NICE National Institute for Health and Care Excellence

NICE guidance

Dapagliflozin in combination therapy for treating type 2 diabetes

Technology appraisal guidance
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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 is partially replaced by TA418.

1 Recommendations

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

1.3 This recommendation has been updated and replaced by NICE's technology appraisal guidance on dapagliflozin in triple therapy for treating type 2 diabetes.

1.4 People currently receiving dapagliflozin in a dual therapy regimen that is not recommended for them in 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop.

2 Information about dapagliflozin

2.1 Dapagliflozin (Forxiga, Bristol-Myers Squibb and AstraZeneca) is a sodium–glucose cotransporter-2 (SGLT-2) inhibitor that blocks the reabsorption of glucose in the kidneys and promotes excretion of excess glucose in the urine. It has a UK marketing authorisation 'in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control 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 agents including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control'.

The subject of this appraisal is the add-on therapy indication.

2.2 The summary of product characteristics lists the following adverse reactions for dapagliflozin: hypoglycaemia (when used with a sulfonylurea or insulin), urinary tract and genital infection, back pain, dysuria, polyuria, dyslipidaemia and elevated haematocrit. Dapagliflozin is not recommended for use in people with moderate to severe renal impairment (patients with a creatinine clearance rate of less than 60 ml/min or an estimated glomerular filtration rate of less than 60 ml/min/1.73 m^2) because its efficacy is dependent on renal function. Dapagliflozin is also not recommended for use in combination with pioglitazone. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The list price of dapagliflozin is £36.59 for 28 5-mg or 10-mg tablets (excluding VAT; BNF edition 64). Dapagliflozin is administered orally as a single dose of 10 mg per day. Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The manufacturers' submission

The Appraisal Committee considered evidence from a number of sources.

Clinical effectiveness

3.1 The manufacturers carried out a systematic literature search to identify all relevant trials of dapagliflozin and potential comparators in adults with type 2 diabetes. The manufacturers identified 5 randomised controlled trials of dapagliflozin (10 mg once daily): 3 in patients with type 2 diabetes inadequately controlled with metformin alone (studies 14, 12 and 4), and 2 in patients with type 2 diabetes inadequately controlled with insulin with or without oral antidiabetic drugs (studies 9 and 6).

3.2 Of the 3 trials of dapagliflozin as an add-on to metformin, 2 were placebo controlled with follow-up of 24 weeks (studies 14 and 12) and 1 compared dapagliflozin with a sulfonylurea for up to 52 weeks of follow-up (study 4). The primary outcomes assessed were change in HbA_{1c} from baseline (studies 14 and 4) and changes in body weight from baseline (study 12). Secondary outcomes included change in fasting plasma glucose, the proportion of patients whose HbA_{1c} levels reached a specific target, change in body weight, change in blood pressure, the proportion of patients reporting hypoglycaemia, adverse reactions and tolerability. Baseline patient characteristics in the 3 trials were broadly similar: mean age 52.7 to 60.8 years, HbA_{1c} level 7.16% to 8.11%, body weight 86.1 kg to 92.1 kg and systolic blood pressure 126.0 mmHg to 135.9 mmHg.

3.3 The 2 trials of dapagliflozin as an add-on to insulin were both placebo controlled, with follow-up of 12 weeks (study 9) and 24 weeks (study 6). The primary outcome assessed was change in HbA_{1c} from baseline. Secondary outcomes included change in fasting plasma glucose, the proportion of patients whose HbA_{1c} reached a specific target, change in body weight, change in the daily dose of insulin, adverse reactions and tolerability. Baseline patient characteristics in the 2 trials were broadly similar: mean age 55.7 to 59.3 years, HbA_{1c} level 8.40%

to 8.57%, body weight 94.5 kg to 103.4 kg and systolic blood pressure 128.9 mmHg to 140.6 mmHg.

3.4 In the add-on to metformin trials (studies 12 and 14), dapagliflozin was associated with a statistically significant reduction in HbA_{1c} compared with placebo at 24 weeks. In study 14 (n=272), reduction in HbA_{1c} was −0.84% for dapagliflozin versus −0.30% for placebo ($p<0.0001$). In study 12 (n=182), reduction in HbA_{1c} was −0.39% for dapagliflozin compared with −0.10% for placebo ($p<0.0001$). Dapagliflozin was associated with a statistically significant reduction in body weight compared with placebo at 24 weeks in both study 12 (−2.96 kg versus −0.88 kg, $p<0.0001$) and study 14 (−2.86 kg versus −0.89 kg, $p<0.0001$). Dapagliflozin was associated with a reduction in systolic blood pressure compared with placebo at 24 weeks in both study 14 (−5.1 mmHg versus −0.2 mmHg, p value not reported) and study 12 (−2.70 mmHg versus +0.10 mmHg, $p=0.06$). Dapagliflozin was not associated with a statistically significant increased risk of hypoglycaemia compared with placebo at 24 weeks in either study.

3.5 In study 4 (n=814), dapagliflozin was shown to be non-inferior (based on a non-inferiority margin of 0.35%) to a sulfonylurea with respect to HbA_{1c} reduction at 52 weeks. Dapagliflozin was associated with a statistically significant change in body weight compared with a sulfonylurea at 52 weeks (−3.22 kg versus +1.44 kg, $p<0.0001$). Dapagliflozin was associated with a statistically significant change in systolic blood pressure compared with a sulfonylurea at 52 weeks in study 4 (−4.3 mmHg versus +0.8 mmHg, $p<0.0001$). Dapagliflozin also resulted in a statistically significantly lower proportion of patients experiencing at least 1 hypoglycaemic event (3.5% versus 40.8%, $p<0.0001$) compared with a sulfonylurea by 52 weeks.

3.6 In the add-on to insulin trials, dapagliflozin was associated with a reduction in HbA_{1c} compared with placebo at 12 weeks (study 9) and 24 weeks (study 6). In the 12-week study (n=47), the change in HbA_{1c} was −0.61% for dapagliflozin versus +0.09% for placebo (p value not reported). In the 24-week study (n=387), the reduction in HbA_{1c} was −0.96 for dapagliflozin versus −0.39 for placebo ($p<0.001$). Dapagliflozin was associated with a statistically significant reduction in body weight (−1.67 kg versus +0.02 kg, $p<0.0001$) and systolic blood pressure (−6.9 mmHg versus −3.9 mmHg, $p=0.02$) compared with placebo at 24 weeks. A

higher proportion of patients treated with dapagliflozin had experienced at least 1 hypoglycaemic event (42.3% versus 35.0%) compared with placebo by 24 weeks. Dapagliflozin was associated with a statistically significant reduction in the calculated mean daily insulin dose (−1.16 versus +5.08 international units per day, $p<0.0001$) compared with placebo at 24 weeks.

3.7 The manufacturers conducted pre-planned analyses to determine if there were any variations in the clinical effectiveness of dapagliflozin for the following subgroups (as defined by the manufacturers): race, ethnicity, baseline HbA_{1c}, age, sex and baseline body mass index (BMI). Subgroup analyses were conducted on pooled data as well as some of the individual studies of dapagliflozin. The manufacturers reported that no statistically significant differences in clinical effectiveness across subgroups were observed, except for baseline HbA1c. Dapagliflozin treatment generally resulted in greater HbA_{1c} reductions from baseline in people with higher baseline HbA_{1c}.

3.8 The manufacturers conducted network meta-analyses to compare the clinical effectiveness of dapagliflozin as an add-on to metformin or insulin with comparator therapies listed in the scope. Four outcomes were assessed: mean change in HbA_{1c} from baseline, mean change in weight from baseline, mean change in systolic blood pressure from baseline, and the proportion of patients experiencing at least 1 hypoglycaemic episode. Random-effects models were selected over fixed-effects models because of variations in the study characteristics. The manufacturers presented analyses that were both adjusted and unadjusted for the potential modifying effects of baseline HbA_{1c}.

3.9 For dapagliflozin as an add-on to metformin, the manufacturers created separate networks for the outcome of systolic blood pressure at 24 weeks (±6 weeks) and for the other 3 outcomes at 24 weeks (±6 weeks) and 52 weeks (±6 weeks). For the 24-week analysis of systolic blood pressure, the network included dapagliflozin, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, sulfonylureas, thiazolidinediones and placebo in 8 studies. For the 24-week analysis of outcomes other than systolic blood pressure, the network included dapagliflozin, DPP-4 inhibitors, GLP-1 analogues, thiazolidinediones and placebo in 15 studies. For the 52-week analysis, the network included dapagliflozin, DPP-4 inhibitors, thiazolidinediones and sulfonylureas in 6 studies.

3.10 The numerical results of the 24-week network meta-analyses for the add-on to metformin comparisons were provided as academic in confidence. After adjusting for baseline HbA_{1c}, dapagliflozin was associated with a statistically significant reduction in HbA_{1c} compared with placebo. No statistically significant differences in the change in HbA_{1c} were reported between dapagliflozin and other therapies. Dapagliflozin was associated with a statistically significant reduction in body weight compared with placebo, DPP-4 inhibitors and thiazolidinediones, but not compared with GLP-1 analogues. Dapagliflozin was associated with a statistically significant reduction in systolic blood pressure compared with placebo and sulfonylureas. However, no statistically significant differences in change in systolic blood pressure were reported between dapagliflozin and the other 3 drug therapies. No statistically significant differences in the risk of hypoglycaemia were reported between dapagliflozin and other drug therapies.

3.11 For dapagliflozin as an add-on to insulin, the manufacturers conducted a single network meta-analysis for all outcomes except systolic blood pressure at 24 weeks (±8 weeks). The network included dapagliflozin, DPP-4 inhibitors, thiazolidinediones and placebo in 4 studies. The 12-week study of dapagliflozin (study 9) and 3 other studies comparing thiazolidinediones with placebo were excluded from this analysis because they allowed up-titration of insulin to maintain glycaemic control. One of the studies identified, a study comparing thiazolidinediones with placebo, was excluded from the main analysis of mean change in HbA_{1c} at 24 weeks because of the higher reported baseline HbA_{1c} values compared with the other 3 studies. The outcome of change in systolic blood pressure at 24 weeks could not be analysed because, of the 4 identified studies, 3 either did not report changes in systolic blood pressure or involved up-titration of insulin.

