for empagliflozin as an add-on to insulin. The ERG did not use second-order sampling in its exploratory analyses so that the results of the analysis were truly deterministic.

3.36 The deterministic results of the ERG's new exploratory analysis are shown in

tables 6a to d. Each treatment was compared with the next least costly treatment in each treatment regimen. If the previous treatment was dominated, the treatment was compared with the next least costly treatment that was not dominated. The results in the table are based on using the clinical effectiveness of empagliflozin 10 mg for any parameters of the comparators for which clinical-effectiveness data were not available from the network meta-analyses. There were slight differences in the results when the clinical effectiveness of empagliflozin 25 mg was used instead, but they did not have a substantial effect on the ICERs.

Table 6a Results of the ERG's new exploratory analyses: Dual therapy with metformin

Treatment	Costs	Net	QALYs	Net	ICER
Sitagliptin 100 mg	£41,554	–	8.136	–	–
Canagliflozin 100 mg	£41,626	£72	8.161	0.025	£1,220
Empagliflozin 25 mg	£41,646	£20	8.203	0.042	£400
Dapagliflozin 10 mg	£41,675	£29	8.161	−0.042	Dominated
Empagliflozin 10 mg	£41,767	£121	8.178	−0.025	Dominated
Canagliflozin 300 mg	£42,192	£546	8.202	−0.001	£136,500

Table 6b Results of the ERG's new exploratory analyses: Triple therapy with metformin and a sulfonylurea

Treatment	Costs	Net	QALYs	Net	ICER
Empagliflozin 25 mg	£39,399	–	7.834	–	–
Canagliflozin 100 mg	£39,439	£40	7.864	0.030	£2,105
Empagliflozin 10 mg	£39,479	£40	7.841	−0.023	Dominated
Canagliflozin 300 mg	£39,596	£157	7.894	0.030	£3,568
Sitagliptin 100 mg	£39,602	£6	7.782	−0.112	Dominated

Table 6c Results of the ERG's new exploratory analyses: Triple therapy with metformin and a thiazolidinedione

Treatment	Costs	Net	QALYs	Net	ICER
Sitagliptin 100 mg	£39,392	–	7.858	–	–

Treatment	Costs	Net	QALYs	Net	ICER
Canagliflozin 100 mg	£39,522	£130	7.850	–0.008	£4,063
Empagliflozin 10 mg	£39,522	£130	7.814	–0.044	Dominated
Empagliflozin 25 mg	£39,633	£241	7.836	–0.022	Dominated
Canagliflozin 300 mg	£39,872	£480	7.865	0.007	£12,069

Table 6d Results of the ERG's new exploratory analyses: Add on to insulin

Treatment	Costs	Net	QALYs	Net	ICER
Empagliflozin 10 mg	£40,580	–	7.814	–	–
Sitagliptin 100 mg	£40,810	£230	7.817	0.003	Dominated
Canagliflozin 100 mg	£40,951	£371	7.832	0.018	£12,367
Dapagliflozin 10 mg	£41,008	£57	7.810	–0.022	Dominated
Empagliflozin 25 mg	£41,023	£72	7.804	–0.028	Dominated
Canagliflozin 300 mg	£41,292	£341	7.858	0.026	£11,367

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Note: comparator effectiveness was based on empagliflozin 10 mg where data were not available from the network meta-analyses. A BMI coefficient of –0.0038 was used. A treatment is 'dominated' when it is both less effective and more costly than its comparator.

ERG's sensitivity analyses

3.37   The ERG did a sensitivity analysis for the impact of different quality of life values associated with changes in BMI, because BMI has been an important parameter in similar NICE technology appraisals. For the sensitivity analyses, the ERG used no decrease and a decrease of 0.0061 in quality of life for each point change in BMI. The ERG used no decrease because it was easy to implement in the IMS CORE model. The decrease of 0.0061 was used because the ERG believed it was the coefficient that corresponded with the relevant interval of the EQ-5D social tariff, and was the true coefficient applied by Bagust and Beale (2005).

3.38   In general, the ICERs decreased when the 0.0061 decrease in quality of life was used. For some comparisons, the comparators were no longer dominated and ICERs of above £70,000 per QALY gained were reported. The most notable change to the ICERs was for canagliflozin 300 mg compared with empagliflozin 25 mg in triple therapy with metformin and a thiazolidinedione. In this comparison, the ICER decreased from £68,571 per QALY gained to £9,358 per QALY gained when a quality of life decrement of 0.0061 was used. For the analyses as an add-on to insulin therapy, the ICER for sitagliptin 100 mg compared with empagliflozin 10 mg changed from £76,667 per QALY gained to being dominated by empagliflozin 10 mg.

