NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Empagliflozin combination therapy for treating type 2 diabetes

This premeeting briefing presents:

- the key evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- What is the Committee's view on empagliflozin' s likely place in the treatment pathway considering current NICE guidance (notably NICE clinical guideline 87 'The management of type 2 diabetes', technology appraisal guidance 288 'Dapagliflozin in combination therapy for treating type 2 diabetes' and technology appraisal guidance 315 'Canagliflozin in combination therapy for treating type 2 diabetes')?
- What are the main relevant comparators in clinical practice for empagliflozin in dual therapy, triple therapy and as add-on to insulin? Does the Committee agree with the manufacturer's rationale not to consider the clinical effectiveness of empagliflozin in certain combinations specified in the NICE scope?

- The comparators for empagliflozin specified in the scope also included thiazolidinediones and glucagon-like peptide-1 (GLP-1) analogues along with dipeptidyl peptidase 4 inhibitors (gliptins) and other sodium glucose cotransporter 2 inhibitors (SGLT-2 inhibitors; dapagliflozin and canagliflozin). The comparators for empagliflozin considered in the manufacturer's decision problem included dipeptidyl peptidase 4 inhibitors (gliptins) along with other sodium glucose cotransporter 2 inhibitors. The manufacturer did not consider thiazolidinedione (pioglitazone) as comparator of empagliflozin stating that the thiazolidinediones are rarely used and their use is falling. The ERG agreed with the manufacturer even though it noted that use of pioglitazone in year 2012/2013 was comparable to gliptins. Does the Committee consider pioglitazone is still a clinically relevant comparator?
- The empagliflozin trials recruited globally with limited enrolment in the UK. Does the Committee consider that the trial data are generalisable to the patient population in England?
- Because of an absence of head-to-head trials comparing empagliflozin with other SGLT2 inhibitors and DPP4 inhibitors, the relative effectiveness of empagliflozin was estimated by the manufacturer through indirect comparisons in network meta-analyses (NMA). Is the network meta-analysis a suitable source of clinical-effectiveness data for decision-making rather than direct evidence from the trials?
- The ERG identified many issues with the manufacturer's NMA (see sections 3.20 to 3.23 below or the ERG report page 56-60 for details). What is the Committee's view of the appropriateness, quality and reporting of these analyses?

Cost effectiveness

- The ERG identified several serious issues with the logical construct and the implementation of the economic model used to estimate the incremental cost-effectiveness ratios of empagliflozin (see sections 4.6 to 4.10 below or Chapter 4 of the ERG report for details) which could mean that the submitted results are not valid. The clinical effectiveness of empagliflozin is deemed equivalent to other recommended options like sodium glucose contransporter-2 inhibitors (dapagliflozin and canagliflozin) and DPP-4 inhibitors (sotagliptin) and the costs are also similar. Does the Committee think that, in the absence of reliable ICERs,

clinical equivalence and similar price to recommended precursors, is sufficient basis to formulate recommendations?

- The manufacturer's model estimated complications of diabetes based on risk equations of the United Kingdom Prospective Diabetes Study Outcomes Model risk equations (UKPDS 68). The newer version of UKPDS risk equations (UKPDS82) is available now. The manufacturer agreed that this new version is more representative of clinical practice. However, the manufacturer justified using the older version citing absence of trial data on additional variables in the newer version (for example white blood cell count and haemoglobin level) and for consistency with other NICE appraisals. Does the Committee consider this to be appropriate?
- The manufacturer's model assumed that once patient's HbA_{1C} rose above 7.5% threshold, patients will switch to insulin therapy. It did not include the option of long-acting glucagon like peptide-1 (GLP-1) analogue such as weekly injections of exenatide which could also decrease the weight. What is the Committee's view on appropriateness of treatment pathway assumed in the model?
- The health-related quality of life and cost inputs are drawn mainly from UKPDS publications in preference to the data from the trials. Does the Committee consider this approach is appropriate and that the values have been appropriately identified and are plausible?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of empagliflozin within its licensed indication for treating type 2 diabetes.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the manufacturer	Comments from the ERG
Population	**Dual therapy** Adults with type 2 diabetes that is inadequately controlled on monotherapy with either metformin or a sulfonylurea. **Triple therapy** Adults with type 2 diabetes that is inadequately controlled on dual therapy with either: • Metformin in combination with a sulfonylurea • Metformin or a sulfonylurea in combination with a thiazolidinedione, a DPP-4 inhibitor, or a GLP-1 analogue. **Add-on therapy to insulin** Adults with type 2 diabetes that is inadequately controlled on monotherapy with insulin or on therapy with insulin and one or more other oral agents.	**Dual therapy** Adults with type 2 diabetes that is inadequately controlled on monotherapy with metformin. **Triple therapy** Adults with type 2 diabetes that is inadequately controlled on dual therapy with either of the following: • Metformin in combination with a sulphonylurea • Metformin in combination with a thiazolidinedione **Add-on therapy to insulin** Adults with type 2 diabetes that is inadequately controlled on monotherapy with insulin or on therapy with insulin and up to two other oral agents	**Dual therapy** Empagliflozin in combination with a sulphonylurea has been excluded due to the absence of direct trial evidence for this indication. **Triple therapy** Empagliflozin has only been studied in combination with metformin and a sulphonylurea and in combination with metformin and thiazolidinedione	

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the manufacturer	Comments from the ERG
Intervention	Empagliflozin in combination with oral antidiabetic agents and/or insulin	Empagliflozin (in combination with oral antidiabetic agents and/or insulin)	Empagliflozin in combination with: • Metformin • Metformin and sulphonylurea • Metformin and thiazolidinedione • Insulin The choice of combinations reflects the options utilised in the clinical trial program. There was no clinical evidence for other combinations	
Comparator	**Dual therapy** For the combination of empagliflozin and metformin, the comparators are: • Sulfonylureas (with metformin) • Pioglitazone (with metformin) • DPP-4 inhibitors (with metformin) • GLP-1 analogues (with metformin)	**Dual therapy** For the combination of empagliflozin and metformin, the comparators are: • Sulfonylureas (with metformin) • DPP-4 inhibitors (with metformin) • Dapagliflozin (with metformin)	NICE guidance has demonstrated that selective sodium glucose-cotransporter 2 (SGLT-2) inhibitors have been placed in the same treatment position as DPP-4 inhibitors. Specifically the following treatments were excluded because: • Pioglitazone was considered not relevant since thiazolidinediones are currently very rarely	The ERG agreed with the manufacturer that DPP-4 inhibitors (gliptins) are the key comparator of the SGLT-2 inhibitors. However it also commented that the manufacture's submission is too dismissive of the thiazolidinediones (TZDs). The ERG agreed that use of the TZDs has fallen but noted that in 2012/13 pioglitazone was used almost as commonly as sitagliptin.

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the manufacturer	Comments from the ERG
	• Dapagliflozin (with metformin). For the combination of empagliflozin and sulfonylurea, the comparators are: • Pioglitazone (with a sulfonylurea) • DPP-4 inhibitors (with a sulfonylurea) • GLP-1 analogues (with a sulfonylurea) **Triple therapy** For the combination of empagliflozin, metformin and a sulfonylurea, the comparators are: • pioglitazone (with metformin and a sulfonylurea) • DPP-4 inhibitors (with metformin and a sulfonylurea) • GLP-1 analogues (with metformin and a sulfonylurea) • Insulin (with metformin	**Triple therapy** For the combination of empagliflozin, metformin and a SU, the comparators are: • DPP-4 inhibitors (with metformin and a SU) • Canagliflozin For the combination of empagliflozin, metformin and pioglitazone, the comparators are: • DPP-4 inhibitors (with metformin and pioglitazone) • Canagliflozin	used. • Glucagon-like peptide-1 receptor agonists (GLP-1 analogues) were considered irrelevant as an injectable they are considered at a different point in the treatment pathway and they are currently only recommended in specific populations • Insulin was not considered an appropriate comparator since as an injectable it is used at a different point in the treatment pathway. • Canagliflozin was added to the scope as it was considered relevant as the only other licensed SGLT2i currently available	The ERG agreed with the manufacturer that GLP-1 analogues should not be a comparator in dual and triple therapy.

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the manufacturer	Comments from the ERG
	and a sulfonylurea) For the combination of empagliflozin, metformin and pioglitazone, the comparators are: • DPP-4 inhibitors (with metformin and pioglitazone) • GLP-1 analogues (with metformin and pioglitazone) • Insulin (with metformin and pioglitazone). For the use of empagliflozin in any other triple therapy regimen, the comparator is • Insulin (alone or in combination with one or more oral antidiabetic agents). **Add-on therapy to insulin** • One or more oral antidiabetic agents (in combination with insulin).	**Add-on therapy to insulin** One or more oral antidiabetic agents (in combination with insulin) • DPP-4 inhibitors • Dapagliflozin • Canagliflozin		

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the manufacturer	Comments from the ERG
Outcome	The outcome measures to be considered include: • HbA1c/glycaemic control • Frequency and severity of episodes of hypoglycaemia • Change in cardiovascular risk factors (including estimated glomerular filtration rate, albumin creatinine ratio, blood pressure and/or serum lipids) • Weight change • Complications of diabetes e.g. Cardiovascular, renal and eye • Mortality • Adverse effects of treatment (including genitourinary tract infection) • Health-related quality of life.	The outcome measures to be considered include: • HbA_1c /glycaemic control • Frequency and severity of episodes of hypoglycaemia • Change in cardiovascular risk factors (including estimated glomerular filtration rate, albumin creatinine ratio, blood pressure and/or serum lipids) • Weight change • Complications of diabetes e.g. cardiovascular, renal and eye • Mortality • Adverse effects of treatment (including genitourinary tract infection) • Health-related quality of life	All outcomes included within the clinical trial program have been included	The manufacturer's submission did not include trial results for change in lipid levels

The technology

1.2 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.

