

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Dapagliflozin in combination therapy for treating type 2 diabetes

This premeeting briefing is a summary of:

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

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

Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- The scope for this appraisal includes dapagliflozin in dual therapy, triple therapy and as add-on therapy to insulin. However, the manufacturers restricted their main submission to add-on therapy to metformin and add-on therapy to insulin. Preliminary clinical and cost-effectiveness evidence was presented in an addendum to the manufacturers' submission for dapagliflozin in triple therapy. What is the Committee's view on the likely place of dapagliflozin in UK clinical practice? Should dapagliflozin in triple therapy be considered?
- The manufacturers have not presented an analysis of the clinical effectiveness of dapagliflozin in people with type 2 diabetes that is inadequately controlled on sulfonylurea monotherapy. This is because [NICE clinical guideline 87 \(The management of type 2 diabetes\)](#) recommends sulfonylurea monotherapy as an alternative to metformin only for a restricted patient subgroup (see Appendix B). There is published clinical trial evidence of dapagliflozin as an add-on to sulfonylurea

monotherapy in adults with type 2 diabetes, although this was not included in the manufacturers' submission. Does the Committee agree with the manufacturers' decision not to consider the clinical effectiveness of dapagliflozin in this patient group?

- Although GLP-1 analogues (liraglutide and long-acting exenatide) were listed in the scope as relevant comparator treatments in the dual therapy setting the manufacturers did not include a comparison with dapagliflozin on the basis that current NICE guidance (NICE technology appraisals 203 and 248) recommends liraglutide and long-acting exenatide on a restricted basis. GLP-1 analogues were also excluded as comparators in the add-on to insulin setting. Does the Committee agree that it is appropriate to exclude GLP-1 analogues as comparator treatments in the add-on to metformin and add-on to insulin settings?
- The dapagliflozin trials are international with limited enrolment in the UK, further a professional group considered that the exclusion criteria may reduce the applicability of the results to the wider UK population. Does the Committee consider that the trial data may be applied to the UK context?
- Because of an absence of head-to-head trials comparing dapagliflozin with a number of relevant comparators listed in the scope (dipeptidyl peptidase-4 [DPP-4] inhibitors and thiazolidinediones), the clinical-effectiveness data were largely drawn from network meta-analyses conducted by the manufacturers. What is the Committee's view of the methodological quality and reporting of these analyses?
- The clinical effectiveness of dapagliflozin in triple therapy (for people with type 2 diabetes that is insufficiently controlled by metformin and sulfonylurea) was based on pooled data of a subset of patients in 2 randomised controlled trials of older people with cardiovascular disease.
 - What is the Committee's view on the robustness of these data?
 - Is it appropriate for the manufacturers to limit the triple therapy combination to dapagliflozin added to metformin and sulfonylurea?

- Is it appropriate for the manufacturers not to compare dapagliflozin with insulin in the triple therapy setting?
- Adverse events (except for hypoglycaemic events) associated with dapagliflozin were presented by the manufacturers as pooled estimates. What is the Committee's view on the safety of dapagliflozin for the treatment of type 2 diabetes and the importance of these data to the economic modelling?

Cost effectiveness

- The decision support unit (DSU) highlighted a number of issues about the description and functioning of the economic model submitted by the manufacturers. Is the Committee confident that the economic model functions as described in the manufacturers' submission?
- What is the Committee's view about whether the assumptions in the model in terms of the HbA_{1c} threshold applied for switching treatment and treatment pathways modelled adequately reflect UK clinical practice for people with type 2 diabetes?
- Does the Committee consider the risk equations from the UKPDS 68 study (used to estimate the probability of diabetic complications) to be correctly implemented in the model?
- The health-related quality of life and cost inputs are drawn from a range of different sources. Does the Committee consider that the values have been appropriately identified and are plausible?
- The quality-adjusted life year (QALY) gains associated with dapagliflozin were largely driven by the impact of changes in body weight on health-related quality of life. Does the Committee consider the utility values associated with changes in body weight used by the manufacturers to be appropriate?
- Despite the issues highlighted by the DSU and the ERG, does the Committee consider the results from the economic model sufficiently robust

to suggest that dapagliflozin as a dual therapy or triple therapy is a cost-effective use of NHS resources?

1 Background: clinical need and practice

- 1.1 Diabetes mellitus is a chronic metabolic disorder characterised by elevated blood glucose levels (hyperglycaemia) resulting from a lack of the hormone insulin or resistance to its action. There are 2 main types of diabetes. Type 1 diabetes is caused by an absolute loss of insulin production. Type 2 diabetes is caused by reduced tissue sensitivity to insulin (known as insulin resistance) and a failure of insulin secretion to compensate for this. Type 2 diabetes is associated with obesity.
- 1.2 In people with untreated type 2 diabetes, symptoms include excessive production of urine (polyuria), thirst, weight loss and fatigue. Type 2 diabetes is also associated with an increased cardiovascular risk. This can manifest as coronary artery disease (leading to heart attacks and angina), peripheral artery disease (leading to leg claudication and gangrene), and carotid artery disease (linked to strokes and dementia). If not managed effectively, diabetes can also lead to complications including kidney failure, blindness, limb amputation, and damage to the nervous system, peripheral vasculature and skin. Cardiovascular disease is the most common complication associated with type 2 diabetes and is the greatest cause of morbidity and premature death.
- 1.3 There were approximately 2.9 million people in the UK aged 17 or older with diabetes mellitus in 2011, 90% of whom had type 2 diabetes. However, there are many people with undiagnosed type 2 diabetes so the real number is likely to be higher. Type 2 diabetes is particularly prevalent in people of African, South Asian and