3.12 Results of the 24-week network meta-analyses for the add-on to insulin comparisons were provided as academic in confidence. Dapagliflozin was associated with a statistically significant reduction in HbA_{1c} compared with placebo. No statistically significant differences in changes in HbA_{1c} were reported between dapagliflozin and DPP-4 inhibitors. When the study comparing thiazolidinediones with placebo was included as a sensitivity analysis, dapagliflozin was less effective in reducing HbA_{1c} compared with thiazolidinediones. Dapagliflozin was associated with a statistically significant reduction in body weight compared with placebo and DPP-4 inhibitors, and

changes were reported to be similar to thiazolidinediones. Dapagliflozin was associated with a statistically significantly lower risk of experiencing a hypoglycaemic event compared with thiazolidinediones. However, no statistically significant differences were reported for the comparison of dapagliflozin with DPP-4 inhibitors and placebo.

3.13 Data on the risks of adverse reactions associated with dapagliflozin were presented using pooled results from the placebo-controlled randomised controlled trials, including dapagliflozin as monotherapy and add-on therapy. Most results presented were based on short-term studies (24 weeks). The manufacturers reported that dapagliflozin was associated with a higher incidence of genital and urinary tract infections and a slightly higher incidence of volume depletion events (hypotension, hypovolaemia or dehydration) compared with placebo. Renal impairment or failure events were reported for a small proportion of patients (less than 1.5%) with no apparent difference between treatment groups. The manufacturers reported that the incidence of cancer was similar between patients who received dapagliflozin (1.47%) and patients who received placebo (1.35%). However, rates of bladder cancer (0.16% versus 0.03%), prostate cancer (0.34% versus 0.16%) and breast cancer (0.40% versus 0.22%) were higher in patients treated with dapagliflozin than in those treated with placebo respectively. In terms of cardiovascular safety, a meta-analysis of 14 randomised controlled trials did not find any evidence that dapagliflozin is associated with increased cardiovascular risk for a composite end point of cardiovascular death, myocardial infarction and stroke (hazard ratio [HR] 0.79, 95% CI 0.54 to 1.17).

3.14 Evidence on the clinical and cost effectiveness of dapagliflozin in triple therapy for people with type 2 diabetes that is inadequately controlled with metformin and a sulfonylurea was submitted in an addendum to address the comparisons specified in the scope. The manufacturers stated that dapagliflozin is currently being studied in an ongoing trial as a triple therapy add-on to 2 other oral agents. Therefore, data were pooled from a subset of people who were given metformin and a sulfonylurea at baseline from 2 placebo-controlled trials (studies 18 and 19), which were designed to assess the efficacy and safety of dapagliflozin in older people (average age 63 to 64 years) with type 2 diabetes and cardiovascular disease. A post-hoc analysis of this subset was conducted for changes from baseline in HbA_{1c}, weight, systolic blood pressure and hypoglycaemic events at 24 weeks (results provided as academic in confidence).

3.15 No trials of dapagliflozin compared with active comparators in triple therapy were reported by the manufacturers. Therefore, the assessment of the clinical effectiveness of dapagliflozin compared with DPP-4 inhibitors, GLP-1 analogues and thiazolidinediones was based on indirect evidence. The manufacturers did not conduct a systematic review of triple therapy for people with type 2 diabetes that is inadequately controlled with metformin and a sulfonylurea. However, they referred to a literature review of add-on therapy to metformin and sulfonylureas for type 2 diabetes produced in 2009 by the Canadian Agency for Drugs and Technologies in Health. A summary of the results of this review suggested that DPP-4 inhibitors, GLP-1 analogues and thiazolidinediones were associated with statistically significant reductions in HbA_{1c} compared with continued therapy with metformin and sulfonylureas. No statistically significant differences in HbA_{1c} reduction were reported between DPP-4 inhibitors, GLP-1 analogues and thiazolidinediones. Thiazolidinediones, but not DPP-4 inhibitors or GLP-1 analogues, were associated with statistically significant weight gain compared with metformin and sulfonylureas. The manufacturers noted that since 2009, new data have become available including studies of the DPP-4 inhibitors linagliptin and saxagliptin.

Cost effectiveness

3.16 The manufacturers submitted an economic model to evaluate the cost effectiveness of dapagliflozin for use:

- in dual therapy as an add-on to metformin in adults with type 2 diabetes for whom metformin alone (with diet and exercise) does not provide adequate glycaemic control
- as an add-on to insulin (with or without other oral antidiabetic therapies) when the underlying treatment regimen including insulin does not provide adequate glycaemic control and
- in triple therapy for people with type 2 diabetes that is inadequately controlled with metformin and a sulfonylurea.

  For the add-on to metformin analysis, the comparator treatments were sulfonylureas, DPP-4 inhibitors and thiazolidinediones (pioglitazone). For the

add-on to insulin analysis, the comparator treatments were DPP-4 inhibitors. For the triple therapy analysis, the comparator treatments were DPP-4 inhibitors, thiazolidinediones and GLP-1 analogues.

3.17 The manufacturers developed a simulation model run within an Excel front end but with the main calculations performed using C++ programming. The patient cohort entered the model with a set of baseline patient characteristics and modifiable risk factors that included HbA_{1c}, total body weight, total cholesterol to high-density lipoprotein cholesterol ratio 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 the UK Prospective Diabetes Study (UKPDS number 68) risk factor equations. The model then predicted the incidence of 7 specific macro- and microvascular events on the basis of the UKPDS 68 event risk equations. Macrovascular events predicted in the model included ischaemic heart disease, myocardial infarction, congestive heart failure and stroke. Microvascular events included amputation, nephropathy (end-stage renal failure) and blindness. 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.

3.18 Simulated patients moved through the model in 6-month cycles over a 40-year time horizon. At the start of the model, patients were assumed to have no complications associated with type 2 diabetes. 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, they moved to the next cycle in which they remained at risk of treatment-related adverse events and long-term macro- or microvascular events. Once a diabetes-related death or death from other causes occurred, then costs, life years and quality-adjusted life years (QALYs) were updated and the simulation ended for that patient.

3.19 The model simulated a cohort of patients who received dapagliflozin (the 'treatment' cohort), and a cohort with the same baseline characteristics who received comparator treatments (the 'comparator' cohort). Simulated patients in each cohort received a particular therapy until their HbA_{1c} increased up to a

specified threshold (representing inadequate glycaemic control), at which point they stopped therapy and moved on to the second-line therapy (assumed to be the same in both cohorts). For the metformin and insulin add-on analyses, the model included up to 2 additional therapy lines after dapagliflozin and the comparator. The manufacturers assumed that second-line therapy was metformin and insulin, and third-line therapy for the remainder of the patients' simulated lifetime was intensified insulin (assumed to be a 50% increase from the starting dose). For the insulin add-on analysis, second-line therapy was intensified insulin for the remainder of the simulation. For the triple therapy analysis, all comparator triple therapies were assumed to be preceded by dual therapy with metformin and a sulfonylurea. The manufacturers assumed that after triple therapy, all patients would receive metformin and insulin. An NHS and personal social services perspective was taken and costs and benefits were discounted at 3.5%.

3.20 For the metformin add-on analyses, baseline patient characteristics, clinical-effectiveness data and adverse event rates were taken from study 4 for the comparison of dapagliflozin and a sulfonylurea and from the manufacturers' network meta-analysis (at 24 weeks) for all of the other comparisons. For the insulin add-on analysis, baseline patient characteristics, clinical-effectiveness data and adverse event rates were taken from the network meta-analysis (at 24 weeks). For the triple therapy analysis, clinical-effectiveness data were drawn from a pooled analysis of a subset of patients treated with dapagliflozin in 2 clinical trials (studies 18 and 19) and the Canadian Agency for Drugs and Technologies in Health's review of oral antidiabetic drugs as triple therapy. The manufacturers commented that the baseline patient characteristics from studies 18 and 19 were not representative of the triple therapy patient population. Therefore, baseline patient characteristics were taken from study 4 comparing dapagliflozin with a sulfonylurea in patients with type 2 diabetes inadequately controlled with metformin alone.

3.21 The HbA_{1c} thresholds for switching treatment were based on baseline HbA_{1c} values taken from the same sources. In the metformin add-on analyses, a threshold value of 7.72% taken from study 4 was used for the comparison of dapagliflozin and a sulfonylurea and a value of 8.17% from the metformin add-on network meta-analyses was used for the comparison of dapagliflozin with DPP-4 inhibitors and thiazolidinediones. In the insulin add-on analysis, a threshold value

of 8.90% was used based on the insulin add-on network meta-analyses. In the triple therapy analysis, the HbA_{1c} threshold for switching treatment was 7.72%, taken from study 4.

3.22 The economic model included changes in weight associated with treatment. UKPDS risk equations based on BMI were included in the model. Therefore, changes in patient weight over time were converted to a BMI value based on baseline weight and height characteristics. If a treatment was associated with weight loss, this involved assumptions about how long the weight loss was maintained for along with the subsequent time until the loss of effect and return to the baseline body weight. In the dapagliflozin therapy group for the add-on to metformin and insulin analyses, weight reduction was assumed to be maintained for 2 years in the model based on 2-year extension data from the trial of dapagliflozin compared with a sulfonylurea. After year 2, weight was assumed to return to its baseline value until treatment was switched in a linear trend for the dapagliflozin therapy group. After this, a natural progression in weight gain of 0.1 kg per year was assumed. Because no data were available for DPP-4 inhibitors, the same assumptions were applied. All other treatments were associated with a weight gain, which was applied in the first year, after which a natural progression in weight gain of 0.1 kg per year was assumed.