Treatment pathway

1.3 NICE clinical guideline 87 'Type 2 diabetes: The management of type 2 diabetes' (CG87) recommends diet and lifestyle modifications to initially manage type 2 diabetes. For people who are overweight or obese and whose blood glucose is inadequately controlled by diet and lifestyle modifications, the oral antidiabetic drug, metformin is recommended. A sulfonylurea (for example, gliclazide, glipizide, or glimepiride) may be considered as a monotherapy option if the person is not overweight, does not tolerate metformin or a rapid response is needed because of hyperglycaemia.

1.4 If blood glucose control remains inadequate on monotherapy with metformin, a sulfonylurea should be added. A thiazolidinedione (pioglitazone) or a dipeptidyl peptidase-4 (DPP-4) inhibitor such as sitagliptin or vildagliptin can only be used as an add-on therapy to monotherapy with metformin or a sulfonylurea if the combination of metformin and sulfonylurea as dual therapy is not considered appropriate. Dapagliflozin in combination with metformin is recommended as a dual therapy regimen in NICE technology appraisal guidance 288 (TA288), only if it is used as described for DPP‑4 inhibitors in NICE clinical guideline 87. NICE technology appraisal guidance 315 (TA315) recommends canagliflozin in combination with metformin only if a sulfonylurea is contraindicated or not tolerated or the person is at significant risk of hypoglycaemia or its consequences. The glucagon-like peptide 1 (GLP-1) analogues (exenatide and liraglutide) are

recommended in NICE technology appraisal guidance 203 and 248 as options for dual therapy only if metformin or a sulfonylurea is contraindicated or not tolerated and a thiazolidinedione and a DPP-4 inhibitor is contraindicated or not tolerated.

1.5 For people whose disease is not controlled on dual therapy, NICE clinical guideline 87 recommends starting insulin in preference to adding other drugs. However, if insulin is considered unacceptable (because of employment, social, recreational or other personal issues), either sitagliptin or pioglitazone are recommended as options for add-on therapy to metformin and sulfonylurea. Dapagliflozin in a triple therapy regimen in combination with metformin and a sulfonylurea is recommended in TA288 only as a part of clinical trial while canagliflozin (in TA315) is recommended in a triple therapy regimen in combination with metformin along with a sulfonylurea or a thiazolidinedione.

1.6 The injectable GLP-1 analogues (twice-daily or prolonged-release exenatide and once-daily liraglutide) may be prescribed in a triple-therapy regimen for people with obesity and associated psychological or medical problems or for those in whom insulin could have significant occupational implications (see sections 1.6.1 -1.6.3 NICE clinical guideline 87 and technology appraisal guidance 203 and 248).

1.7 For people whose disease is not controlled by insulin alone, oral antidiabetic drugs may be used as an add-on treatment. NICE clinical guideline 87 states that combining pioglitazone with insulin therapy may be considered for a person who has previously had a marked glucose-lowering response to thiazolidinedione therapy (pioglitazone), or who is on high-dose insulin therapy and whose blood glucose is inadequately controlled. Dapagliflozin in combination with insulin with or without other antidiabetic drugs is recommended in NICE technology appraisal guidance 288. Similarly canagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes (TA 315).

Figure 1. Simplified treatment pathway showing NICE recommendations on pharmacological treatments for type 2 diabetes (clinical guideline 87 and technology appraisal guidance 203, 248, 288 and 315)

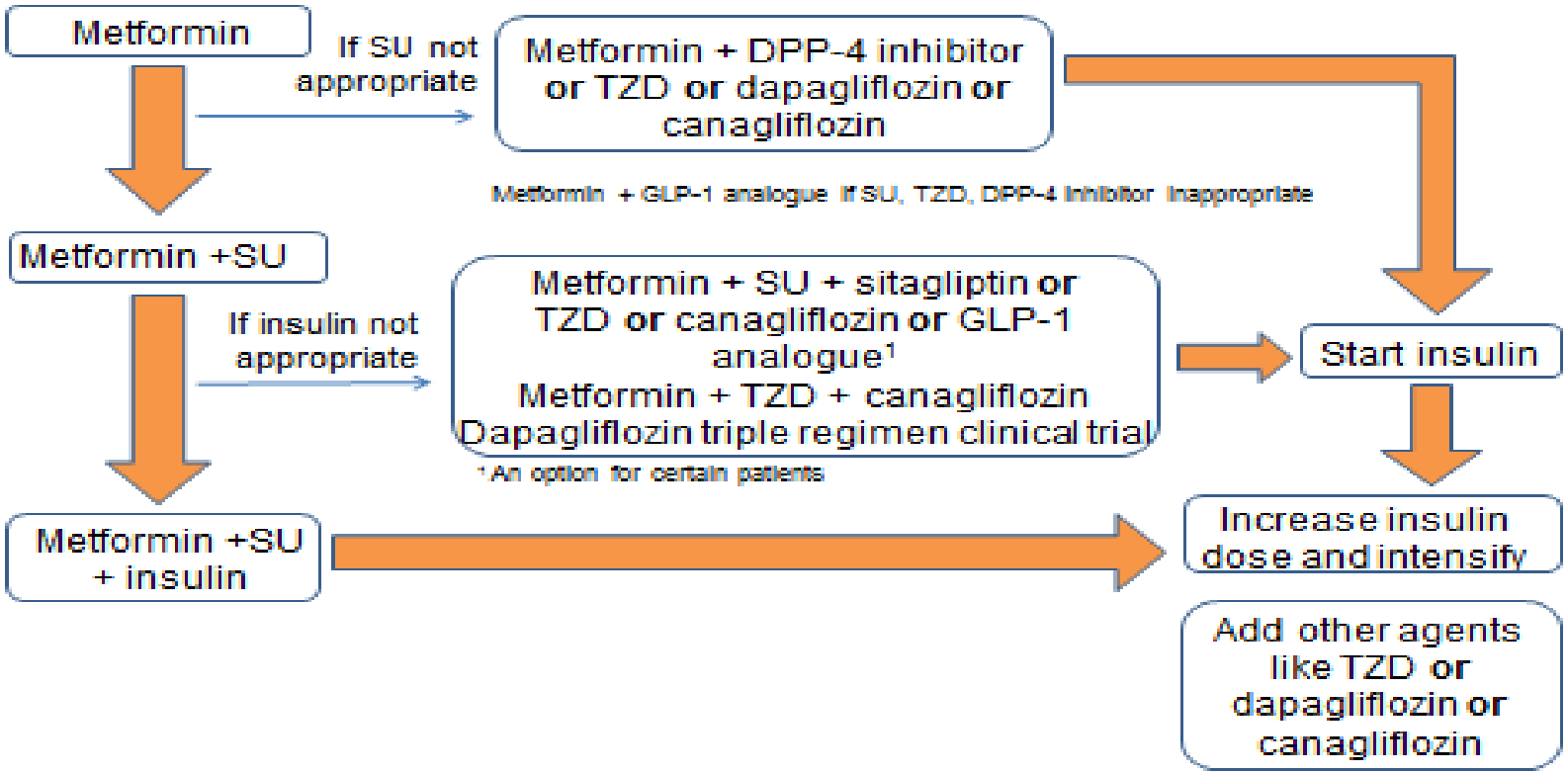


Table 2. Technology

	Intervention	Other selective sodium glucose cotransporter 2 inhibitors	
	Empagliflozin	**Canagliflozin**	**Dapagliflozin**
Marketing authorisation	Empagliflozin (Jardiance, Boehringer Ingelheim) is indicated for the treatment of type 2 diabetes mellitus to improve glycaemic control in adults as: <u>Monotherapy</u> When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance. <u>Add-on combination therapy</u> In combination with other glucose–lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control	Canagliflozin (Invokana, Janssen-Cilag) is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as: <u>Monotherapy</u> 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. <u>Add-on therapy</u> Add-on therapy with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.	Dapagliflozin (Forxiga, Bristol-Myers Squibb/AstraZeneca) is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as: <u>Monotherapy</u> When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance. <u>Add-on combination therapy</u> In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control
Administration	Oral	Oral	Oral
Setting	Primary care, secondary care or specialist clinics	Primary care, secondary care or specialist clinics	Primary care, secondary care or specialist clinics

	Intervention	Other selective sodium glucose cotransporter 2 inhibitors	
	Empagliflozin	**Canagliflozin**	**Dapagliflozin**
Acquisition cost	According to the manufacturers' submission the acquisition cost of empagliflozin (excluding VAT) will be £36.59 per pack of 28 (10 and 25 mg)	According to the British National Formulary (June 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).	According to the British National Formulary (June 2014), the drug's price (excluding VAT) is £36.59 per pack of 28 (5 mg or 10 mg tablets).
Dosage	The recommended starting dose is 10 mg empagliflozin once daily for monotherapy and add-on combination therapy with other glucose lowering medicinal products including insulin. In patients tolerating empagliflozin 10 mg once daily who have an eGFR ≥60 ml/min/1.73 m2 and need tighter glycaemic control, the dose can be increased to 25 mg once daily. The maximum daily dose is 25 mg	The recommended starting dose of canagliflozin is 100 mg once daily. In patients tolerating canagliflozin 100 mg once daily who have an eGFR ≥ 60 mL/min/1.73 m2 or CrCl ≥ 60 mL/min and need tighter glycaemic control, the dose can be increased to 300 mg once daily	The recommended dose is 10 mg dapagliflozin once daily for monotherapy and add-on combination therapy with other glucose-lowering medicinal products including insulin.
Total acquisition cost	The expected annual cost of empagliflozin is £470.30	The expected annual cost of canagliflozin is £476.93 for the 100 mg daily dosage and £608.21 for the 300 mg daily dosage.	The expected annual cost of dapagliflozin would be £476.98 or £953.95 depending upon 5mg tablet twice daily or 10 mg tablet once daily is used.
See Summary of Product Characteristics for details on adverse reactions and contraindications.			