Caribbean family origin. The prevalence of type 2 diabetes in the UK is rising due to the increasing prevalence of obesity and decreased physical activity, but also increased longevity after diagnosis because of better cardiovascular risk protection. Life expectancy is reduced by up to 10 years in people with diabetes.

- 1.4 NICE clinical guideline 87 recommends diet and lifestyle modifications to initially manage type 2 diabetes. For people who are overweight or obese and whose blood glucose is inadequately controlled by diet and lifestyle modifications, the oral anti-diabetic drug, metformin is recommended. A sulfonylurea (for example, gliclazide, glipizide, or glimepiride) may be considered as a monotherapy option if the person is not overweight, does not tolerate metformin or a rapid response is needed because of hyperglycaemia. If blood glucose control remains inadequate on monotherapy with metformin, a sulfonylurea should be added. A thiazolidinedione (pioglitazone) or a dipeptidyl DPP-4 inhibitor such as sitagliptin or vildagliptin can be used as an add-on therapy to monotherapy with metformin or a sulfonylurea if the combination of metformin and sulfonylurea as dual therapy is not considered appropriate. The glucagon-like peptide-1 (GLP-1) analogues (exenatide and liraglutide) are recommended in NICE technology appraisal guidance [203](#) and [248](#) as options for dual therapy if metformin or a sulfonylurea is contraindicated or not tolerated and a thiazolidinedione and a DPP-4 inhibitor is contraindicated or not tolerated.
- 1.5 For people whose disease is not controlled on dual therapy, NICE clinical guideline 87 recommends starting insulin in preference to adding other drugs. However, either sitagliptin or pioglitazone are recommended as options for add-on therapy to metformin and sulfonylurea if insulin is considered unacceptable (because of

employment, social, recreational or other personal issues). The twice-daily or the prolonged-release regimens of exenatide (an incretin mimetic) may be prescribed in line with NICE clinical guideline 87 and technology appraisal guidance 248, [Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes](#). Exenatide is recommended as an option for triple therapy for people with a high body mass index ($\geq 35 \text{ kg/m}^2$) in those of European descent (with an adjustment for other ethnic groups) if certain criteria are met, and blood glucose control remains/becomes inadequate on metformin and sulfonylurea treatment. It is also recommended for use in patients with a body mass index lower than 35 kg/m^2 if therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities. Liraglutide is recommended in NICE technology appraisal guidance 203 as a triple therapy if it is used as described for exenatide in NICE clinical guideline 87. Please see Appendix B for a summary of all relevant recommendations from NICE clinical guideline 87 and NICE technology appraisal guidance 203 and 248.

2 The technology

- 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 sulphonylurea or insulin), urinary tract 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 $\text{CrCl} < 60 \text{ ml/min}$ or $\text{eGFR} < 60 \text{ ml/min/1.73 m}^2$) because its efficacy is dependent on renal function.

Dapagliflozin is also not recommended for use in combination with pioglitazone because of the increased risk of bladder cancer in people treated with pioglitazone. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The manufacturer submission states that the cost of dapagliflozin is £36.59 for 28 tablets (excluding VAT). 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 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was to appraise the clinical and cost effectiveness of dapagliflozin within its licensed indication for the treatment of type 2 diabetes.

	Final scope issued by NICE	Decision problem addressed in the submission
Population	<p>Dual therapy Adults with type 2 diabetes that is inadequately controlled on monotherapy with either metformin or a sulfonylurea.</p> <p>Triple therapy Adults with type 2 diabetes that is inadequately controlled on dual therapy with either of the following:</p> <ul style="list-style-type: none"> • metformin in combination with a sulfonylurea • metformin or a sulfonylurea in combination with a thiazolidinedione, a DPP-4 inhibitor, or a GLP-1 analogue. <p>Add-on therapy to insulin Adults with type 2 diabetes that is inadequately controlled on monotherapy with insulin or on therapy with insulin and up to 2 other oral agents.</p>	<p>Dual therapy Adults with type 2 diabetes that is inadequately controlled on monotherapy with metformin.</p> <p>Triple therapy Adults with type 2 diabetes that is inadequately controlled on dual therapy with:</p> <ul style="list-style-type: none"> • metformin in combination with a sulfonylurea. <p>Add-on therapy to insulin Adults with type 2 diabetes that is inadequately controlled on monotherapy with insulin or on therapy with insulin and up to 2 other oral agents.</p>

Dual therapy

The manufacturers did not include adults with type 2 diabetes that is inadequately controlled on sulfonylurea monotherapy in their submission. The manufacturers considered that sulfonylureas are only recommended if the person exhibits osmotic symptoms that need rapid control, is not overweight or does not tolerate metformin. Although it was not included as part of the manufacturer submission, a randomised controlled trial of dapagliflozin in adults with type 2 diabetes that is inadequately controlled on sulfonylurea monotherapy has also been published (Strojek et al. 2011)¹. The ERG

¹ Strojek et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. *Diabetes Obes Metab.* 2011 Oct;13 (10):928-38.

commented that the standard first-line monotherapy in type 2 diabetes is metformin, which is usually tolerated.