3.23 The model estimated the impact of macro- and microvascular complications of diabetes, changes in body weight and other adverse events on health-related quality of life. An age-dependent baseline utility function was derived from the Department of Health Survey for England (2003) which collected EQ-5D data from patients with no major complications. Data on the impact on health-related quality of life of diabetes complications were taken from UKPDS (number 62) except for end-stage renal disease. In the UKPDS 62, the EQ-5D questionnaire was completed by 3667 UK patients. This resulted in the following utility decrements: −0.09 (ischaemic heart disease), −0.055 (myocardial infarction), −0.108 (congestive heart failure), −0.164 (stroke), −0.28 (amputation) and −0.074 (blindness). The impact of end-stage renal disease on health-related quality of life was taken from the Health Outcomes Data Repository, a database of diabetic inpatients treated at Cardiff and Vale National Health Service Hospitals Trust, resulting in a loss in utility of −0.263. The impact of change in body weight on health-related quality of life was taken from a study of 100 Canadian patients with type 2 diabetes who completed a time trade-off exercise, which was

commissioned by the manufacturers. Separate values were calculated for the changes in utility caused by a 1-unit decrease (+0.0171) or increase (−0.0472) in BMI. The impact of hypoglycaemic events on health-related quality of life was taken from a study by Currie et al. (2006) that estimated separate EQ-5D utility decrements for symptomatic, nocturnal and severe events in UK patients with type 2 diabetes. The resulting utility decrements reported in the manufacturers' submissions were −0.042, −0.0084 and −0.047 respectively. The impact of urinary tract infections on health-related quality of life was taken from a study of urinary tract infections in ambulatory women, resulting in a utility decrement of −0.00283. In the absence of any other available data, the same utility values were used for genital infections.

3.24 The economic model included the acquisition costs of antidiabetic drugs taken from the England and Wales drug tariff (February 2012). The cost of insulin in the model was applied as a cost per kilogram of body weight per day, and therefore, varied in line with changes in patient body weight in the model simulation. The manufacturers assumed that insulin used as second- or third-line treatment in the model (with or without an oral antidiabetic) involved a 50% increase in dose over the initial starting dose in the add-on to metformin analysis, and a 25% increase in the add-on to insulin analysis.

3.25 The annual costs of macro- and microvascular diabetic complications, except for end-stage renal failure, were taken from UKPDS 65, which calculated the healthcare resource use of 3488 patients with type 2 diabetes. The UKPDS 65 study provided estimates of the first year event costs and the subsequent annual maintenance costs for patients who survived until the end of the simulation. The annual cost of end-stage renal failure (£34,806) was based on the weighted average cost of automated peritoneal dialysis, continuous ambulatory peritoneal dialysis, hospital haemodialysis and satellite unit-based haemodialysis, taken from a separate UK-based study. The cost of a severe hypoglycaemic event (£390) was taken from a study that measured health service costs incurred by 320 patients with type 2 diabetes in Germany, Spain and the UK who had experienced at least 1 hypoglycaemic event in the previous year. It was assumed that symptomatic and nocturnal hypoglycaemic events were not associated with any treatment costs. Urinary tract infections and genital infections were associated with the cost of a GP visit (£36). The costs of renal monitoring (£39), based on a GP visit and urine sample, were also included in the first year of the

model only for the dapagliflozin treatment group. Treatment discontinuation was also assumed to incur the cost of a GP visit.

3.26 The manufacturers' base-case deterministic cost-effectiveness results for the add-on to metformin analyses found that the comparison between dapagliflozin and a sulfonylurea resulted in an incremental cost-effectiveness ratio (ICER) of £2,671 per QALY gained (incremental costs £1,246, incremental QALYs 0.467). The comparisons between dapagliflozin and DPP-4 inhibitors and between dapagliflozin and thiazolidinediones found that dapagliflozin resulted in higher QALYs (incremental gains of 0.02 and 0.42 respectively) and lower costs (−£149 and −£60 respectively). Dapagliflozin therefore dominated both comparator treatments. For the add-on to insulin analysis, the comparison between dapagliflozin and DPP-4 inhibitors resulted in an ICER of £4,358 per QALY gained (incremental costs £517, incremental QALYs 0.119). The manufacturers' base-case deterministic cost-effectiveness results for the triple therapy analyses as add-on to metformin and a sulfonylurea found that dapagliflozin dominated DPP-4 inhibitors, thiazolidinediones and GLP-1 analogues, resulting in lower costs and higher QALYs.

3.27 The manufacturers also presented 2 scenario analyses that included alternative BMI-related utility values. The scenarios applied utilities of ±0.0061 and ±0.0038 respectively for a ±1 unit change in BMI. Both values were taken from a study by Bagust et al. (2005) evaluating the impact of BMI on EQ-5D utility in patients with type 2 diabetes, and had been used in NICE's guideline CG87 on type 2 diabetes (now replaced by NICE's guideline on type 2 diabetes in adults) and NICE's technology appraisal guidance TA248 on exenatide in combination with oral antidiabetic therapy for the treatment of type 2 diabetes (now replaced by NICE's guideline on type 2 diabetes in adults). For the metformin add-on comparisons, the ICERs for dapagliflozin compared with a sulfonylurea were £8,863 and £10,514 per QALY gained respectively. Dapagliflozin remained dominant for the comparison of dapagliflozin with DPP-4 inhibitors and thiazolidinediones. For the comparison of dapagliflozin with DPP-4 inhibitors as add-on to insulin, the ICERs were also sensitive to changes to the BMI-related utility values. When changes in utility of ±0.0061 and ±0.0038 were applied, the ICERs increased to £21,171 and £32,409 per QALY gained respectively.

Evidence Review Group comments

3.28 The ERG commented on the scope of the appraisal and how the manufacturers addressed it in their submission. The ERG noted that the manufacturers did not include adults with type 2 diabetes that is inadequately controlled with sulfonylurea monotherapy in their submission. The ERG commented that the standard first-line monotherapy in type 2 diabetes is metformin, which is usually tolerated. The ERG noted that GLP-1 analogues were not included as a comparator in the dual therapy setting, but considered that this was appropriate because their use in dual therapy is restricted. The ERG stated that NICE's guideline CG87 on type 2 diabetes (now replaced by NICE's guideline on type 2 diabetes in adults) recommends the use of pioglitazone as an alternative add-on treatment to a sulfonylurea in people with type 2 diabetes that is inadequately controlled by metformin. However, it also noted that there are increasing concerns about the adverse reactions associated with pioglitazone. The ERG commented that, in the triple therapy setting, DPP-4 inhibitors would be expected to be given to patients before GLP-1 analogues because they are cheaper and are administered orally. Overall, the ERG considered that DPP-4 inhibitors are the key comparators for dapagliflozin in both the dual therapy and triple therapy settings.

3.29 The ERG stated that the manufacturers' approach to the systematic review of clinical evidence for dapagliflozin, which involved separate network meta-analyses for dapagliflozin as add-on therapy to metformin and as an add-on to insulin, was appropriate. The ERG noted that analyses were conducted for outcomes at 24 weeks and at 52 weeks and that studies reporting outcomes at less than 18 weeks, between 30 and 46 weeks, or greater than 58 weeks were excluded from the review. The ERG commented that it was not clear whether studies of between 31 and 45 weeks or greater than 58 weeks were also identified in the review. However, in response to a request for clarification, the manufacturers provided a full list of identified trials, none of which were between 31 and 45 weeks' duration. The ERG also noted that, for the network meta-analysis of insulin add-on therapies, a post-hoc amendment to the protocol was made to include studies in the range of 24 weeks ±8 weeks instead of ±6 weeks, to allow more studies to be included in the analysis.

3.30 The ERG commented that the manufacturers' approach to presenting the clinical effectiveness of dapagliflozin as a triple therapy add-on to metformin and a

sulfonylurea was not very clear. Overall, the ERG considered that the methodology for the review of dapagliflozin in triple therapy (submitted as an addendum) was less robust than the main submission. However, the ERG acknowledged that the manufacturers had not intended to provide clinical-effectiveness data on dapagliflozin in triple therapy because of ongoing trial-based research due to report in 2013.

3.31 The ERG noted that the decision to switch or intensify treatment in the manufacturers' economic model was based on HbA_{1c} levels above the thresholds recommended in NICE's guideline CG87 on type 2 diabetes (now replaced by NICE's guideline on type 2 diabetes in adults). The ERG also noted that, when the manufacturers changed the HbA_{1c} threshold levels in scenario analyses, along with changes to other input parameters, the ICERs for dapagliflozin increased. Overall, the ERG considered that the HbA_{1c} threshold levels for switching treatment applied in the model reduced its relevance to UK clinical practice.

3.32 The ERG commented that the loss in utility associated with hypoglycaemic events, taken from Currie et al. (2006), may have been too large when applied within the model. The ERG noted from this study that a severe hypoglycaemic event in the previous 3 months was interpreted by the authors as causing a 4.7% loss in utility (−0.047). The ERG considered that the loss in utility associated with hypoglycaemic events should have been applied for 3 months rather than 12 months, resulting in QALY losses of −0.012 and −0.004 for severe and symptomatic hypoglycaemic events respectively.

3.33 The ERG commented on the appropriateness of the utility values applied to weight change in the model. It noted that the majority of QALY gains associated with dapagliflozin arose from direct impact of weight change on health-related quality of life rather than diabetic complications or adverse events. The ERG noted that in study 12, the dapagliflozin treatment group experienced a lower gain in utility (0.018 versus 0.047) compared with placebo at 24 weeks. However, when the utility estimates associated with changes in BMI were applied to the observed weight changes in study 12, the dapagliflozin treatment group experienced a higher gain in utility (0.016 versus 0.000) compared with placebo at 24 weeks. The ERG also noted that the study by Bagust et al. involved a multivariate analysis of EQ-5D utility values that controlled for the complications of diabetes and estimated a smaller change in utility (±0.0061) associated with a

unit increase or decrease in BMI. The ERG considered these alternative utility values, which were applied in the manufacturers' scenario analyses, to be more reasonable.