2 Comments from consultees

2.1 Clinical specialists highlighted that National Diabetes Audit and Quality and Outcomes Framework returns indicate considerable disparity in process measures and outcomes for treatment of type 2 diabetes across the regions. They also noted that some variations are expected because of individualised approach to the care and the availability of a range of therapeutic options.

2.2 Clinical specialists noted that empagliflozin is 3rd SGLT-2 inhibitor to get marketing authorisation but unlike its precursors it has been demonstrated to be effective in modest renal disease and could be most valuable for patients with mild renal disease.

2.3 Clinical specialists also noted that like other drugs in this class it is important to assess risk for genitourinary infections. Empagliflozin should be avoided in elderly with chronic kidney disease and in those with recurrent urinary tract infections. They also noted that genitourinary infections are more common in women than men.

3 Clinical-effectiveness evidence

Overview of the clinical trials

3.1 The manufacturer identified 8 trials that evaluated empagliflozin in combination therapy for treating type 2 diabetes. This included 7 randomised controlled trials and 1 long-term extension study (1245.33). The long-term extension study recruited the patients who participated in 3 randomised controlled trials (in 2 of these trials [1245.19 and 1245.23] empagliflozin had been evaluated as a combination therapy while in the other [1245.20] as monotherapy). In the long-term extension study, outcome data were presented separately for the patients rolling-over from different studies.

3.2 Overview of the trials included in the manufacturer's submission is presented in table 3.

Table 3. Overview of empagliflozin trials

Trial no. (acronym)	Intervention	Comparator	Population	Duration of study	Duration of follow-up
Patients on baseline pioglitazone or pioglitazone plus metformin (dual or triple therapy results presented together)					
1245.19 (EMPA-REG PIO)	Empagliflozin 10 mg or 25 mg once daily add-on to pioglitazone or pioglitazone plus metformin	Placebo	• N=499 • ≥18 years (≤65 years in India only) • HbA_{1C} ≥7.0% to ≤10.0% • BMI ≤45 kg/m^2 • Diet and exercise programme • **Pioglitazone ≥30mg/day; metformin ≥1,500mg/day** • ~25% with background therapy of pioglitazone alone and ~75% with pioglitazone in combination with metformin in all 3 arms • Glucose level ≤13.3 mmol/L • eGFR ≥30 mL/min/1.73 m^2	24 week treatment period (2 week open-label placebo run-in period)	7 days or enrolment in extension trial 1245.31
Patients on baseline metformin or metformin plus a sulfonylurea (dual and triple therapy, results presented separately)					
1245.23 (EMPA-REG MET, EMPA-REG METSU)	Empagliflozin 10mg or 25mg once daily add-on to metformin or metformin plus SU	Placebo	**All studies:** • ≥18 years (and ≤65 years in India) • BMI ≤45kg/m^2 • Diet and exercise programme • Glucose level ≤13.3 mmol/L • eGFR ≥30 mL/min/1.73 m^2 **Metformin only sub-study:** • N=638 • HbA_{1C} ≥7.0% to ≤10% **Open-label metformin only sub-study:** • N=69 • HbA_{1C} >10.0%	24 week treatment period (2 week open-label placebo run-in period)	7 days or enrolment in extension trial 1245.31

Trial no. (acronym)	Intervention	Comparator	Population	Duration of study	Duration of follow-up
			Metformin plus SU sub-study: • N=669 • HbA_{1C} ≥7.0% to ≤10% **Open-label met + SU sub-study:** • N=103 • HbA_{1C} > 10.0%		
Dual therapy: patients on baseline metformin					
1245.28 (EMPA-REG H2H SU)	Empagliflozin 25 mg once daily versus glimepiride 1-4 mg once daily as add-on to metformin	Glimepiride 1-4mg	• N=1,549 • ≥18 years • HbA_{1C} ≥7.0% to ≤10.0% • BMI ≤45 kg/m^2 • **Metformin ≥1,500mg/day** • Glucose level ≤13.3 mmol/L • eGFR ≥60 mL/min/1.73 m^2	2 year treatment period (2-week open-label placebo run-in period	4 weeks
Long-term efficacy and safety of empagliflozin					
1245.31 (EMPA-REG EXTEND)	Empagliflozin long-term safety study	Sitagliptin; Placebo	• N=2,700 • Patients originally enrolled in pivotal studies 1245.19, 1245.20 and 1245.23	52 weeks in addition to time in previous trials (i.e. 76 week minimum treatment period)	4 weeks
Empagliflozin as add-on combination to basal insulin with or without metformin and/or sulphonylureas					
1245.33 (EMPA-REG BASAL)	Empagliflozin 10 mg or 25 mg once daily add-on to basal insulin (glargine or detemir insulin [≥20 IU/day] or NPH insulin [≥14 IU/day] with or	Placebo	• N=494 • T2DM • ≥18years • HbA_{1C} >7.0% to ≤10.0% • BMI ≤45 kg/m2 • **Stable insulin dose ≥12 weeks prior to randomisation**	78 weeks (2 week open-label placebo run-in period)	4 weeks

Trial no. (acronym)	Intervention	Comparator	Population	Duration of study	Duration of follow-up
	without concomitant metformin and/or SU				
Empagliflozin in patients with renal impairment					
1245.36 (EMPA-REG RENAL)	Empagliflozin 10 mg or 25 mg once daily	Placebo	• N=741 • T2DM • ≥18 years • HbA_{1C} >7.0% to ≤10.0% • BMI ≤45 kg/m^2 • **Previously treated with any antidiabetic therapy excluding SGLT2is** • Mild RI: • eGFR ≥60 and <90mL/min/1.73m^2 (n=292) • Moderate RI: • eGFR ≥30 and <60mL/min/1.73m^2 (n=375) • Severe RI: • eGFR ≥15 and • <30ml/min/1.73m^2 (n=74)	52 weeks (2 week open-label placebo run-in period)	3 weeks
Empagliflozin in patients with hypertension					
1245.48 (EMPA-REG BP)	Empagliflozin 10 mg or 25 mg once daily	Placebo	• N=825 • T2DM • ≥18 years • HbA_{1C} >7.0% to ≤10.0% • BMI ≤45 kg/m^2 • Patients with hypertension (mean	12 weeks (2 week open-label placebo run-in period)	2 weeks

Trial no. (acronym)	Intervention	Comparator	Population	Duration of study	Duration of follow-up
			SBP 130-159 mmHg and DBP 80-99 mmHg)		
Empagliflozin add-on to multiple daily injections of insulin					
1245.49 (EMPA-REG MDI)	Empagliflozin 10 mg or 25 mg once daily add-on to multiple daily injections of insulin (total insulin >60IU/day) either alone or with metformin	Placebo	• N=566 • T2DM • ≥18 years • HbA_{1C} >7.5% to ≤10.0% • BMI 30-45kg/m2 • Stable insulin dose ≥12 weeks prior to randomisation	52 weeks (2 week open-label placebo run-in period)	4 weeks

ERG comments

3.3 The ERG considered that only 4 trials (considering 2 sub-studies of the study 1245.23 as 2 separate trials) are most relevant to the decision problem. One of the sub-studies of 1245.23, EMPA-REG MET, assessed efficacy of empagliflozin in dual therapy with metformin and the other, EMPA-REG MET SU examined the efficacy in triple therapy with metformin plus a sulphonylurea. The 2 other studies were in combination with insulin regimens, with basal insulin alone (1245.33, EMPA-REG Basal) and with multiple daily injections (1245.49, EMPA-REG MDI) with or without concomitant metformin and/or a sulphonylurea.

3.4 The ERG explained that the EMPA-REG BP trial (1245.48) is not relevant for this appraisal because it evaluated empagliflozin as a monotherapy in people who had diabetes as well as hypertension with no previous glucose-lowering treatment. The ERG questioned the relevance of EMPA-REG Renal trial which included people with diabetes and renal impairment, stating that European Medicine Agency has recommended against use in moderate renal impairment. For EMPA-REG H2H SU (1245.28) which compared empagliflozin high dose (25 mg) with a sulfonylurea (glimepiride) as an add-on to metformin in dual therapy, the ERG commented that due to very low cost sulfonylureas would be tried before SGLT-2 inhibitors and therefore are not relevant comparator of empagliflozin.

3.5 The ERG did not explain why EMPA-REG PIO (1245.19) (which evaluated empagliflozin as dual or triple therapy in patients on pioglitazone or pioglitazone plus metformin background therapy) should not be considered relevant for this appraisal.

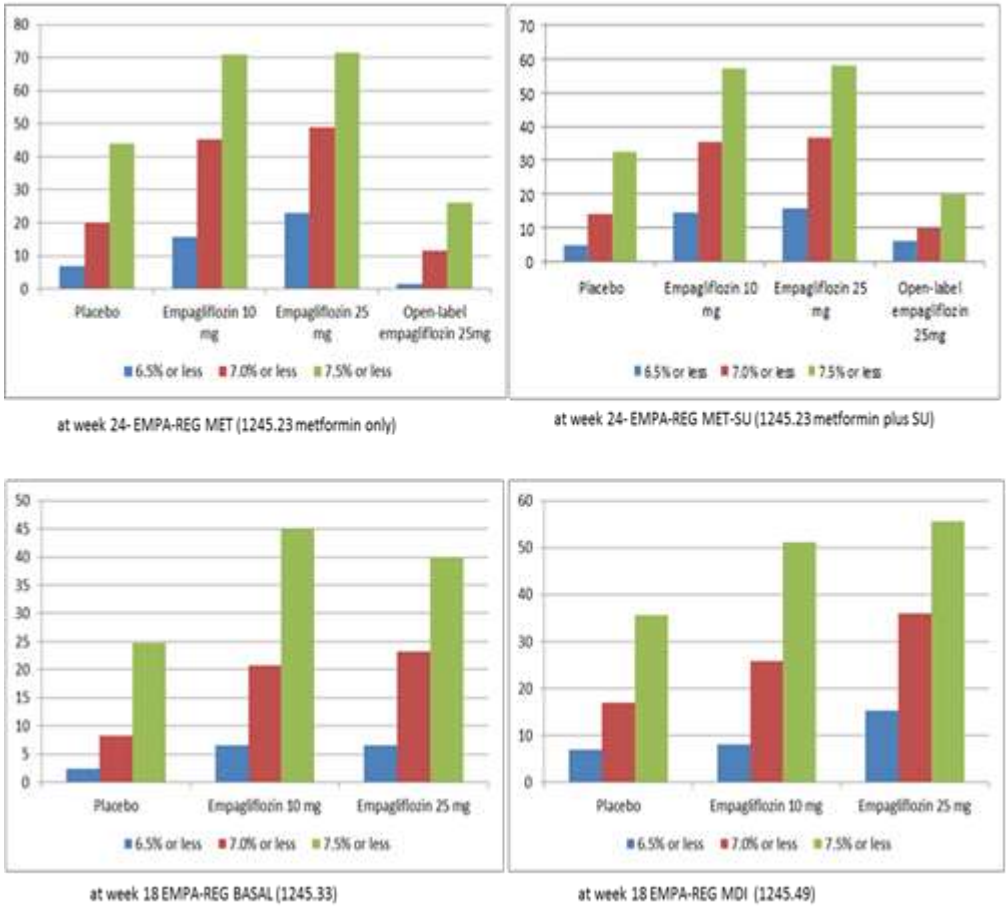
3.6 The ERG considered trials to be good quality; the demographic characteristics were well balanced across treatment groups except in EMPA-REG MDI where the proportion of male patients was significantly lower in the placebo arm compared with the empagliflozin arms (39.9% vs. 52.2% in empagliflozin 10 mg vs. 44.2% in empagliflozin 25 mg).