3.39   Full details of all the evidence are in the committee papers.

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of empagliflozin, having considered evidence on the nature of type 2 diabetes and the value placed on the benefits of empagliflozin by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.1   The Committee discussed the clinical treatment pathway for type 2 diabetes. It heard from the clinical specialists that although focused on reducing glycated haemoglobin (HbA_{1c}) without weight gain or hypoglycaemia, treatment for type 2 diabetes is individualised for each patient. This results in some variation in clinical practice. However, current UK practice broadly follows NICE's guideline on type 2 diabetes in adults: management, which recommends a stepwise approach that includes using diet and exercise, various antidiabetic drugs and insulin. The Committee noted that each of the existing antidiabetic therapies had various advantages and disadvantages affecting their suitability for patients and that many patients do not achieve the target HbA_{1c} levels with the existing therapies. The Committee heard from the clinical specialists that empagliflozin would be most valuable for patients who are overweight with inadequate glycaemic control, who have good renal function and who are not susceptible to genitourinary infections. The Committee understood that a new treatment providing another option would be welcomed by clinicians.

4.2   The Committee discussed the most likely place for empagliflozin in the treatment pathway, and which treatments in the NICE scope were the key comparators. The Committee noted that many combinations of dual and triple therapy specified in the final scope had not been included in the company's submission, such as empagliflozin plus a sulfonylurea as dual therapy. The Committee heard from the clinical specialists that there may be a small group of people for whom metformin is unsuitable because of gastro-intestinal intolerance. In these people, empagliflozin plus a sulfonylurea could be used as dual therapy. The Committee also heard from the clinical specialists that empagliflozin could be used as part of dual therapy plus metformin, if sulfonylureas are not suitable due to a perceived risk of hypoglycaemia. The clinical specialists noted that use of thiazolidinediones is decreasing because of safety concerns, particularly increased risk of bladder

cancer. The Committee heard from the clinical specialists that even though there may be a place for empagliflozin as part of dual therapy, it is more likely to be used as part of triple therapy. The Committee noted that the company's submission only included dipeptidyl peptidase-4 (DPP-4) inhibitors and other sodium-glucose cotransporter-2 (SGLT-2) inhibitors as the comparators of empagliflozin. The Committee heard from the company that the combinations of dual and triple therapy and the comparators included in its submission were informed by the conclusions made during previous SGLT-2 inhibitors appraisals, specifically those for NICE's technology appraisal guidance on dapagliflozin in combination therapy for treating type 2 diabetes and canagliflozin in combination therapy for treating type 2 diabetes. The Committee was persuaded that the combinations and comparators outlined in the company's submission were appropriate for its decision-making.

Clinical effectiveness

4.3   The Committee considered the evidence on the clinical effectiveness of empagliflozin compared with other antidiabetic treatments and noted that most of the trials compared empagliflozin with placebo. The Committee noted the Evidence Review Group (ERG)'s comment that the trials were generally of good methodological quality and that demographic characteristics were well balanced. The Committee noted that in general, compared with placebo, empagliflozin was proven to be effective in reducing HbA_{1c}, body weight and systolic blood pressure in dual therapy (plus metformin), in triple therapy (plus metformin and a sulfonylurea or a thiazolidinedione) or as an add-on to insulin. The Committee also heard from the clinical specialists about their anecdotal experience of using SGLT-2 inhibitors for treating type 2 diabetes in the trials. The clinical specialists were satisfied with their experience so far and recalled that they had not witnessed any immediate safety concerns. They also stated that their patients achieved better glycaemic control and weight reduction than had been suggested by the results in the trials. The clinical specialists also suggested that although the trials did not show any improvement in quality-of-life scores, patients generally valued the weight reduction achieved by empagliflozin. However, the clinical specialists stressed that they had limited experience, having treated only a small number of people with empagliflozin. The Committee concluded that empagliflozin in combination with other antidiabetic agents is

proven to be an effective treatment compared with placebo for type 2 diabetes.