3.34 The ERG noted that the weighted average annual costs of pioglitazone (£414.07), based on the England and Wales NHS drug tariff for February 2012, were substantially higher than those estimated from the November 2012 tariff (£139.16). The ERG also estimated different annual costs of DPP-4 inhibitors as add-on to metformin (£450.51 as opposed to £433.57) and GLP-1 analogues as add-on to metformin and a sulfonylurea (£946.26 as opposed to £886.90). With regard to the costs of macro- and microvascular diabetic complications, the ERG noted that the UKPDS 65 study also included annual inpatient (£157) and non-inpatient (£159) costs for patients who did not experience a complication. The ERG commented that these annual costs of £483 (after inflating from 1999 to 2011 prices) should have been applied in the model for patients who did not experience a diabetic complication.

3.35 The ERG noted that, although the model cycle length was 6 months, the probabilities of macro- and microvascular events estimated from the UKPDS 68 study appeared to be for a 12-month period and that no adjustment was made for this in the model. Further, the ERG noted from the DSU report on the economic model that the annual costs of macro- and microvascular events were not halved to correspond with the 6-month cycle length used in the model but were applied in full immediately on the event occurring. The ERG commented that this would increase the annual costs of these events by half of the annual maintenance costs associated with the event.

3.36 The ERG noted that not all of the risk equations derived from the UKPDS 68 study were implemented in the model. From this study, the model implemented the risk of mortality in the year after a diabetic complication but not the risk of mortality in subsequent years after the event. Furthermore, risk equations for fatal myocardial infarction and fatal stroke were derived from a separate UKPDS study (number 66). This resulted in the risk of fatal myocardial infarction being a function of HbA_{1c} and systolic blood pressure and the risk of fatal stroke being a function of systolic blood pressure only. The ERG considered that there was no obvious justification made by the manufacturers to include risk equations from this separate study. It also noted that this may have reduced the impact of HbA_{1c}

levels and increased the impact of systolic blood pressure in the model.

3.37 The ERG noted that, in the UKPDS 68 risk equations, baseline HbA_{1c} was based on patients with newly diagnosed type 2 diabetes. However, the baseline HbA_{1c} values implemented in the model were the trial baseline value minus the treatment-specific effect on HbA_{1c} and therefore baseline HbA_{1c} values differed between treatment groups. The ERG considered that the baseline HbA_{1c} should have been the same for both treatment groups in the model. It noted that using different treatment-specific baseline HbA_{1c} values resulted in the risk factor curves for both treatment groups not converging over time, whereas if the baseline HbA_{1c} values had been the same for both treatment groups, the curves would have converged after the initial treatment effects. Similar considerations would apply to the other risk factors used in the UKPDS equations. Overall, the ERG concluded that the implementation of the UKPDS risk factor equations in the manufacturers' economic model may have been incorrect.

3.38 Similarly, the ERG noted that the event equation from UKPDS 68 used to estimate congestive heart failure included BMI at diagnosis. The ERG again noted that the baseline BMI values implemented in the model were the trial baseline value minus the treatment-specific effect on BMI and therefore that baseline BMI values differed between treatment groups. Because dapagliflozin was associated with a greater reduction in body weight compared with comparator drug therapies, the ERG considered that this may have biased the risk of congestive heart failure in favour of dapagliflozin. Furthermore, because the risk of congestive heart failure was associated with an increased risk of myocardial infarction and stroke, any overestimate of the rate of congestive heart failure would also result in an overestimate of the rate of myocardial infarction and stroke, along with the associated risk of fatality.

3.39 In the triple therapy analyses, the ERG considered that it was unnecessary for the model to include dual therapy with metformin and a sulfonylurea before switching to triple therapy. Because the model structure only permitted 3 lines of treatment, this resulted in patients switching to insulin and metformin after triple therapy. Therefore, unlike the dual therapy analyses, the triple therapy analysis did not enable patients to receive intensified insulin, which is associated with higher costs and additional weight gain.

Decision Support Unit comments

3.40 The DSU was commissioned by NICE to examine the economic model submitted by the manufacturers. The DSU was asked to report on whether the model functioned as described in the manufacturers' submission, to report any important aspects of the model that were not described in the submission, to examine whether the C++ programming code followed the steps described by the manufacturers and used the data described in the submission, and to check that the economic model produced the results described in the submission.

3.41 The DSU identified several differences between the economic model described in the submission and the executable model provided by the manufacturers. There were some differences between the macro- and microvascular event equations and risk factor equations in the model and those described in the manufacturers' submission. The effect of treatment on body weight was applied immediately in the model rather than gradually over the first year of treatment. All-cause mortality was not adjusted for fatal stroke and myocardial infarction events. The model did not apply the cost of renal monitoring to all patients who started treatment with dapagliflozin, although the DSU noted that this was unlikely to have a significant impact on the ICERs. There were some differences between the written submission and the model in regard to the time periods over which some of the costs and changes in utility were applied. The DSU also noted that the process used to sample from the relevant distributions in the probabilistic sensitivity analysis did not produce appropriately distributed samples, which may have underestimated the uncertainty around the QALYs estimated in the model.

3.42 The DSU identified several aspects of the executable model that were not described in the manufacturers' submission. In the manufacturer's model, the probability of an event occurring in a 6-month cycle was calculated as the difference between the output of the event equation for the current cycle and the output of the event equation for the previous cycle. Treatment discontinuations applied in the first cycle of the model resulted in the patient switching treatment immediately without incurring costs or QALYs from the initial treatment except for the cost of discontinuation. The impact of treatment-related changes to BMI on health-related quality of life in the probabilistic sensitivity analysis was based on mean parameter values, which may have resulted in an underestimate of the uncertainty around the QALY differences estimated in the model.

3.43 The DSU commented that it was unable to reproduce the results of the probabilistic sensitivity analyses reported in the manufacturers' submission on the basis of the C++ programming code provided. However, the ICERs generated by the DSU did not vary substantially from those reported in the submission and it was noted that these differences may have arisen because of differences in the steps taken by the DSU to set up the probabilistic sensitivity analyses. When the DSU ran the model using the C++ programming code provided for the mean parameter values (deterministic analysis), it was also unable to reproduce the results of the deterministic analyses reported in the manufacturers' submission. Furthermore, when the DSU ran this code, it did not appear to have produced a stable estimate of the incremental QALYs after 100 runs. Finally, the DSU commented that the results generated by the programming code for the probabilistic sensitivity analyses when all parameters were set to their mean values did not match the results generated by the programming code that used mean parameter values. The DSU considered that similar results should have been produced and that this affected the confidence that could be placed on the results from the model.

Manufacturers' response to the appraisal consultation document

3.44 The manufacturers provided a response to the concerns raised by the DSU in its report on the economic model. The manufacturers stated that the economic model produced a stable estimate of the incremental costs and QALYs after 1000 rather than 100 simulations. The manufacturers implemented changes to the risk factor progression and event equations, and to the gamma and beta distributions applied to the cost and utility parameters in the probabilistic sensitivity analysis. The manufacturers also amended the model source code to correct for errors in the calculation of transition probabilities and the adjustment of all-cause mortality.

3.45 The manufacturers presented revised network meta-analyses for the dual therapy and add-on to insulin therapy comparisons, based on the WinBUGs programme code included in the technical support documents published by the DSU (Technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials). The manufacturers also presented a validation exercise, which compared the results

of the revised network meta-analyses with those presented in its original submission. The manufacturers commented that the revised analyses, which were provided as academic in confidence, produced similar results compared with the original analyses. The results of the revised 52-week network meta-analysis were applied for the revised dual therapy analyses because these data enabled the same set of baseline characteristics and risk factors to be used for each comparator in the dual therapy analyses. The revised network meta-analysis at 24 weeks was applied for the add-on to insulin analysis in the manufacturers' revised economic model.

3.46 The manufacturers provided further clarification about how changes in body weight were modelled over time for the different treatments. In addition, the manufacturers provided unpublished follow-up data from study 4 which, they stated, showed that patients who remained on dual therapy of dapagliflozin and metformin maintained their weight loss for up to 4 years. The manufacturers therefore suggested that, for treatments associated with weight loss, the assumption in the model that this weight loss was maintained for 2 years may have been conservative.

3.47 The manufacturers made a number of revisions to the economic model to address the ERG's concerns. The revised economic model applied the same baseline risk factors for all treatment groups, which were taken from the revised network meta-analyses for the dual therapy and add-on to insulin analyses. The manufacturers applied an HbA_{1c} threshold level of 7.5%, as currently recommended NICE's guideline CG87 on type 2 diabetes (now replaced by NICE's guideline on type 2 diabetes in adults), for switching treatment for the dual therapy analyses. However, the manufacturers commented that this threshold may not reflect UK clinical practice because patients with type 2 diabetes are reviewed by their clinicians only once or twice a year and are therefore likely to have HbA_{1c} levels that exceed 7.5% at the time of review. For the triple therapy and add-on to insulin analyses, the manufacturers applied HbA_{1c} thresholds of 8.61% and 9.04% respectively for switching treatment. For the triple therapy analyses, the manufacturers also revised the sequence of treatments in the revised model so that the starting treatment was triple therapy rather than dual therapy.

3.48 In their revised model, the manufacturers applied utility values of ±0.0061 per unit

increase or decrease in BMI taken from the study by Bagust et al. The manufacturers commented that the ERG had misinterpreted how the loss in utility associated with hypoglycaemic events was applied over a 6-month cycle in the economic model. Therefore, the manufacturers did not reduce the loss in QALYs associated with hypoglycaemia to −0.012 for a severe event and −0.004 for a symptomatic event in their revised base-case analyses (instead, retaining the original utility values). In scenario analyses, the manufacturers applied a range of upper (−0.0104) and lower (−0.000657) estimates of the loss in utility associated with urinary tract and genital infections taken from a systematic literature review as requested by the Committee. The manufacturers also reduced the average annual cost of pioglitazone from £414.07 to £112.18 and included an annual cost of £483 for people not experiencing diabetic complications in the revised economic model.

3.49 The manufacturers presented ICERs for the revised dual therapy analyses, which included clinical-effectiveness data from the revised 52-week network meta-analyses, changes to the model in response to the DSU report, the same baseline patient characteristics and risk factors for all treatment groups, and an HbA_{1c} switch threshold of 7.5%. As a result of these changes, the ICER for the comparison between dapagliflozin and sulfonylureas was £1,498 per QALY gained. For the comparisons between dapagliflozin and DPP-4 inhibitors and thiazolidinediones, the ICERs were £689 and £5,342 per QALY gained respectively. A scenario analysis which applied the upper and lower estimates of the loss in utility associated with urinary tract and genital infections resulted in very small changes to the ICERs for all comparisons.