3.7 The manufacturer's submission did not report outcome data on change in lipid levels for any trial, however the ERG found that change in lipid profiles (serum levels of total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides) for study EMPA-REG MET (1245.23) had already been published (Haring et al 2014). The results are presented in the table 3 of the ERG report (page 32) and showed that in comparison with placebo both doses of empagliflozin were associated with significant reduction in most of the components of serum lipids. The change in lipid levels for study EMPA-REG PIO trial was also published (Kovacs et al 2014) and presented in the table of the addendum of the ERG report (page 5). The results showed that in comparison with placebo both dose of empagliflozin reduced high density lipoprotein cholesterol (HDL-C) statistically significantly. The changes in other fractions of lipid were not statistically significant.

Clinical trial results

3.8 The primary outcome measure in the trials was change in the levels of glycated haemoglobin (HbA_{1c}) from the baseline. The secondary outcomes included change in fasting plasma glucose (FPG), mean daily glucose (MDG), body weight, blood pressure, total insulin dose in addition to the safety and tolerability. The results for key outcomes (HbA_{1C}, body-weight and blood pressure) are presented in the tables 4-7. At the clarification stage, the manufacturer also provided the proportions of patients who achieved the HbA_{1c} targets of 6.5% or less, 7.0% or less and 7.5% or less for 4 key trials. The proportions of patients achieving various target levels of HbA_{1C} in different arms of the trial are presented graphically in figure 2.

Figure 2: Proportion of patients achieving target HbA1C level



3.10 The trial results showed that empagliflozin in both doses (10 or 25 mg) was associated with a statistically significant reduction of mean HbA_{1c} compared with placebo in patients on different background therapies, including insulin and these reductions were maintained throughout the duration treatment in the long-term extension study (EMPA-REG EXTEND 1245.31). The glycaemic control achieved with empagliflozin 25 mg in patients with metformin background therapy was statistically non-inferior compared with glimepiride (a sulfonylurea) at week 104 in EMP-REG H2H trial (1245.28). The empagliflozin also demonstrated statistically significantly better reduction in HbA_{1C} compared with placebo in patients with mild-to-moderate renal impairment (1245.36).

Table 4. Primary outcome: Change in mean HbA_{1c} level

Trial		Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg	Active comparator/ Open label arm
Patients on baseline pioglitazone or pioglitazone plus metformin (dual or triple therapy) No interaction for the subgroup by background medication (pioglitazone alone and pioglitazone plus metformin; p=0.8821)*.					
EMPA-REG PIO (1245.19)		N=165	N=165	N=168	
	Adjusted mean change from baseline at 24 weeks (%) ± SE	−0.11 ± 0.07	−0.59 ± 0.07	−0.72 ± 0.07	
	P value		<0.0001	<0.0001	
EMPA-REG EXTEND (1245.31) Background of pioglitazone (1245.19 roll-over)	Adjusted mean change from baseline at week 76 (%) ± SE	-0.01 + 0.07	-0.61 + 0.07	-0.70	
	P value		<0.0001	<0.0001	
Dual therapy: patients on baseline metformin					
EMPA-REG MET (1245.23 metformin only)		N=207	N=217	N=213	Open-label empagliflozin 25mg (n=69)
	Adjusted mean change from baseline at week 24 (%) ± SE	-0.13 ± 0.05	-0.70 ± 0.05	-0.77 ± 0.05	-2.78 ± 0.21†
	P value		<0.0001	<0.0001	
EMPA-REG EXTEND (1245.31) on background metformin (1245.23 roll-over)	Adjusted mean change from baseline at week 76 (%) ± SE	-0.01 + 0.05	-0.62 + 0.05	-0.74 + 0.05	
	P value		<0.0001	<0.0001	
EMPA-REG H2H SU (1245.28)				Empagliflozin 25mg (N=765)	Glimepiride 1-4mg (N=780)
	Adjusted mean change from baseline			-0.66 + 0.03	-0.55 + 0.03

Trial		Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg	Active comparator/ Open label arm
	at week 104 (%) ± SE				
	P value (non-inferiority)			<0.0001	
Triple therapy: patients on baseline metformin plus SU or metformin plus pioglitazone					
EMPA-REG MET-SU (1245.23 metformin plus SU)		N=225	N=225	N=216	Open-label empagliflozin 25mg (n=101)
	Adjusted mean change from baseline at week 24 (%) ± SE	-0.17 ± 0.05	-0.82 ± 0.05	-0.77 ± 0.05	-2.53 ± 0.15†
	P value		<0.001	<0.001	
EMPA-REG EXTEND (1245.31) on background metformin plus SU (1245.23 roll-over)	Adjusted mean change from baseline at week 76 (%) ± SE	-0.03 + 0.06	-0.74 + 0.06	-0.72 + 0.06	
	P value		<0.0001	<0.0001	
Add-on to insulin: patients on baseline insulin ± other antidiabetics					
EMPA-REG BASAL (1245.33)		N=125	N=132	N=117	
	Adjusted mean change from baseline at week 18 (%) ± SE	-0.01 ± 0.07	-0.57 ± 0.07	-0.71 ± 0.07	
	P value		<0.0001	<0.0001	
		N=112	N=127	N=110	
	Adjusted mean change from baseline at week 78 (%) ± SE	-0.02 ± 0.09	-0.48 ± 0.08	-0.64 ± 0.09	
	P value		<0.0001	<0.0001	
EMPA-REG MDI		N=188	N=186	N=189	

Trial		Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg	Active comparator/ Open label arm
(1245.49)	Adjusted mean change from baseline at week 18 (%) ± SE	-0.50 ± 0.06	-0.94 ± 0.06	-1.02 ± 0.06	
	P value		<0.0001	<0.0001	
		N=115	N=119	N=118	
	Adjusted mean change from baseline at week 52 (%) ± SE	-0.81 ± 0.08	-1.18 ± 0.08	-1.27 ± 0.08	
	P value (non-inferiority)		<0.0001	<0.0001	
Empagliflozin in patients with renal impairment					
EMPA-REG RENAL (1245.36) Mild renal impairment		N=95	N=98	N=97	
	Adjusted mean change from baseline at week 24 (%) ± SE	0.06 ± 0.07	-0.46 ± 0.07	-0.63 ± 0.07	
	P value		<0.0001	<0.0001	
	Adjusted mean change from baseline at week 52 (%) ± SE	0.06 ± 0.08	-0.57 ± 0.08	-0.60 ± 0.08	
	P value		<0.0001	<0.0001	
EMPA-REG RENAL (1245.36) Moderate renal impairment		N=187		N=187	
	Adjusted mean change from baseline at week 24 (%) ± SE	0.05 ± 0.05		-0.37 ± 0.05	
	P value			<0.0001	
	Adjusted mean change from baseline at week 52	0.12 ± 0.06		-0.32 ± 0.06	

Trial		Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg	Active comparator/ Open label arm
	(%) ± SE				
	P value			<0.0001	
Empagliflozin in patients with hypertension					
EMPA-REG BP(1245.48)		N=271	N=276	N=276	
	Adjusted mean change from baseline at week 12 (%) ± SE	0.03 ± 0.04	-0.59 ± 0.04	-0.62 ± 0.04	
	P value		<0.0001	<0.0001	

3.11 Empagliflozin was also associated with statistically significant weight loss in most of the trials. In the key study for dual therapy (EMPA-REG MET), compared with placebo empagliflozin 10mg resulted in mean weight loss of 1.6 kg while empagliflozin 25 mg resulted in the loss of 2.0 kg. Similarly in triple therapy (in the study EMP-REG METSU) empagliflozin reduced weight by 1.8 and 2.0 kg with empagliflozin 10mg and 25 mg respectively. The long-term extension study (EMPA-REG EXTEND) confirmed that weight loss from baseline achieved at week 24 was largely maintained at week 76. Empagliflozin in combination with basal insulin regimens (in the study EMP-REG BASAL) was associated with much higher weight loss compared with placebo at week 78 that is 3.6 kg with empagliflozin 10 mg and 3.1 kg with empagliflozin 25 mg while in combination with multiple daily injections insulin (EMPA-REG MDI), empagliflozin reduced mean body weight by 2.39 kg and 2.48 kg with empagliflozin 10mg and 25 mg respectively.