4.4   The Committee discussed the original network meta-analyses which reported the relative effectiveness of empagliflozin with the relevant comparators in the absence of head-to-head trials. The Committee noted the ERG's concerns with the way in which the original network meta-analyses were done and reported. The Committee was reassured by the company, which stated that it had corrected many of the errors identified by the ERG and that the overall conclusion was that empagliflozin, canagliflozin, dapagliflozin and sitagliptin had similar clinical effectiveness. The Committee also considered the new network meta-analyses provided by the company in response to the appraisal consultation document. It noted that the results of the new analyses also showed that the clinical effectiveness of empagliflozin, canagliflozin, dapagliflozin and sitagliptin was similar. The Committee heard from the ERG that results of an independent unpublished network meta-analysis, comparing SGLT-2 inhibitors as dual therapy plus metformin, support the conclusion of similar clinical effectiveness among SGLT-2 inhibitors. The Committee concluded on the basis of the network meta-analyses that empagliflozin as part of dual therapy, triple therapy and as an add-on to insulin appeared to provide comparable glycaemic control both to other SGLT-2 inhibitors and DPP-4 inhibitors.

4.5   The Committee discussed the adverse events associated with empagliflozin. It noted that common adverse events associated with SGLT-2 inhibitors include urinary tract and genital infections, and that these are more common in women than in men. The Committee heard from the clinical specialists that in their experience, in patients treated with empagliflozin the incidence of these infections was low. The Committee was aware that the European public assessment report for empagliflozin reported that cardiovascular adverse events were lower for empagliflozin compared with placebo, even though the follow-up was short and the analysis included a small number of people. The Committee was concerned about the lack of long-term efficacy and safety data and heard from the clinical specialists that like other SGLT-2 inhibitors, empagliflozin therapy would be stopped in patients in whom no adequate clinical response was seen within 6 months. The Committee concluded that the short-term adverse events of empagliflozin seemed similar to those of other SGLT-2 inhibitors. The Committee also noted that like other SGLT-2 inhibitors, long-term outcomes of empagliflozin treatment were uncertain because of a lack of data.

Cost effectiveness

4.6 The Committee then discussed the original economic model submitted by the company. The Committee noted the ERG's comments regarding its quality and robustness, with the ERG highlighting several errors in the construct of the model which would invalidate any results. The Committee concluded that the company's original model was inherently flawed and so its results could not be considered reliable for making recommendations. The Committee requested further analyses from the company which included revised estimates of the incremental cost-effectiveness ratios (ICERs) for empagliflozin using a validated economic model, informed by the corrected results of network meta-analyses and compared with relevant comparators (SGLT-2 inhibitors and DPP-4 inhibitors).

4.7 The Committee discussed the new cost-effectiveness model the company had provided. It noted that as requested in the appraisal consultation document, the new model was a validated model and had been used for previous NICE technology appraisal guidance. The Committee noted that the clinical-effectiveness data used in the new model were mostly sourced from the new network meta-analyses. The Committee concluded that the new model and associated results provided a suitable basis for decision-making.

4.8 The Committee considered the most plausible ICERs for empagliflozin 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 4.2). The Committee noted that both the company's and ERG's analyses showed that the incremental differences between the costs and QALYS for empagliflozin, canagliflozin 100 mg, canagliflozin 300 mg, dapagliflozin and sitagliptin were small (see sections 3.29 and 3.36). The Committee understood that these low incremental costs and health benefits meant the ICERs could vary dramatically in response to even small changes. The Committee considered that it was important to take this into account when interpreting the ICERs. Overall, the Committee concluded that because of the very small differences in costs and QALYs between empagliflozin and either canagliflozin, dapagliflozin or sitagliptin, empagliflozin as part of a dual therapy with metformin had been shown to be a cost-effective use of NHS resources. The Committee therefore recommended empagliflozin 10 mg and 25 mg as a treatment option when the alternative treatments would be canagliflozin,

dapagliflozin or a DPP-4 inhibitor, in line with the recommendations in NICE's guideline on type 2 diabetes in adults: management and NICE's technology appraisal guidance on dapagliflozin in combination therapy for treating type 2 diabetes and canagliflozin in combination therapy for treating type 2 diabetes (that is, if there is a significant risk of hypoglycaemia or its consequences or if a sulfonylurea is not tolerated or contraindicated).

4.9 The Committee considered the most plausible ICERs for empagliflozin with metformin and a sulfonylurea as triple therapy. The Committee noted that both the company's and ERG's results showed that there were only small incremental differences in costs and QALYs between empagliflozin, canagliflozin (100 mg and 300 mg) and sitagliptin. It also noted that in the company's analyses, empagliflozin 10 mg was subject to extended dominance (a treatment is 'extendedly dominated' when its ICER is higher than that of the next, more effective, option when compared with a common baseline). The Committee was aware that the marketing authorisation for canagliflozin allows for dose escalation from 100 mg to 300 mg in people who need tighter glycaemic control. The Committee noted that for people having canagliflozin 300 mg, HbA$_{1c}$ levels would have failed to adequately respond to canagliflozin 100 mg. This is a different population from those who would start empagliflozin in clinical practice. The Committee agreed that there was uncertainty around the ICERs presented for canagliflozin 300 mg compared with empagliflozin 10 mg and empagliflozin 25 mg. Despite this uncertainty, the Committee concluded that because of the small differences in costs and QALYs between empagliflozin, canagliflozin and sitagliptin, empagliflozin 10 mg and 25 mg 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.