3.50 The manufacturers also presented ICERs for the revised dual therapy analyses which included the changes described in section 3.49 and additional changes, which included reduced costs of pioglitazone, adjusted costs of diabetic complications and utility values of ±0.0061 per unit increase or decrease in BMI. As a result of these additional changes, the ICER for the comparison between dapagliflozin and sulfonylureas was £7,735 per QALY gained. For the comparisons between dapagliflozin and DPP-4 inhibitors and between dapagliflozin and thiazolidinediones, the ICERs were £3,337 and £77,615 per QALY gained respectively.

3.51 The manufacturers presented ICERs for the revised add-on to insulin analyses,

which included clinical-effectiveness data from the revised 24-week network meta-analyses, changes to the model in response to the DSU report and an HbA_{1c} switch threshold of 9.04%. As a result of these changes, the ICER for the comparison between dapagliflozin and DPP-4 inhibitors was £2,509 per QALY gained. A scenario analysis that applied the upper and lower estimates of the loss in utility associated with urinary tract and genital infections resulted in very small changes to the ICER. The manufacturers also presented an ICER that included adjusted costs of diabetic complications and utility values of ±0.0061 per unit increase or decrease in BMI. As a result of these additional changes, the ICER increased to £5,634 per QALY gained.

3.52 The manufacturers also presented ICERs for the revised triple therapy analyses, which included altering the treatment sequences in the model so that patients in the model started treatment with triple add-on therapy to metformin and a sulfonylurea, incorporating model structural changes and applying an HbA_{1c} switch threshold of 8.61%. As a result of these changes, dapagliflozin continued to dominate DPP-4 inhibitors, thiazolidinediones and GLP-1 analogues. The manufacturers did not present any additional scenario analyses for the relevant comparisons in triple therapy.

3.53 The manufacturers presented the results of a validation exercise, which compared the results from the revised model with the results that would have been obtained from using the CORE diabetes model for all relevant comparisons in dual therapy, insulin add-on therapy, and triple therapy. For the dual therapy analyses, the CORE model produced an ICER of £8,879 per QALY gained for the comparison of dapagliflozin with sulfonylureas and ICERs of £2,014 and £7,093 per QALY gained for the comparisons of dapagliflozin with DPP-4 inhibitors and with thiazolidinediones. For the insulin add-on analyses, the CORE model resulted in an ICER of £1,675 per QALY gained for dapagliflozin compared with DPP-4 inhibitors. For the triple therapy analyses, the CORE model produced ICERs of £1,759 per QALY gained for the comparison of dapagliflozin with DPP-4 inhibitors and £16,054 per QALY gained for the comparison of dapagliflozin with thiazolidinediones. The CORE model also produced an ICER of £32,243 per QALY lost for the comparison of dapagliflozin with GLP-1 analogues.

3.54 Both the ERG and the DSU reviewed the manufacturers' revised economic model and analyses provided in response to the appraisal consultation document.

Overall, the DSU considered that the manufacturers had adequately addressed all of the significant areas of concern about the model. The ERG noted that the revised dual therapy analyses used clinical-effectiveness data from the revised 52-week network meta-analyses rather than the revised 24-week network meta-analyses, which resulted in significant changes to the model input parameters. The ERG noted that, as a result of applying a lower HbA_{1c} threshold for switching treatment, the revised model resulted in switching treatment earlier and thus reducing the costs of first-line dapagliflozin treatment whilst maintaining any long-term weight loss. The ERG also noted that the manufacturers' revised economic model had incorrectly amended the costs for people who did not experience diabetic complications.

3.55 The ERG highlighted a number of concerns about how changes in body weight were modelled in the manufacturers' revised analyses. The ERG noted that the manufacturers stated that, in order to simulate a linear, gradual regain of weight, the time to loss of weight effect was set such that weight was regained by the time of switch to next treatment. However, the ERG noted that in the manufacturers' comparisons of dapagliflozin with sulfonylureas and with DPP-4 inhibitors in the revised dual therapy analyses, weight loss associated with dapagliflozin was largely maintained and not reversed at the time of switching to next treatment. The ERG also noted that the manufacturers' revised economic model and analyses did not address the Committee's concerns about the duration over which differences in weight change were maintained between treatments.

Additional DSU analysis in response to the revised manufacturers' model

3.56 In response to the concerns about the manufacturers' revised economic model raised by the ERG, the DSU was asked to review the manufacturers' revised economic analyses and to assess further how changes in weight were modelled over time for different treatments in the revised model. The DSU was also asked to conduct a range of further exploratory analyses for dapagliflozin in dual therapy and add-on to insulin therapy.

3.57 The DSU noted that, in the manufacturers' revised economic model, the assumptions about the duration over which any treatment-related weight change

was reversed for the comparison of dapagliflozin with thiazolidinediones as add-on to metformin and the add-on to insulin analyses were consistent with those used in the original model. Therefore, for treatments associated with weight loss, weight was regained before first treatment switch. However, the DSU noted that for the comparisons of dapagliflozin as add-on to metformin with sulfonylureas and DPP-4 inhibitors, treatment-related weight loss was not reversed at treatment switch in the revised model. The DSU suggested that the weight profiles for dapagliflozin and DPP-4 inhibitors may have been incorrectly amended in the model.

3.58 The DSU noted that, for second- and third-line treatments, the weight at the start of treatment in the revised model was based on the weight at the time of switching from the previous treatment. The DSU noted that this was problematic if the treatment switch occurred before the treatment-related weight loss was regained. The DSU stated that where this happened this resulted in a weight difference between treatment groups that is maintained throughout the duration of the model. The DSU amended the manufacturers' revised model to ensure that, if a treatment switch occurred before the weight loss was fully regained, the starting weight at the next line of treatment was set equal to the weight that would have been achieved after the weight regain for the previous treatment. This resulted in a convergence of weight profiles over time for treatments associated with weight loss.

3.59 The DSU applied a number of changes and assumptions to the manufacturers' revised model, in addition to the amendment described in section 3.58. These included:

- for the dual therapy analyses, using clinical-effectiveness data from the revised 24-week network meta-analyses for the comparisons of dapagliflozin with DPP-4 inhibitors and thiazolidinediones and from study 4 for the comparison of dapagliflozin with a sulfonylurea
- applying an HbA_{1c} threshold of 7.5% for switching to second-line and third-line treatment in the dual therapy analysis and for switching to second-line treatment in the add-on to insulin analysis
- for any treatments associated with weight loss, assuming weight regain during year 3 to the level expected in a patient who experiences a natural

weight gain of 0.1 kg per year from the start of treatment

- assuming no diabetic complications at the start of treatment
- reducing the loss in QALYs associated with hypoglycaemia to –0.012 for a severe event and –0.004 for a symptomatic event
- using utility values associated with weight change of ±0.0061 per unit of BMI
- reducing the annual cost of pioglitazone to £69.09 based on the latest NHS drug tariff
- using an annual cost of £483 for people not experiencing diabetic complications.

3.60 For the dual therapy analyses, using data from the 24-week network meta-analysis, the DSU base-case deterministic pair-wise analysis resulted in ICERs of £13,338 per QALY gained for the comparison of dapagliflozin with thiazolidinediones and £13,947 per QALY gained for the comparison of DPP-4 inhibitors with thiazolidinediones. An incremental analysis resulted in ICERs of £13,338 per QALY gained for the comparison of dapagliflozin with thiazolidinediones and £16,847 per QALY gained for the comparison of DPP-4 inhibitors with dapagliflozin (based on incremental costs of £136 and incremental QALYs of 0.008). Using data from study 4, the pair-wise comparison of dapagliflozin and sulfonylureas resulted in an ICER of £12,405 per QALY gained.

3.61 The DSU also conducted a probabilistic sensitivity analysis based on a mean of 1000 samples. Using data from the 24-week network meta-analysis, the analysis resulted in pair-wise ICERs of £15,257 per QALY gained for the comparison of dapagliflozin with thiazolidinediones and £15,511 per QALY gained for the comparison of DPP-4 inhibitors with thiazolidinediones. An incremental analysis resulted in ICERs of £15,257 per QALY gained for the comparison of dapagliflozin with thiazolidinediones and £41,654 per QALY gained for the comparison of DPP-4 inhibitors with dapagliflozin (based on incremental costs of £17 and incremental QALYs of less than 0.001). Using data from study 4, the comparison of dapagliflozin and sulfonylureas resulted in an ICER of £15,148 per QALY gained. The DSU noted that in the probabilistic sensitivity analysis, people spent longer on first-line treatment because of the interaction between baseline HbA_{1c} values, treatment switching threshold and effectiveness data, thus resulting in higher

incremental costs and ICERs than the deterministic analysis. The results of these probabilistic sensitivity analyses also showed that, at £20,000 per QALY gained, dapagliflozin had the highest probability (40.4%) of being cost effective compared with DPP-4 inhibitors (35.5%) and thiazolidinediones (24.1%) and also the highest probability (61.0%) of being cost effective compared with sulfonylureas.

3.62 The DSU conducted a scenario analysis that applied the manufacturers' original utility values associated with hypoglycaemia (–0.047 for a severe event and –0.042 for a symptomatic event). As a result of this change, dapagliflozin was extendedly dominated by DPP-4 inhibitors and thiazolidinediones, because the ICER of dapagliflozin compared with thiazolidinediones was higher than that of the next most effective alternative (DPP-4 inhibitors). The comparison of dapagliflozin and sulfonylureas resulted in an ICER of £10,317 per QALY gained. The DSU also conducted a scenario analysis which used the same clinical-effectiveness data from the 52-week network meta-analysis as those used in the manufacturers' revised model, thus allowing all treatments to be compared with each other in a single analysis. On the basis of a full incremental analysis, DPP-4 inhibitors were dominated by thiazolidinediones. The comparison of thiazolidinediones and sulfonylureas resulted in an ICER of £12,108 per QALY gained and the comparison of dapagliflozin and thiazolidinediones resulted in an ICER of £94,466 per QALY gained.