Table 5: Secondary outcome: Change in body weight (Kg)

Trial		Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg	Active comparator/ Open label arm
Patients on baseline pioglitazone or pioglitazone plus metformin (dual or triple therapy)					
EMPA-REG PIO (1245.19)	Adjusted mean change at week 24	0.34 ± 0.21	−1.62 ± 0.21	−1.47 ± 0.21	
	P value		<0.0001	<0.0001	
EMPA-REG EXTEND (1245.31) Background of pioglitazone (1245.19 roll-over)	Adjusted mean change at week 76	0.50 + 0.26	-1.47 + 0.26	-1.21 + 0.26	
	P value		<0.0001	<0.0001	
Dual therapy: patients on baseline metformin					
EMPA-REG MET (1245.23 metformin only)					Open-label empagliflozin 25mg (n=69)
	Adjusted mean change at week 24	-0.45 ± 0.17	-2.08 ± 0.17	-2.46 ± 0.17	-1.33 ± 0.43†
	P value		<0.0001	<0.0001	
EMPA-REG EXTEND (1245.31) on background metformin (1245.23 roll-over)	Adjusted mean change at week 76	-0.46 + 0.22	-2.39 + 0.21	-2.65 + 0.21	
	P value		<0.0001	<0.0001	
EMPA-REG H2H SU (1245.28)				Empagliflozin 25mg (N=765)	Glimepiride 1-4mg (N=780)
	Adjusted mean change at			-3.11 + 0.13	1.33 + 0.13
	P value (non-inferiority)			<0.0001	
Triple therapy: patients on baseline metformin plus SU or metformin plus pioglitazone					
EMPA-REG MET-SU (1245.23					Open-label empagliflozin 25mg (n=101)

metformin plus SU)	Adjusted mean change at week 24	-0.39 ± 0.15	-2.16 ± 0.15	-2.39 ± 0.16	-1.29 ± 0.30
	P value		<0.001	<0.001	
EMPA-REG EXTEND (1245.31) Background of metformin plus SU (1245.23 roll-over)	Adjusted mean change at week 76	-0.63 + 0.19	-2.44 + 0.19	-2.28 + 0.20	
	P value		<0.0001	<0.0001	
Add-on to insulin: patients on baseline insulin ± other antidiabetics					
EMPA-REG BASAL (1245.33)	Adjusted mean change at t week 18	-0.05 ± 0.68	-2.09 ± 0.66	-0.92 ± 0.72	
	P value		0.0320	0.3818	
	Adjusted mean change at week 78	1.16 ± 0.80	-2.47 ± 0.76	-1.96 ± 0.82	
	P value		0.0012	0.0073	
EMPA-REG MDI (1245.49)	Adjusted mean change at week 52	0.44 ± 0.36	-1.95 ± 0.36	-2.04 ± 0.36	
	P value		<0.0001	<0.0001	
Empagliflozin in patients with renal impairment					
EMPA-REG RENAL (1245.36) Mild renal impairment	Adjusted mean change at week 24	-0.33 ± 0.24	-1.76 ± 0.23	-2.33 ± 0.23	
	P value		<0.0001	<0.0001	
	Adjusted mean change at week 52	-0.44 ± 0.32	-2.00 ± 0.32	-2.60 ± 0.32	
	P value		Not reported	Not reported	
EMPA-REG RENAL (1245.36) Moderate renal impairment	Adjusted mean change at week 24	-0.08 ± 0.18		-0.98 ± 0.18	
	P value			0.0004	
	Adjusted mean change at week 52	0.00 ± 0.21		-1.17 ± 0.21	

	P value			<0.0001	
Empagliflozin in patients with hypertension					
EMPA-REG BP(1245.48)	Adjusted mean change at week 12	-0.18 ± 0.13	-1.68 ± 0.13	-2.16 ± 0.13	
	P value		<0.0001	<0.0001	

3.12 The reductions in systolic blood pressure (SBP) ranged from 1.4mm Hg in the EMPA-REG MDI trial, to 4.8 mg Hg in the EMPA-REG MET. In a trial of 12 weeks duration in patients with hypertension with stable antihypertensive background medication (EMPA-REG BP), SBP reductions from baseline were 3.4 and 4.2mm Hg for empagliflozin 10 mg and 25 mg, respectively.

Table 6. Secondary outcome: Change in Blood Pressure (mm Hg)

Trial		**Placebo**	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**	**Active comparator/ Open label arm**
Patients on baseline pioglitazone or pioglitazone plus metformin (dual or triple therapy)					
EMPA-REG PIO (1245.19)	Adjusted mean change at week 24	0.72 ± 0.85	−3.14 ± 0.85	−4.00 ± 0.84	
	P value		0.0014	<0.0001	
EMPA-REG EXTEND (1245.31) Background of pioglitazone (1245.19 roll-over)	Adjusted mean change at week 76	0.3 ± 0.9	-1.7 ± 0.9	-3.4 ± 0.9	
	P value		0.0987	0.0028	
Dual therapy: patients on baseline metformin					
EMPA-REG MET (1245.23 metformin only)					Open-label empagliflozin 25mg (n=69)
	Adjusted mean change at week 24	-0.4 ± 0.7	-4.5 ± 0.7	-5.2 ± 0.7	-1.8 ± 1.2[†]

Trial		Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg	Active comparator/ Open label arm
	P value		<0.0001	<0.0001	
EMPA-REG EXTEND (1245.31) on background metformin (1245.23 roll-over)	Adjusted mean change at week 76	-0.8 ± 0.8	-5.2 ± 0.8	-4.5 ± 0.8	
	P value		<0.0001	0.0008	
EMPA-REG H2H SU (1245.28)				Empagliflozin 25mg (N=765)	Glimepiride 1-4mg (N=780)
	Adjusted mean change at week 104			-3.1 ± 0.5	2.5 ± 0.5
	P value			<0.0001	
	Adjusted mean change at week 104 (diastolic)			-1.8 ± 0.3	0.9 ± 0.3
	P value			<0.0001	
Triple therapy: patients on baseline metformin plus SU or metformin plus pioglitazone					
EMPA-REG MET-SU (1245.23 metformin plus SU)					Open-label empagliflozin 25mg (n=101)
	Adjusted mean change at week 24	-1.4 ± 0.7	-4.1 ± 0.7	-3.5 ± 0.7	-3.6 ± 1.0†
	P value		<0.001	<0.001	
EMPA-REG EXTEND (1245.31) Background of metformin plus SU (1245.23 roll-over)	Adjusted mean change at week 76	-1.6 ± 0.7	-3.8 ± 0.7	-3.7 ± 0.7	
	P value		0.0213	0.0288	
Add-on to insulin: patients on baseline insulin ± other antidiabetics					
EMPA-REG BASAL (1245.33)	Adjusted mean change at week 18	-0.3 ± 0.9	-3.7 ± 0.9	-3.3 ± 1.0	

Trial		Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg	Active comparator/ Open label arm
	P value		0.0111	0.0267	
	Adjusted mean change at week 78	0.1 ± 1.0	-4.1 ± 1.0	-2.4 ± 1.1	
	P value		0.0040	0.0987	
EMPA-REG MDI (1245.49)	Adjusted mean change at week 18	-1.2 ± 0.8	-3.6 ± 0.8	-2.9 ± 0.8	
	P value		0.0366	0.1409	
	Adjusted mean change at week 52	-2.6 ± 0.8	-3.9 ± 0.8	-4.0 ± 0.8	
	P value		0.2337	0.2097	
Empagliflozin in patients with renal impairment					
EMPA-REG RENAL (1245.36) Mild renal impairment	Adjusted mean change at week 24	0.65 ± 1.19	-2.92 ± 1.17	-4.47 ± 1.18	
	P value		0.0333	0.0024	
	Adjusted mean change at week 52	1.57 ± 1.32	-1.74 ± 1.30	-6.18 ± 1.30	
	P value		0.0745	<0.0001	
EMPA-REG RENAL (1245.36) Moderate renal impairment	Adjusted mean change at week 24	0.40 ± 0.94		-3.88 ± 0.94	
	P value			0.0013	
	Adjusted mean change at week 52	-0.79 ± 0.98		-5.06 ± 0.98	
	P value			0.0023	
Empagliflozin in patients with hypertension					
EMPA-REG BP(1245.48)	Adjusted mean change	0.48 ± 0.49	-2.95 ± 0.48	-3.68 ± 0.48	

Trial		Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg	Active comparator/ Open label arm
	at week 12				
	P value		<0.0001	<0.0001	
	Adjusted mean change at week 12 (diastolic)	0.32 ± 0.29	-1.04 ± 0.28	-1.40 ± 0.28	
	P value		0.0008	<0.0001	

3.13 Health-related quality of life data were collected in 6 trials comparing empagliflozin with placebo (that also included a trail 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 6 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 pooled data from the 6 trials are presented at different time points (weeks 4,6,12,18,24,40 and 52) in the table 26 of the manufacturer's submission. The manufacturer also stated that no differences in EQ-5D score were evident in any subgroups based on age, sex, BMI, country, BP, HbA1c level at baseline, eGFR at baseline, prior CV events, time since diagnosis(years), race, CV risk predictor. The trials also collected data using EQ-5D VAS and the manufacturer reported that change from baseline EQ-5D VAS was similar across all treatment groups at all time-points.

ERG comments

3.14 The ERG commented that lack of head to head trials of empagliflozin against the main comparators (gliptins or other SGLT-2 inhibitors) is the main weakness of the evidence base. The ERG also identified data on the change in lipid profiles (serum levels of total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides) for study EMPA-REG Met (1245.23) (Haring et al 2014). The results are presented in the table 3 (page 32) of

the ERG report. The results showed that compared with placebo both doses of empagliflozin were associated with significant reduction in most of the components of serum lipids.

Manufacturer's network meta-analysis

3.15 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. A total of 37 studies for dual therapy and 18 as triple therapy were included in the manufacturer's network meta-analysis (NMA).

3.16 To estimate the effectiveness of empagliflozin in combination with metformin, metformin and SU, metformin and TZD and insulin compared with the comparators identified in the decision problem an indirect comparison was conducted. Five types of NMA were undertaken (represented by figures 28 to 32 on pages 162-164 in the manufacturer's submission) and listed below.