4.10 The Committee considered the most plausible ICERs for empagliflozin with metformin and a thiazolidinedione as triple therapy. The Committee noted that there were only small differences in costs and QALYs between the addition of empagliflozin compared with canagliflozin or sitagliptin. The Committee concluded that empagliflozin 10 mg and 25 mg with metformin and a thiazolidinedione as part of 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.

4.11   The Committee considered the most plausible ICERs for empagliflozin as an add-on treatment to insulin. The Committee concluded that empagliflozin 10 mg and 25 mg had been shown to be a cost-effective use of NHS resources compared with canagliflozin, dapagliflozin or sitagliptin as an add-on treatment to insulin because of its very small incremental costs and incremental QALYs. The Committee recommended empagliflozin as a treatment option for people with diabetes that is inadequately controlled by insulin with or without other oral antidiabetic drugs.

5 Implementation

5.1 <u>Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013</u> requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

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

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

6 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

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

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

Dr Jeremy Braybrooke

Consultant Medical Oncologist, University Hospitals BristolNHS Foundation Trust

Dr Gerardine Bryant

GP, Swadlincote, Derbyshire

Dr Simon Bond

Senior Statistician, Cambridge Clinical Trials Unit

Dr Andrew England

Senior Lecturer, Directorate of Radiography, University ofSalford

Dr Peter Heywood

Consultant Neurologist, Frenchay Hospital, Bristol

Dr Sharon Saint Lamont

Head of Clinical Quality, NHS England (North)

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

Senior lecturer in Health Economics, London School of Hygiene and Tropical Medicine

Dr Mohit Misra

GP, Queen Elizabeth Hospital, London

Sarah Parry

CNS Paediatric Pain Management, Bristol Royal Hospital for Children

Pamela Rees

Lay member

Dr Ann Richardson
Lay member

Stephen Sharp
Senior Statistician, University of Cambridge MRCEpidemiology Unit

Dr Brian Shine
Consultant Chemical Pathologist, John Radcliffe Hospital

Dr Peter Sims
GP, Devon

David Thomson
Lay member

Professor Olivia Wu
Professor of Health Technology Assessment, 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.

Dr Anwar Jilani and Ella Fields
Technical Leads

Dr Sally Doss
Technical Adviser

Bijal Joshi
Project Manager

7 Sources of evidence considered by the Committee

The Evidence Review Group (ERG) report for this appraisal was prepared by Warwick Evidence:

- Shyangdan D, Jacob R, Connock M et al. Empagliflozin combination therapy for treating type 2 diabetes:A Single Technology Appraisal. July 2014

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). Companies were also invited to make written submissions. Professional or specialist and patient or carer groups, and other consultees, had the opportunity to give their expert views. Companies, professional or specialist and patient or carer groups, and other consultees, also have the opportunity to appeal against the final appraisal determination.

Company:

- Boehringer Ingelheim

Professional or specialist and patient or carer groups:

- Association of British Clinical Diabetologists

- Black and Ethnic Minority Diabetes Association

- Royal College of Nursing

- Royal College of Pathologists

- Royal College of Physicians

- United Kingdom Clinical Pharmacy Association

Other consultees:

- Department of Health

- NHS England

- Welsh Government

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

- AstraZeneca

- Department of Health, Social Services and Public Safety for Northern Ireland

- Healthcare Improvement Scotland

- Janssen

- Merck Sharp and Dohme

- Novo Nordisk

- National Institute for Health Research Health Technology Assessment Programme

- Warwick Evidence

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

- Dr Peter Winocour, Consultant Diabetologist and Clinical Director, nominated by Association of British Clinical Diabetologists and Royal College of Physicians – clinical specialist

- Dr T Sathyapalan, Reader and Honorary Consultant Diabetologist, nominated by Association of British Clinical Diabetologists and Royal College of Physicians – clinical specialist

- Aderonki Kuti, Chief Executive Officer, nominated by Black Ethnic Minority Diabetes Association

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

- Boehringer Ingelheim

ISBN: 978-1-4731-1094-6