3.63 The DSU conducted an additional scenario analysis to explore the impact of weight convergence between treatment groups at the time of switching to the last line of treatment. In the manufacturers' revised model for the dual therapy analyses, the DSU modelled weight convergence between dapagliflozin (associated with weight loss) and a sulfonylurea (associated with weight gain) by increasing the weight gain for the last treatment in the sequence (insulin treatment). For this scenario analysis the DSU presented pair-wise ICERs using the data from the 24-week network meta-analysis and separately the data from study 4. Applying the 24-week meta-analysis data resulted in a higher ICER of £60,965 per QALY gained for the pair-wise comparison of dapagliflozin with thiazolidinediones and an ICER of £16,847 per QALY gained for the comparison of DPP-4 inhibitors with dapagliflozin. The ERG noted that the latter ICER was largely unchanged from its base-case analysis because the weight profiles at last treatment switch were very similar across the 2 treatment groups. The pair-wise

comparison of dapagliflozin and sulfonylureas using study 4 data resulted in an ICER of £21,200 per QALY gained.

3.64 The DSU noted that in the manufacturers' revised add-on to insulin analysis, the time to weight regain was set to occur before first treatment switch based on an HbA_{1c} threshold of 9.04%, resulting in a switch to second-line treatment at 8 years. The DSU explored the impact of setting a time to weight regain of 1 year and an HbA_{1c} switching threshold of 7.5% in line with the dual therapy analyses. The DSU also applied all other changes as described in section 3.59. The DSU base-case deterministic pair-wise analysis of dapagliflozin compared with DPP-4 inhibitors resulted in an ICER of £3,706 per QALY gained. The probabilistic sensitivity analysis resulted in a longer duration of first-line treatment and incremental costs for dapagliflozin, and consequently in a higher ICER of £7,402 per QALY gained. When the DSU applied the manufacturers' original utility values associated with hypoglycaemia, the ICER was reduced to £2,959 per QALY gained. When the DSU applied the assumption of weight convergence at last treatment switch, the ICER increased to £12,879 per QALY gained. The DSU noted that this scenario resulted in longer first-line treatment duration for people before switching to insulin treatment in both treatment groups and consequently, higher incremental costs for dapagliflozin.

Consideration of the evidence

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

3.66 The Committee discussed the clinical treatment pathway for type 2 diabetes. The Committee heard from the clinical specialists that treatment for type 2 diabetes is individualised for each patient (focusing on HbA_{1c} reduction without weight gain or hypoglycaemia), resulting in some variation in clinical practice. However, although treatment is individualised, current UK practice broadly follows NICE's guideline CG87 on type 2 diabetes (now replaced by NICE's guideline on type 2 diabetes in adults), which recommends a stepwise approach that includes using

diet and exercise, various antidiabetic drugs and insulin. The Committee heard from the clinical specialists that each of the existing antidiabetic therapies had various advantages and disadvantages affecting their suitability for patients and that many patients do not achieve target HbA_{1c} levels with existing therapies. The Committee heard from the clinical specialists that dapagliflozin may be more likely to be used as a triple therapy but could be used as a dual therapy if there was a perceived risk of hypoglycaemia. It was noted that its use may be limited by the restrictions in the marketing authorisation, which states that dapagliflozin is not recommended for use in people with moderate to severe renal impairment. The Committee understood that a new treatment providing an additional option would be valued by clinicians.

3.67 The Committee discussed the antidiabetic drugs that were used at each point in the treatment pathway for type 2 diabetes. The Committee heard from the clinical specialists that most people start treatment with metformin and that the use of a sulfonylurea as first-line therapy is diminishing because of the associated weight gain and the high incidence of hypoglycaemia compared with other oral therapies. The Committee heard from the clinical specialists that a sulfonylurea is often added to metformin as a dual therapy but if patients are unable to take a sulfonylurea because of concerns about weight gain or hypoglycaemia, then thiazolidinediones (pioglitazone), DPP-4 inhibitors and GLP-1 analogues may be used. The clinical specialists also commented that the same treatments could be used in triple therapy and as add-on to insulin therapy. The Committee heard from the clinical specialists that the use of DPP-4 inhibitors was increasing and that the use of pioglitazone was decreasing because of concerns about safety. It was also aware that GLP-1 analogues were used less frequently and usually later on in the treatment pathway because they are administered by subcutaneous injection and are more costly than other antidiabetic drugs. The Committee concluded that on the basis of the evidence from the clinical specialists, dapagliflozin was most likely to be used if a sulfonylurea was not appropriate, and the main comparator for dapagliflozin would be the DPP-4 inhibitors.

3.68 The Committee heard evidence from the patient experts that an advantage of dapagliflozin is that it will provide a further treatment option for people with type 2 diabetes who are reluctant to start treatment with insulin or wish to avoid insulin therapy because of fear of hypoglycaemia and its impact on their lifestyle

(for example, the threat of losing their driving licence or their job). The Committee heard from the patient experts that the potential disadvantages of dapagliflozin include more frequent urinary tract and genital infections. However, the patient experts commented that the importance of these events would vary between individual patients and that, for some patients, the higher risk of urinary or genital infections could be balanced by the lower risk of hypoglycaemia. The Committee also heard from the patient experts that because dapagliflozin causes the excretion of glucose through the urine, this may cause anxiety for some patients who understand an absence of glucose in the urine to be a sign of good diabetes management and that this may lead to non-adherence to dapagliflozin therapy. However, the clinical specialists suggested that this was a risk that could be managed by providing appropriate information to people with diabetes.

Clinical effectiveness

3.69 The Committee considered the evidence on the clinical effectiveness of dapagliflozin compared with other antidiabetic therapies, noting that most of the data came from the network meta-analyses submitted by the manufacturers. The Committee noted that, although the WinBUGs programme code used to run the original network meta-analyses provided in the manufacturers' submission differed from the code recommended by the NICE DSU in their technical support document, the manufacturers had also provided revised network meta-analyses that were based on the recommended code. The Committee also noted that the results of the manufacturers' revised network meta-analyses were similar to those from the original analyses. The Committee concluded that the results of the manufacturers' revised network meta-analyses provided an appropriate basis for making decisions about the clinical effectiveness of dapagliflozin and other antidiabetic therapies.

3.70 The Committee discussed the outcomes collected in the clinical trials and network meta-analyses, noting that the primary outcomes were intermediate rather than clinical outcomes. The Committee noted that studies including the UKPDS had then been used to provide a link between these intermediate outcomes and long-term clinical outcomes including micro- and macrovascular complications. The Committee heard from the clinical specialists that there was some uncertainty about the impact of HbA_{1c} reduction on longer-term

macrovascular complications. The Committee also heard from the manufacturers that follow-up data were available for the clinical trials of dapagliflozin but that, because most of the trials of other antidiabetic drug therapies were of shorter duration, the clinical-effectiveness data used in the cost-effectiveness analysis had to be based on the short-term clinical trial data. The Committee concluded that, despite some uncertainty about the impact of HbA_{1c} reduction on longer-term macrovascular complications, it was prepared to accept the link between the intermediate outcomes collected in the clinical trials and the longer-term clinical outcomes.

3.71 The Committee considered the clinical effectiveness of dapagliflozin in dual therapy for people whose type 2 diabetes is inadequately controlled by metformin alone. The Committee noted that the evidence came from 3 clinical trials and a network meta-analysis. The Committee also noted that only 1 of the clinical trials of dapagliflozin had an active comparator (sulfonylureas), and that the clinical trial results were based on a relatively small number of patients who were given dapagliflozin at its licensed dose. However, on the basis of these clinical trial results, the Committee considered dapagliflozin to have greater efficacy than sulfonylureas for the outcomes of weight loss and systolic blood pressure reduction and similar efficacy for HbA_{1c} reduction. The Committee concluded that, on the basis of the results of the network meta-analyses (see sections 3.10 and 3.45), dapagliflozin in dual therapy as add-on to metformin appeared to provide similar glycaemic control to other antidiabetic drugs but may result in greater weight loss.

3.72 The Committee further considered the clinical effectiveness of dapagliflozin as dual therapy, noting that the manufacturers had not provided data on dapagliflozin as add-on therapy to a sulfonylurea, despite clinical trial data being available. The Committee accepted that most of the patients would start on metformin monotherapy, but noted the evidence provided by the clinical specialists that a proportion of patients who cannot tolerate metformin or for whom it is contraindicated would receive sulfonylurea monotherapy. It noted that the clinical effectiveness of dapagliflozin as an add-on to a sulfonylurea appeared to be consistent with its effectiveness when used as an add-on to metformin. The Committee concluded that, because the manufacturers had not provided clinical evidence on dapagliflozin as an add-on to a sulfonylurea, it could not make recommendations on this combination regimen.

3.73 The Committee considered the clinical effectiveness of dapagliflozin for people whose type 2 diabetes is inadequately controlled by insulin, noting that the evidence came from 2 clinical trials and a network meta-analysis. The Committee noted that both trials were placebo controlled and that 1 of these was of 12 weeks' duration only. Again, the Committee noted that the clinical trial results for dapagliflozin were based on a relatively small number of patients who were treated with dapagliflozin at its licensed dose. Further, the Committee noted that the network meta-analysis excluded trials of GLP-1 analogues because they were not comparable to other trials included in the analysis and therefore consideration of the full range of possible comparators was restricted by the available evidence. The Committee concluded that, on the basis of the results of the network meta-analyses (see sections 3.12 and 3.45), dapagliflozin as add-on therapy to insulin appeared to have greater efficacy than DPP-4 inhibitors for the outcome of weight loss and similar efficacy for HbA_{1c} reduction.