- RCTs comparing the interventions for patients no longer responding adequately to metformin (dual therapy)
- RCTs comparing the interventions for patients no longer responding adequately to metformin plus SU (triple therapy)
- RCTs comparing the interventions for patients no longer responding adequately to TZDs (triple therapy)
- RCTs comparing the interventions for patients no longer responding adequately to TZDs and metformin (triple therapy)
- RCTs comparing the interventions for patients no longer responding adequately to insulin therapy plus other oral antidiabetic drugs (add-on to insulin therapy)

3.17 The outcomes compared in the NMA were those needed to populate the economic model, for example change from baseline in HbA_{1C}, systolic BP

and body weight and safety outcomes which included hypoglycaemia (severe and non-severe), urinary tract infection and genitourinary infection. For continuous outcomes the mean differences in change from the baseline values and associated 95% credible intervals between all interventions were obtained using Bayesian network meta-analysis. For dichotomous outcomes, the proportions of events were modelled in a logistic regression framework, and relative risks and associated 95% credible intervals were estimated.

3.18 For the dual therapy (as an add-on to metformin background therapy), several trials were available and uninformed random-effects model was applied. For the other 3 background therapies (as an add-on to metformin plus a sulfonylurea, metformin plus thiazolidinedione and insulin) all comparisons were informed by single trials (with the exception of empagliflozin vs placebo for insulin inadequate responders). To account for heterogeneity in these comparisons a conventional fixed-effect model was employed.

3.19 The manufacturer presented detailed results of NMA in tables 31 to 39 (pages 173-198) of its submission. The relevant results for 24 ± 4 weeks of treatment for key outcomes (change in HbA_1c, body weight and systolic blood pressure) in the comparisons of interest (empagliflozin versus canagliflozin, dapagliflozin and sitagliptin) in dual, triple and insulin add on therapies have been summarised in Appendix A. Results at 52 ± 4 weeks were based on less evidence and were similar to those for 24 ± 4 weeks. The results from the indirect comparison showed empagliflozin was in general comparable to the other SGLT2 inhibitors. Empagliflozin was more likely to result in reductions in body weight when compared with placebo and other therapies. Empagliflozin was statistically comparable to other treatment for adverse events of urinary tract and genital tract infections.

ERG comments

3.20 The ERG identified many potential weaknesses in the manufacturer's NMA. The ERG commented that the description of process of systematic review was inadequate lacking details on inclusion criteria for studies, justification for excluded studies, quality assessment and data extraction process of included studies. The ERG was also concerned that no sensitivity analyses or statistical tests were conducted for any of NMA.

3.21 The ERG also identified discrepancies between input data, identification of treatments, and WINBUGS codes which in its opinion were human errors, resulting from insufficient scrutiny during data extraction process. The ERG noted that it did not have sufficient time to check more of the coding and warned that more errors might have been found. It also noted that all the WinBUGS coding has not been provided by the manufacturer.

3.22 The ERG noted that the network for dual therapy on a background of metformin included only one study comparing metformin plus placebo with metformin plus a sulfonylurea (Charpentier et al 2001). The ERG was aware of many other published studies for this comparison. At clarification stage the manufacturer agreed that this study was included inappropriately and provided revised results after removing this study from the network. The ERG confirmed that removal of that study has minimal impact on the reported results but commented that it is not appropriate to exclude the studies comparing metformin with metformin plus a sulfonylurea as inclusion of these studies may have effect on base-line values used in the manufacture's model.

3.23 The ERG also identified that data on over-all hypoglycaemia, non-severe hypoglycaemia and urinary tract infection from many studies listed in the network were not used in the actual analysis in the WinBUGs. WinBUGs analysis also included some data which were not reported anywhere in the submission (see ERG report page 56-60 for details).

3.24 The ERG had access to an independent academic unpublished NMA comparing clinical effectiveness of dapagliflozin, canagliflozin and empagliflozin in dual therapy which found no clinically significant differences between empagliflozin and canagliflozin.

Adverse effects of treatment

3.25 The manufacturer presented adverse events reported in the individual studies (see tables 40-48 in the manufacturer's submission). In general, the proportions of patients who experienced any adverse events, any severe adverse events and adverse events leading to discontinuation of trial medication were similar between both empagliflozin groups and placebo across all trials. In most trials, the frequency of adverse events leading to discontinuation was numerically higher in the placebo group than in the empagliflozin groups. Adverse events occurring in more than 5% of patients in any randomised group in the trials included urinary tract infections (UTI), balanitis, upper respiratory tract infection, bronchitis, naso-pharyngitis, influenza, cough, diarrhoea, hypoglycaemia, hyperglycaemia, dyslipidaemia, hypertension, arthralgia, back-pain, pain in extremity, headache, dizziness and depression.

3.26 Hypoglycaemic events, urinary tract infection, genital infections, volume depletion and fractures were considered 'adverse event of special interest' and reported separately. The data showed that treatment with empagliflozin did not lead to an increase of hypoglycaemic events in most trials except in trials where empagliflozin was administered in addition to a sulfonylurea (12345.23 Met+SU sub-study and roll-over patients from 12345.23 Met+SU sub-study in extension study 12345.31) or insulin as background therapy (1245.33 and 1245.49). Across all trials, the frequencies of genital infections were consistently higher in the empagliflozin groups than in the comparator groups, although these infections were generally of mild or moderate intensity. The incidence of UTIs was similar across both empagliflozin groups and placebo, although it was reported that empagliflozin was associated with a greater frequency

of UTIs in females compared with placebo. In addition, both genital infections and UTIs were more common in females than males. The frequency of volume depletion was low across all clinical studies and comparable between all treatment groups with the highest incidences (1-2.8%) were observed in patients with moderate renal impairment in the study evaluating empagliflozin in patients with renal impairment (1245.36).

ERG comments

3.27 The ERG noted that the manufacturer's submission did not define which events were considered serious adverse events or what events led to discontinuation of the treatment. From the manufacturer's NMA the ERG noted that in both dual and triple therapy, the probability of overall hypoglycaemia including non-severe hypoglycaemia was numerically lower with empagliflozin 25 mg than with empagliflozin 10 mg but the difference was not statistically significant. It also highlighted that in comparison with empagliflozin the probability of hypoglycaemia was numerically lower than with dapagliflozin (in dual therapy) but was higher than canagliflozin (in triple therapy) although no comparison showed a statistically significant difference.

4 Cost-effectiveness evidence

Model structure

4.1 The manufacturer's submission included economic analyses comparing empagliflozin with dapagliflozin, canagliflozin and sitagliptin using the following regimens:

- Dual therapy in combination with metformin
- Triple therapy in combination with metformin and a sulfonylurea (glimepride)
- Triple therapy in combination with metformin and a thiazolidinedione (pioglitazone)

- Add-on treatment to insulin (with or without other anti-hyperglycaemic agents).

4.2 The manufacturer submitted a patient level state transition model which used Microsoft Excel as front and back ends (to store input parameters and to present the model output, respectively) but with the main calculations performed using Visual Basic Applications. It modeled individual patients' transitions between health states using a fixed cycle length of 6 months. The patient entered the model with a set of baseline patient characteristics and modifiable risk factors which included HbA_1c, total body weight, total cholesterol (TC) to high density lipoprotein (HDL) cholesterol ratio (TC:HDL) and systolic blood pressure. The value of these variables changed as the model simulation progressed, as a result of the effects of antidiabetic treatment and through natural progression, calculated from UK Prospective Diabetes Study (UKPDS number 68) risk equations.

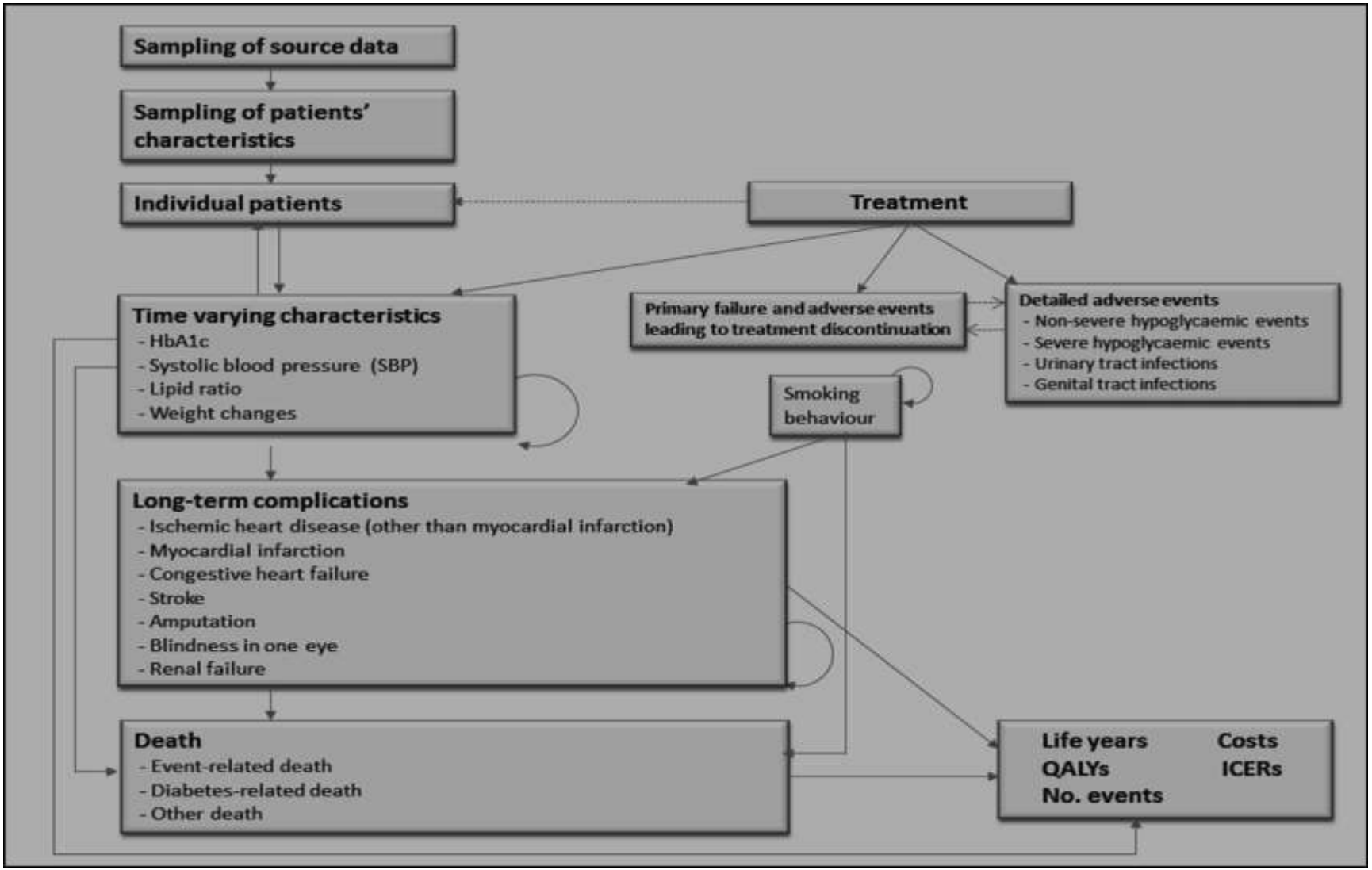
4.3 UKPDS risk equations are also used to predict the occurrence of 7 diabetes-related specific macro- and micro-vascular complications and death. Macro-vascular events predicted in the model included ischaemic heart disease, myocardial infarction, congestive heart failure and stroke. Micro-vascular events included amputation, renal failure and blindness in one eye.

4.4 The model also calculated the probability of drug-related hypoglycaemic events (non-severe and severe), other adverse events including urinary tract infections and genital infections, and treatment discontinuation caused by adverse events. A schematic of the model is presented in figure 2.

4.5 Simulated patients moved through the model in 6-month cycles over a 40-year time horizon. At the end of the first 6 month cycle, the UKPDS risk equations determined the probability of fatal and non-fatal complications in addition to diabetes-related deaths (myocardial infarction, congestive

heart failure, stroke and amputation) and deaths from other causes (estimated separately from UK life tables). If a patient survived beyond the first cycle it moved to the next cycle during which it remained at risk of treatment-related adverse events and long-term macro- or micro-vascular events. Once a diabetes-related death or death from other causes occurred, costs, life years and quality adjusted life years (QALYs) were updated and the simulation ended for that patient. An NHS and personal social services perspective was taken and costs and benefits were discounted at 3.5%.

Figure 2. Schematic diagram of the manufacturer's economic model



ERG comments

4.6 The ERG identified many issues with the logical construct and implementation of the manufacturer's model (detailed on the ERG report page 83 to 110). The ERG could only cross-check some of the visual basic codes but found many issues with them as well.

4.7 The ERG thought that in the model, it appeared that for each simulation, a single random number was used for each of 100 patients simulated together. That random number was used to determine whether an event would happen to the patient or not. Consequently it meant that patients who had same base-line characteristic would experience the same complications and adverse events and accrue identical cost and QALYs. According to the ERG, for a patient level simulation model, different random numbers should have been used for each simulated patients. Since the sampling is a key consideration within an individual patient model, the ERG thought this would invalidate the modelling in the submission.

4.8 The ERG considered that 300 iterations for100 patients done to generate model results was an unusually low number for both patients and iterations. The ERG was concerned whether the results obtained by such a low number of simulations would produce robust results given the limitations in the random sampling method (see section 4.7).

4.9 The ERG indicated that the manufacturers modelling of HBA_1c, SBP, lipids ratio did not appear to be in line with the UKPDS 68 equations and may be incorrect. The ERG also noted errors in the implementation utility decrement with the weight changes and adverse effects of the treatment.

4.10 The ERG also noted that the manufacturer's model only applied half the overall QALY decrements associated with adverse events and the complications of diabetes in calculation of the total QALYs. The ERG did not get time to correct this error and examine its effect on the ICERs.

However, the ERG thought it would largely invalidate the results of the manufacturer's model.

4.11 The other minor issues in the manufacturer's model identified by the ERG involved the adjustment to age and lipid levels, derivation of 6 monthly probabilities, treatment effect and second order sampling, derivation of UKPDS 68 covariance, rare occurrence of some patients appearing to die twice, random ordering of the sequencing of events and random sampling.

Model details

4.12 Most of the baseline characteristics of the modelled patients including baseline HbA_{1C}, SBP and the lipid ratio were sourced from base-line values of a subgroup of newly diagnosed patients in the UKPDS study. Age at initiation of dual therapy was obtained from EMPA-REG H2H (1245.28) while age at initiation of triple therapy and some characteristic like cardiovascular complications were sourced from trials, literature, and also from NICE clinical guideline 87.

4.13 Each patient was assigned baseline risk factors (baseline body mass index [BMI] and HbA_1c, SBP and lipid ratio levels) and a specific disease history (in terms of whether patients had experienced previous complications such as ischemic heart disease, myocardial infarction or stroke, and the number of years passed since the patient was diagnosed with diabetes). As patients progressed, their profiles were updated according to time varying risk factors as well as experienced adverse events and complications.

4.14 The model compared patients with the same baseline characteristics who would receive empagliflozin or comparator treatments. In total, 60,000 simulations were conducted, considering a sample of 30,000 patients per treatment arm (300 samples of 100 patients each). Simulated patients received a particular therapy until their HbA_1c level increased up to a specified threshold (7.5%), at which point they were initiated on insulin.

4.15 The treatment changes were also applied in 2 more situations; primary failure, that is lack of efficacy during the first treatment cycle and patients experiencing adverse events leading to discontinuation. However, in these situations patients received another treatment within the same treatment line and treatment efficacy of the initial treatment was retained. For patients on dual or triple oral antidiabetic therapy the next line of treatment was add-on to NPH insulin. For patients already on insulin, rescue insulin with glargine was added. Patients were assumed to remain on rescue insulin until the time horizon was reached or the patient had died.

4.16 At the beginning of each cycle the model checked whether a modification in the treatment was to be made. Due to addition of a treatment to the existing background therapy the HbA_{1C} level would decrease which was assumed to last for 1 year. After this period of controlled HbA1c, the HbA1c level started to increase, according to the UKPDS risk equations.

4.17 Treatment effectiveness was modelled as the impact of treatment on the HbA_1c levels, SBP and BMI. Each treatment was associated with an initial effect upon each of the risk factors (HbA_1c, SPB and weight changes). Lipid ratio (TC:HDL) which was also a factor in UKPDS equation assumed to remain constant. The manufacturer stated that it is because no clinical evidence on this outcome was identified.

4.18 With each new treatment combination, changes in HbA_1c and SBP followed three stages. Firstly, a drop in the levels of the risk factors occurred during the first cycle after treatment initiation. This effect was maintained for a period of time (assumed to be 1 year in the base-case). Once the maintenance period was over, the levels of the risk factors increased based on the UKPDS risk equations.

4.19 To model the treatment effect on weight change, it was assumed that the weight change would happen gradually (distributed equally in each cycle) as long as the patient continued receiving the same treatment. The weight change was assumed to be maintained over 6 months after the full weight

change had been achieved. Whenever a patient switched to a different treatment, it was assumed that the weight at the beginning of the new treatment would be equal to their baseline weight plus the natural weight gain (that is 0.1 kg multiplied by the number of years since treatment initiation). The impact on weight of the previous treatments was not taken in to the account.

4.20 Treatment-related adverse events included in the model were hypoglycaemic events (severe versus non-severe), urinary tract infections and genital infections. Hypoglycaemias could occur as long as patients were on treatment in contrast to urinary tract and genital infections which were assumed to occur only within the first cycle after initiation of the treatment.

4.21 In each cycle a patient was at risk of dying as a result of diabetes or other causes. The risk of event-related mortality and diabetes-related mortality followed the UKPDS equations and was dependent on previous complications. Death from other causes also followed the corresponding UKPDS risk equation but it was not influenced by the occurrence of other diabetes related complications.

4.22 To model the clinical effectiveness, data derived from the manufacturer's NMA were used in the model most of the time. The results at week 24 from the NMA were used for the base-case analysis in preference to results at week 52, which were used in a sensitivity analysis. The clinical effectiveness data used in the model have been summarised in the table 56, 57 and 58 of the manufacturer's submission. When insulin was added on to existing treatments the efficacy estimates from an observation study (Khunti et al 2013) were used to model the impact of adding insulin.

4.23 Quality of life values were attached to the health states of the model, these being largely drawn from UKPDS publications. Utility decrements associated with adverse events were obtained from the NICE technology appraisal of dapagliflozin (TA288) while values for BMI changes were

taken from another study (Bagust and Beale 2005). For this, the average baseline height and weight of patients entering the model was considered and the disutility was proportionally allocated per kilogram of weight increased. The utility values used in the base-case analysis are summarised in the table 8.

Table 8 Summary of utility values used in the manufacturers' model

State	Utility value	Reference
Diabetes without complications	0.77	UKPDS 62
IHD	-0.09	Dapa ERG (UKPDS 62)
MI	-0.055	Dapa ERG (UKPDS 62)
CHF	-0.108	Dapa ERG (UKPDS 62)
Stroke	-0.164	Dapa ERG (UKPDS 62)
Amputation	-0.28	Dapa ERG (UKPDS 62)
Blindness in one eye	-0.074	Dapa ERG (UKPDS 62)
Renal failure	-0.0963	Sullivan et al 2011
Hypoglycaemic events (non-severe)	-0.0035	NICE clinical guideline
Hypoglycaemic events (severe)	-0.01	NICE clinical guideline
UTIs	-0.00282	Dapa ERG (UKPDS 62)
GTIs	-0.00282	Dapa ERG (UKPDS 62)
Weight gain (per kg)	-0.0159	Bagust and Beale (2005)

4.24 The utility decrement for adverse events of the treatment was applied once per event (in a single cycle) while decrements due to complications were applied for the rest of the time horizon after the patient experienced that event. For a patient who experienced multiple complications, it was assumed that multiple decrements had an additive effect. For weight changes, it was assumed that weight loss did not have an impact on utilities while weight gain would result in a decrease of utility. This disutility was applied whenever the weight gain was higher than the baseline weight of the patient as a result of a treatment-related weight gain. No disutility was applied for the assumed natural increase of weight.