3.74 The Committee considered the evidence on the clinical effectiveness of dapagliflozin in triple therapy. The Committee noted that dapagliflozin is currently being studied as a triple therapy add-on to 2 other oral agents and that, in the absence of any other currently available clinical-effectiveness data, the manufacturers provided a post-hoc analysis of pooled data from a subset of older patients with type 2 diabetes and cardiovascular disease recruited in 2 trials of dapagliflozin as an add-on to metformin and a sulfonylurea. The Committee also noted that no direct head-to-head studies comparing dapagliflozin with other antidiabetic drugs currently exist and that the clinical-effectiveness data used to indirectly compare dapagliflozin with other antidiabetic drugs were taken from a previously published systematic review that had not been updated since 2009. It was aware of the limitations of these analyses highlighted by the manufacturer and therefore concluded that significant caution should be taken when interpreting the results of these preliminary analyses on the clinical effectiveness of dapagliflozin in the triple therapy setting.

3.75 The Committee considered the adverse events associated with dapagliflozin. It noted that common adverse events included urinary tract and genital infections and that these events were more common in women than in men. However, the Committee heard from the manufacturers that the recurrence of these events in the clinical trials was low. It also heard from the manufacturers that, because of the mechanism of action of dapagliflozin, the clinical trials had actively looked for

such infections and that only a small proportion of these infections needed treatment. The Committee also noted that the incidence of hypoglycaemia was low when dapagliflozin was added to metformin and that the currently available evidence suggested that dapagliflozin was not associated with increased risk of cardiovascular events. However, it was aware that regulatory agencies had identified some uncertainty about the risk of some cancers associated with dapagliflozin. The Committee heard from the patient experts that adverse events were a concern for patients with type 2 diabetes if they result in the need for additional drug therapies, especially for patients who are already receiving many drug therapies for their condition. However, it also recognised that a new drug therapy that was associated with a lower risk of hypoglycaemia than some other existing therapies would also be valued by patients for whom driving might be a significant factor in their lifestyle or livelihood. The Committee concluded that the adverse-events profile of dapagliflozin was different from those of other antidiabetic therapies and that it was important to examine these adverse events when considering the manufacturers' economic model.

Cost effectiveness

3.76 The Committee considered the cost effectiveness of dapagliflozin as an add-on to metformin and insulin and as triple therapy in the manufacturers' submission, and the critique and exploratory analyses provided by the DSU and the ERG. The Committee noted that the manufacturers had provided a revised economic model in order to address concerns raised by the DSU about the original model and that the DSU considered that their concerns had been addressed. However, it also noted that the DSU and the ERG had identified a number of errors in the revised model which were subsequently addressed by the DSU in its exploratory analyses. The Committee concluded that the manufacturers' revised economic model with the subsequent amendments made by the DSU was acceptable for assessing the cost effectiveness of dapagliflozin in combination therapy for treating type 2 diabetes.

3.77 The Committee discussed the validation report provided by the manufacturers which compared the results from the revised model with the results that would have been obtained using the CORE diabetes model, which has been used in previous appraisals of treatments for type 2 diabetes (such as NICE's technology

appraisal guidance TA203 on liraglutide for the treatment of type 2 diabetes mellitus and exenatide in combination with oral antidiabetic therapy for the treatment of type 2 diabetes [both now replaced by NICE's guideline on type 2 diabetes in adults]). The Committee noted that the results generated from the CORE diabetes model were comparable to those obtained from the manufacturers' original and revised economic models for the dual therapy and insulin add-on therapy analyses. The Committee concluded that the results of the validation exercise with the CORE diabetes model provided reassurance about the integrity of the results obtained from the manufacturers' revised economic model.

3.78 The Committee discussed the cost-effectiveness analyses presented by the manufacturers, noting that these included a more restricted set of comparators than were specified in the scope. It was aware that GLP-1 analogues had been included in the network meta-analysis for dual therapy but then subsequently excluded from the cost-effectiveness analysis. The Committee considered that it would have been more appropriate for all treatments in the network meta-analysis to have been included in the cost-effectiveness analysis. However, it noted the comments from the ERG and clinical specialists that GLP-1 analogues were used in dual therapy on a restricted basis. On balance, the Committee concluded that the manufacturers had included an adequate range of comparators for the cost-effectiveness analysis of dapagliflozin in dual therapy as an add-on to metformin.

3.79 The Committee discussed the clinical-effectiveness data that were applied in the economic models. The Committee noted that the DSU had completed analyses of dual therapy add-on to metformin using different sources of clinical-effectiveness data. One analysis used the 24-week network meta-analysis data for dapagliflozin, DPP-4 inhibitors and thiazolidinediones and presented a separate comparison using head-to-head data from study 4 for dapagliflozin and sulfonylureas. The other analysis considered all treatments in a single analysis using the 52-week network meta-analysis data. It heard from the manufacturers that, for the metformin add-on analyses, the trials of other antidiabetic therapies as add-on to metformin used a fixed dose but the trials of sulfonylureas did not have a stable dose over 24 weeks. Therefore, trials of sulfonylureas as an add-on to metformin were excluded from the 24-week network meta-analysis. The Committee discussed which set of analyses was the most appropriate, noting

that the estimates of efficacy differed between analyses. It considered that it was more appropriate to use a single source as was available in the 52-week network meta-analysis, but was aware of the limited number of trials informing this analysis. The Committee noted that the 24-week network meta-analysis only excluded sulfonylureas, and that the evidence from the clinical specialists suggested that dapagliflozin would be used where sulfonylureas were not appropriate. On this basis the 24-week network meta-analysis data were appropriate. The Committee concluded that the results of the revised 24-week network meta-analysis provided the most appropriate clinical-effectiveness data for the dual therapy analyses.

3.80 The Committee discussed the manufacturers' assumptions about the decision to switch or intensify treatment in the model, noting that this was based on baseline HbA_{1c} levels taken from the clinical trials and network meta-analysis. The Committee noted that the HbA_{1c} threshold levels for switching treatment in the original dual therapy and triple therapy analyses were above those recommended in NICE's guideline CG87 on type 2 diabetes and therefore may not reflect UK clinical practice. However, the Committee noted that the DSU's revised analyses applied an HbA_{1c} threshold for switching treatment that is recommended in NICE's guideline CG87 on type 2 diabetes (now replaced by NICE's guideline on type 2 diabetes in adults). The Committee heard from the DSU that the results from the revised model were sensitive to the timing of treatment switching in the model which was dependent on the relationship between HbA_{1c} at the start of treatment, treatment-related changes in HbA_{1c} levels and the HbA_{1c} threshold levels for switching treatment. The Committee concluded that HbA_{1c} threshold levels for switching treatment as recommended in NICE's guideline CG87 on type 2 diabetes (now replaced by NICE's guideline on type 2 diabetes in adults) were appropriate to use in the economic modelling and as a basis for decision-making.

3.81 The Committee discussed the manufacturers' approach to modelling changes in body weight. The Committee noted that in the revised model the effect of treatment on changes in weight was applied gradually over the course of the first year, and considered that this was more plausible than the original model in which the effect of treatment on changes in weight was applied immediately. The Committee noted that, for treatments associated with weight loss, the manufacturers made assumptions about how long weight loss was maintained in the model (weight plateau), and about how long it took for the weight to increase

to its baseline level after the plateau (loss of effect). The Committee understood that the changes made by the DSU meant that for treatments associated with weight loss, the weight profiles of the treatment groups now converged over time, but that for treatments associated with weight gain, differences in weight were maintained over the model time horizon. The Committee acknowledged that unpublished data from the clinical study of dapagliflozin and sulfonylureas as add-on to metformin provided by the manufacturers showed that patients who remained on dapagliflozin treatment without switching to other treatments maintained their weight loss over 4 years. However, the Committee considered that uncertainty remained about the effects of stopping treatment with dapagliflozin and the impact on weight gain. Therefore, it concluded that the scenario analysis conducted by the DSU, which involved the convergence of differences in weight profiles between treatment groups at the time of switching to the last line of treatment, was more appropriate for decision-making.

3.82 The Committee considered the utility values applied in the model, noting that in all analyses the majority of the QALY gains associated with dapagliflozin arose from the direct impact of weight change on health-related quality of life rather than from a reduction of diabetic complications and other adverse events. The Committee noted that utility values associated with changes in BMI were taken from a study commissioned by the manufacturers and that the methods by which these values were obtained were not in line with the NICE reference case for measuring and valuing health effects. The Committee also noted that this study produced different utility values associated with a 1-unit increase or decrease in BMI and that these were larger than other utility values that were identified in the literature. The Committee acknowledged that the manufacturers presented scenario analyses using alternative utility values for weight change and that these resulted in higher ICERs for the metformin and insulin add-on analyses. The Committee also noted that the loss in utility associated with a 1-unit increase in BMI (−0.0472) was similar to the loss in utility associated with a myocardial infarction (−0.055), which may not be credible. The Committee concluded that the utility values associated with changes in weight may have been too large and that the values (±0.0061 per BMI unit decrease or increase) applied in the manufacturers' scenario analyses and DSU analyses were more reasonable.

3.83 The Committee considered the utility values associated with hypoglycaemic events. The Committee heard from the ERG that they considered that the loss in

QALYs associated with hypoglycaemic events may have been too large. The Committee was also aware that the loss in utility associated with severe hypoglycaemic events (−0.047) was higher than that applied in the economic model of third-line therapy with insulins, thiazolidinediones or exenatide in NICE's guideline CG87 on type 2 diabetes (−0.010). However, the Committee noted that after the publication of this guideline, the Driving and Vehicle Licensing Agency issued new regulations for people who have experienced a severe hypoglycaemic event in the previous 12 months. Therefore, the Committee acknowledged that any loss in utility associated with severe hypoglycaemic events may be higher in people for whom driving might be a significant factor in their lifestyle or livelihood. The Committee noted that the DSU had completed analyses that included both the higher and lower estimates of loss of utility associated with hypoglycaemic events, and that these had made small differences to the estimates of the ICER. The Committee therefore concluded that the utility values associated with hypoglycaemic events were not a critical factor in the decision-making.