4.25 The manufacturer stated that NHS reference costs related to the management of long-term conditions were inappropriate for modelling because these cover a number of different and potentially irrelevant conditions which may not be representative of the true cost of diabetes

management. Therefore, the manufacturer sourced the relevant costs of management of complications and adverse events from the published studies (mainly from UKPDS) and previous NICE appraisals and inflated them to the 2013 prices using the hospital and community health services (HCHS) pay and price inflation. No cost was allocated to weight gain as no reliable data were identified. The medication costs were based on British National Formulary No. 66 (BNF) and NHS drug tariff. The cost of insulin treatment was based on the average units of insulin used plus costs of blood sugar test strips and other activities per day. The direct annual per patient medical cost of following up patients was estimated to be £483. This cost was applied to all patients, independently of whether they had experienced a complication.

ERG comments

4.26 The ERG commented that some baseline characteristics taken from UKPDS may not be representative of a diabetes population noting that people over 66 years were not recruited in the UKPDS and median age was only 54 years. The ERG pointed out that the trial data on lipid ratio were available from at least one trial (EMP-REG-MET) and should have been used in the model. It however, agreed that clinical data more or less matched the assumption of no effect of the treatment on the ratio of total cholesterol to high density lipoproteins used in the model.

4.27 The ERG also noted that in the model, to calculate absolute effect of treatment, the manufacturer had added the effect observed with placebo (for example decrease in HbA_{1C} associated with placebo) to the treatment effect derived from the NMA. The ERG was of the view that placebo effect should have been subtracted from the treatment effect. At the clarification stage, the manufacturer justified its approach and also provided revised ICERs using the approach suggested by the ERG. The ERG noted that the differences between the 2 approaches in terms of accrued QALYs and cost were small and would not cause any substantial difference in the base-case ICERs.

4.28 The ERG considered the assumption that decrease in weight would be maintained only for 6 months after treatment was pessimistic and would not adequately reflect the benefit of decrease in body weight with empagliflozin observed in the trials. It also noted that the assumption that weight loss would not have an impact on utility while weight gain would result in decrement in utility was conservative which would disadvantage the drugs which reduce weight, like empagliflozin.

4.29 The ERG noted that the annual cost of insulin treatment was sourced from the manufacture's own study. The cost of insulin pen and needle were similar to the cost reported in the NICE clinical guideline 87 but the test strip costs were on the higher side. It agreed that this would not affect the overall results.

Manufacturer's base case results and sensitivity analysis

4.30 The manufacturer's presented base-case ICERs in a fully incremental analysis. The results are summarised in table 9.

Table 9. Base-case ICERs in the manufacturer's analysis

Dual therapy (on background metformin)					
Intervention	**QALY**	**Δ QALY**	**Cost**	**Δ Cost**	**ICER**
Sitagliptin 100 mg	7.425	-	£32,046	-	-
Dapagliflozin 10 mg	7.404	-0.021	£32,179	£133	Dominated by sitagliptin 100 mg
Canagliflozin 100 mg	7.415	-0.01	£32,300	£255	Dominated by sitagliptin 100 mg
Empagliflozin 25 mg	7.433	0.008	£32,353	£307	£38,425
Empagliflozin 10 mg	7.424	-0.009	£32,654	£301	Dominated by empagliflozin 25 mg
Canagliflozin 300 mg	7.418	-0.015	£32,737	£384	Dominated by empagliflozin 25 mg
Triple therapy (on background metformin plus a sulfonylurea)					
Canagliflozin 100 mg	6.98	-	£31,217	-	-
Sitagliptin 100 mg	6.959	-0.021	£31,365	£148	Dominated by canagliflozin 100 mg
Empagliflozin 10 mg	6.991	0.011	£31,409	£192	£17,445

Empagliflozin 25 mg	6.978	-0.013	£31,557	£148	Dominated by empagliflozin 10 mg
Canagliflozin 300 mg	6.976	-0.015	£32,087	£679	Dominated by empagliflozin 10 mg
Triple therapy (on background metformin plus a thiazolidinedione)					
Sitagliptin 100 mg	6.967	-	£31,303	-	-
Canagliflozin 100 mg	6.983	0.016	£31,329	£26	£1,644
Empagliflozin 25 mg	6.999	0.016	£31,486	£157	£9,806
Canagliflozin 300 mg	6.978	-0.021	£31,866	£380	Dominated by empagliflozin 25 mg
Empagliflozin 10 mg	6.996	-0.003	£31,869	£383	Dominated by empagliflozin 25 mg
In combination with insulin					
Canagliflozin 100 mg	6.944	-	£30,418	-	-
Dapagliflozin 10 mg	6.953	0.009	£30,545	£128	£14,178
Empagliflozin 10 mg	6.947	-0.006	£30,564	£18	Dominated by dapagliflozin 10 mg
Empagliflozin 25 mg	6.948	-0.005	£30,653	£108	Dominated by dapagliflozin 10 mg
Sitagliptin 100 mg	6.912	-0.041	£30,682	£137	Dominated by dapagliflozin 10 mg
Canagliflozin 300 mg	6.957	0.004	£30,842	£296	£74,075

4.31 The manufacturer conducted a range of sensitivity analyses which included

- applying clinical effectiveness results at week 52 instead of results at week 24
- alternative set of utility values taken from the UK catalogue of utilities with and without applying age-related disutility
- assuming discontinuation rate similar to empagliflozin 10 mg
- varying the adverse events by applying the lowest number of adverse events observed across treatments

- assuming that BMI changes did not impact the incidence of CHF or the disutility of patients due to weight changes
- assuming that the weight change would initially occur over the first cycle and the weight change would be maintained over one year instead of gradual increase over the treatment period
- assuming the duration of treatment effect would last for two years instead of one year.
- varying the life time horizon from 40 years to 10 years.
- assuming different discount rates (0% and 6%) on costs and effects.

4.32 All performed sensitivity analyses confirmed no significant difference between treatments and the difference in cost and QALYs were insignificant across comparison.

4.33 The manufacturer's submission also detailed the verification exercises undertaken to check internal validity of the model (see page 326). These included checking face validity of the model output after each cycle and performing some 'extreme' sensitivity analyses (assuming cost of the drug and other resources, efficacy of the intervention, utility decrement due to complication, probability of adverse events and discount rates to be 0 and assuming probability of treatment discontinuation and treatment failure to be 1). The manufacturer did not provide any data but reported that the results were logical and intuitive and confirmed accurate programming of the model.

4.34 To check the validity of the model further, the manufacturer evaluated exenatide against NPH insulin as a third-line treatment and compared the model results to the cost-effectiveness results underpinning recommendations in the NICE clinical guideline 66. The results showed that in the manufacturer's model both exenatide and NPH insulin accrued substantially more QALYs and less costs compared with the analyses

done for the NICE clinical guideline 66. The manufacturer thought that the difference might have occurred because of different assumptions regarding some base-line characteristics (for example smoking) and different utility decrements applied for hypoglycaemia and nausea.

4.35 As a further validation exercise for its model, the manufacturer submitted an economic evaluation of empagliflozin based on IMS-CORE diabetes model (see appendix 12 of the manufacturer's submission). For that, the manufacturer compared empagliflozin with dapagliflozin in dual therapy (in combination with metformin) as well as an add-on to insulin and with canagliflozin in triple therapy (in combination with metformin and a sulfonylurea) in a series of pairwise analyses. The results showed that the patients in each arm accrued more QALYs and costs than the manufacture's model. However, the incremental differences in QALYs and costs between empagliflozin and other SGLT2 inhibitors were minimal. From that the manufacturer concluded that the cost-effectiveness of empagliflozin could be considered comparable to its precursors SGLT2-inhibitors.

ERG comments

4.36 The ERG re-ran the model removing second order uncertainty. Due to the nature of the model re-running the base case analyses produces different probabilistic and deterministic results. Overall the differences in total cost were only a few hundreds of pounds, and differences between QALYs amounts were tiny - fewer than a few days between treatments. The ERG highlighted the results could only be considered reliable if the ERG's concerns regarding the structure of the model were proved wrong. The ERG did not report any exploratory analysis.

Innovation

4.37 The manufacturer stated that all of the currently available classes of antidiabetic agents have some limitations and SGLT2 inhibitors represent a novel treatment by providing HbA_{1C} control and associated weight and SBP reductions. In addition, this class is associated with low incidence of

hypoglycaemia and other adverse events. The manufacturer also highlighted the ease of medication with an oral tablet taken once a day. Clinical specialists noted that empagliflozin is 3rd selective sodium glucose-cotransporter 2 (SGLT-2) inhibitor to get marketing authorisation but unlike other drugs in this group it has been demonstrated to be effective in modest renal disease and could be most valuable for patients with mild renal disease.

5 Equalities issues

5.1 During scoping process it was highlighted that the vast majority of the UK Muslim population have South Asian family origin in whom type 2 diabetes is particularly prevalent. It was noted that there is no guidance to treat people with type 2 diabetes mellitus who may wish to fast during the month of Ramadan. The initial view was that issues related to differences in prevalence or incidence of a disease between population groups cannot be addressed in a technology appraisal and lack of guidance for treating diabetic patients who may wish to fast may be better addressed in the relevant clinical guideline. However, this was not considered to be an equality issue that can be addressed in a Technology Appraisal.

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