3.84 The Committee considered the utility values applied to urinary tract and genital infections in the model, noting that the loss in utility associated with these events was much smaller than the loss in utility associated with other adverse events. The Committee considered that it was likely that there would be a greater loss in utility associated with these events than had been proposed by the manufacturers. The Committee also noted that the study commissioned by the manufacturers to examine the impact of weight change on health-related quality of life had also estimated the impact of urinary tract and genital infections, although these data were not presented in the manufacturers' submission. The Committee noted that in scenario analyses the manufacturers had applied a range of estimates for the loss in utility associated with urinary tract and genital infections. It was also aware that the results of the revised analyses were not sensitive to changes in these utility values. The Committee concluded that, although the loss in utility associated with urinary tract and genital infections was likely to be greater than that proposed by the manufacturers, it was satisfied that this did not significantly impact on the relative cost effectiveness of dapagliflozin as dual therapy or add-on to insulin.

3.85 The Committee was aware that the ERG had proposed alternative estimates for some costs, including drug acquisition costs for pioglitazone and the costs

associated with diabetic complications. The Committee noted that pioglitazone is now off-patent and that the latest acquisition costs are substantially lower than those presented in the manufacturers' submission. The Committee acknowledged that the manufacturers were unable to provide this estimate in their submission, but considered that the DSU estimate of an average annual cost of £69.09 was reasonable. The Committee also noted that the manufacturers' revised model did not correctly adjust the annual inpatient and non-inpatient costs (estimated as £483 in the UKPDS 65 study) for people who did not experience a macro- or microvascular diabetic complication. The Committee concluded that it was appropriate to consider the latest acquisition cost of pioglitazone and that the manufacturers' revised model should be amended to correctly account for the annual costs incurred by people who did not experience a macro- or microvascular diabetic complication.

3.86 The Committee considered the most plausible ICERs for dapagliflozin as dual therapy in combination with metformin. The Committee considered that, on the basis of clinical specialist opinion that suggested that the use of pioglitazone in UK clinical practice was decreasing, a thiazolidinedione was not a key comparator in the dual therapy setting. The Committee also noted the evidence from the clinical specialists supported by the manufacturers that, in clinical practice, dapagliflozin would predominantly be used in combination with metformin when a sulfonylurea is not appropriate. Therefore, the Committee also considered that sulfonylureas were not a relevant comparator in the dual therapy setting. The Committee considered the DSU deterministic analysis and scenario analyses, which included the convergence of differences in weight between treatment groups at the time of switching to the last line of treatment. It noted that these showed that DPP-4 inhibitors were associated with higher costs and QALYs than dapagliflozin, but that these differences were small. It noted further that in the DSU probabilistic sensitivity analysis these differences were even smaller. The Committee noted that the differences in QALYs were largely explained by the changes in health-related quality of life (utility) associated with changes in weight (BMI). Overall, the Committee concluded that because of the small differences in costs and QALYs between dapagliflozin and DPP-4 inhibitors, dapagliflozin in a dual therapy regimen in combination with metformin could be recommended as a treatment option for people with type 2 diabetes that is inadequately controlled with metformin alone if it is used in the same scenario as described for the use of DPP-4 inhibitors in NICE's guideline CG87 on type 2 diabetes (now replaced by

NICE's guideline on type 2 diabetes in adults).

3.87 The Committee considered the most plausible ICERs for dapagliflozin as add-on to insulin. It noted that in all the analyses conducted by the DSU the estimate of the ICER for dapagliflozin compared with DPP-4 inhibitors was below £20,000 per QALY gained. The Committee considered that, in comparison to DPP-4 inhibitors, dapagliflozin had been shown to be a cost-effective use of NHS resources. The Committee recommended dapagliflozin as a treatment option for people with diabetes inadequately controlled by insulin with or without other oral antidiabetic drugs.

3.88 The Committee discussed the results of the manufacturers' revised base-case analyses for dapagliflozin as triple therapy add-on to metformin and a sulfonylurea. It noted that the sequence of treatments in the manufacturers' revised economic model had been amended so that the approach was consistent with the dual therapy and insulin add-on analyses, with patients in the model starting treatment with triple add-on therapy. The Committee noted that in both the manufacturers' original and revised triple therapy analyses, dapagliflozin dominated other comparator drug therapies, meaning that dapagliflozin was associated with lower costs and higher QALYs than the comparators. However, the Committee noted that the clinical-effectiveness data applied in the triple therapy model were based on an indirect comparison of pooled data of 2 trials of dapagliflozin and a separate systematic review of other antidiabetic drug therapies conducted in 2009. The Committee was also aware that dapagliflozin is currently being studied as a triple therapy add-on to 2 other oral agents. The Committee considered that the cost-effectiveness analyses should be considered as exploratory in nature. The Committee concluded that dapagliflozin as triple therapy in combination with metformin and a sulfonylurea should not be recommended for treating type 2 diabetes except as part of the ongoing clinical trials.

4 Implementation

4.1 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 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

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

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

5 Recommendations for further research

5.1 The Committee supported the ongoing research investigating dapagliflozin as part of a triple therapy regimen as add-on to 2 oral antidiabetic drugs.

6 Appraisal Committee members and NICE project team

6.1 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

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

Professor A E Ades
Professor of Public Health Science, Department of Community Based Medicine, University of Bristol

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

Dr Jeremy Braybrooke

Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

Dr Gerardine Bryant
General Practitioner, Heartwood Medical Centre, Derbyshire

Dr Fiona Duncan
Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Mr Andrew England
Lecturer in Medical Imaging, NIHR Fellow, University of Liverpool

Professor Jonathan Grigg
Professor of Paediatric Respiratory and Environmental Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University London

Dr Brian Hawkins
Chief Pharmacist, Cwm Taf Health Board, South Wales

Dr Peter Heywood
Consultant Neurologist, Frenchay Hospital

Dr Sharon Saint Lamont
Head of Quality and Innovation, North East Strategic Health Authority

Dr Ian Lewin
Consultant Endocrinologist, North Devon District Hospital

Dr Louise Longworth
Reader in Health Economics, HERG, Brunel University

Dr Anne McCune
Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

Professor John McMurray
Professor of Medical Cardiology, University of Glasgow

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

Dr Mohit Misra
General Practitioner, Queen Elizabeth Hospital, London

Ms Sarah Parry
CNS Paediatric Pain Management, Bristol Royal Hospital for Children

Ms Pamela Rees
Lay Member

Dr Ann Richardson
Lay Member

Ms Ellen Rule
Programme Director, NHS Bristol

Mr Stephen Sharp
Senior Statistician, MRC Epidemiology Unit

Dr Peter Sims
General Practitioner, Devon

Dr Eldon Spackman
Research Fellow, Centre for Health Economics, University of York

Mr David Thomson
Lay Member

Dr John Watkins
Clinical Senior Lecturer/Consultant in Public Health Medicine, Cardiff University and National Public Health Service Wales

Dr Olivia Wu
Reader in Health Economics, University of Glasgow

6.2 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.

Matthew Dyer
Technical Lead

Zoe Garrett
Technical Adviser

Bijal Joshi
Project Manager

Sources of evidence considered by the Committee

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

- Cummins E, Scott N, Rothnie K et al. Dapagliflozin for the treatment of type 2 diabetes. Aberdeen HTA Group, Institute of Applied Health Sciences, University of Aberdeen, November 2012.

The Decision Support Unit (DSU) reports for this appraisal are:

- Davis S, Sheard J. A review of the Bristol-Myers Squibb/AstraZeneca economic model on the cost-effectiveness of dapagliflozin, November 2012.
- Davis S. Dapagliflozin for the treatment of type 2 diabetes: Additional analyses requested by the Committee following the second meeting, April 2013.

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). Manufacturers or sponsors 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. Manufacturers or sponsors, Professional or specialist and patient or carer groups, and other consultees, also have the opportunity to appeal against the final appraisal determination.

Manufacturers or sponsors:

- Bristol Myers-Squibb and AstraZeneca

Professional or specialist and patient or carer groups:

- Black Ethnic Minority Diabetes Association
- Diabetes UK
- National Diabetes Nurses Consultant Group
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

Other consultees:

- Department of Health
- Welsh Assembly Government
- NHS Middlesbrough

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

- Aberdeen HTA Group
- Boehringer Ingelheim and Lilly UK (linagliptin)
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Eli Lilly (exenatide, insulin)
- Health Improvement Scotland
- National Institute for Health Research Health Technology Assessment Programme
- Novo Nordisk (insulin, liraglutide)
- Pfizer (glipizide)

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

- Professor Eric Kilpatrick, Consultant in Chemical Pathology, Hull and East Yorkshire Hospitals NHS Trust nominated by organisation representing Royal College of Pathologists – clinical specialist (first Committee meeting)
- Dr Peter Winocour, Consultant Physician and Clinical Director of Diabetes and Endocrine Services nominated by organisation representing Association of British Clinical Diabetologists (ABCD) and Royal College of Physicians (RCP) – clinical specialist (first Committee meeting)
- Professor Jiten Vora, Consultant Physician and Endocrinologist nominated by organisation representing Royal College of Physicians and Association of British Clinical Diabetologists – clinical specialist (second Committee meeting)
- Mrs Cathy Moulton, Clinical Advisor nominated by organisation representing Diabetes UK – patient expert
- Ms Aderonke Kuti, Executive Director, nominated by organisation representing Black and Ethnic Minority Diabetes Association – patient expert

The following individuals were nominated as NHS Commissioning experts by the selected Commissioning Group allocated to this appraisal. They gave their expert/NHS commissioning personal view on dapagliflozin by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Ms Joanne Linton, Assistant Director Medicines Management selected by NHS Tees – NHS commissioning expert
- Dr Victoria Ononeze, Public Health Specialist selected by NHS Tees – NHS commissioning expert

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

- Bristol Myers-Squibb and AstraZeneca (dapagliflozin)

Update information

November 2016: Recommendation 1.3 has been amended in response to the publication of NICE's technology appraisal guidance on dapagliflozin in triple therapy for treating type 2 diabetes.

December 2015: Recommendation 1.1 and the related NICE guidance section have been amended in response to the publication of the updated NICE guideline CG87 on type 2 diabetes in adults (now replaced by NICE's guideline on type 2 diabetes in adults).

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