Triple therapy

The manufacturers stated that dapagliflozin is currently being studied as a triple therapy (as add-on to 2 other oral agents). They commented that there are no studies of dapagliflozin in combination with GLP-1 analogues and that dapagliflozin is not recommended for use in people taking pioglitazone (a thiazolidinedione).

	Final scope issued by NICE	Decision problem addressed in the submission
Intervention	Dapagliflozin (in combination with oral anti-diabetic agents and/or insulin).	Dapagliflozin 10mg once daily (in combination with oral anti-diabetic agents and/or insulin)

	Final scope issued by NICE	Decision problem addressed in the submission
<p>Comparators</p>	<p>Dual therapy</p> <p>For the combination of dapagliflozin and metformin, the comparators are:</p> <ul style="list-style-type: none"> • sulfonylureas (with metformin) • pioglitazone (with metformin) • DPP-4 inhibitors (with metformin) • GLP-1 analogues (with metformin). <p>For the combination of dapagliflozin and sulfonylurea, the comparators are:</p> <ul style="list-style-type: none"> • pioglitazone (with a sulfonylurea) • DPP-4 inhibitors (with a sulfonylurea) • GLP-1 analogues (with a sulfonylurea). <p>Triple therapy</p> <p>For the combination of dapagliflozin, metformin and a sulfonylurea, the comparators are:</p> <ul style="list-style-type: none"> • pioglitazone (with metformin and a sulfonylurea) • DPP-4 inhibitors (with metformin and a sulfonylurea) • GLP-1 analogues (with metformin and a sulfonylurea) • insulin (with metformin and a sulfonylurea). <p>For the combination of dapagliflozin, metformin and pioglitazone, the comparators are:</p> <ul style="list-style-type: none"> • DPP-4 inhibitors (with metformin and pioglitazone) • GLP-1 analogues (with metformin and pioglitazone) • insulin (with metformin and pioglitazone). 	<p>Dual therapy</p> <p>For the combination of dapagliflozin and metformin:</p> <ul style="list-style-type: none"> • sulfonylureas (with metformin) • thiazolidinediones (with metformin) • DPP-4 inhibitors (with metformin) <p>Triple therapy</p> <p>For the combination of dapagliflozin, metformin and a sulfonylurea:</p> <ul style="list-style-type: none"> • thiazolidinediones (with metformin and a sulfonylurea) • DPP-4 inhibitors (with metformin and a sulfonylurea) • GLP-1 analogues (with metformin and a sulfonylurea)

	<p>For the use of dapagliflozin in any other triple therapy regimen, the comparator is:</p> <ul style="list-style-type: none"> insulin (alone or in combination with 1 or more oral anti-diabetic agents). <p>Add-on therapy to insulin</p> <p>One or more oral anti-diabetic agents (in combination with insulin).</p>	<p>Add-on therapy to insulin</p> <p>DPP-4 (with insulin).</p>
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Dual therapy

The manufacturers considered that a comparison with GLP-1 analogues is not appropriate in this setting because these therapies are recommended by NICE clinical guideline 87 only if metformin or a sulfonylurea is not tolerated or is contraindicated, and a thiazolidinedione and a DPP-4 inhibitor is contraindicated or not tolerated. The manufacturers stated that the proportion of people in this setting who receive a GLP-1 analogue is less than 5% and therefore that these therapies are not considered routine clinical practice. The ERG supports this position, citing the recommendations in technology appraisal guidance 203 and 248 that the use of liraglutide and long-acting exenatide as dual therapies should be very restricted. The ERG stated that NICE clinical guideline 87 recommends the use of pioglitazone as an alternative add-on treatment to 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. Overall, the ERG considered that a DPP-4 inhibitor is the key comparator for dapagliflozin in the dual therapy setting.

Triple therapy

The ERG noted that insulin is not often used in triple therapy because of its side effects and the need for intensive treatment to maintain glycaemic

control. The ERG also commented that it would expect a DPP-4 inhibitor (with metformin and a sulfonylurea) to be used before long-acting exenatide on the grounds of cost and the need to inject exenatide. Therefore, again the ERG considered that a DPP-4 inhibitor is the key comparator for dapagliflozin in triple therapy.

	Final scope issued by NICE	Decision problem addressed in the submission
Outcomes	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> • HbA_{1c}/glycaemic control • frequency and severity of episodes of hypoglycaemia • calculated cardiovascular risk (including blood pressure and/or serum lipids) • weight change • complications of diabetes for example, cardiovascular, renal and eye • mortality • adverse effects of treatment (including genitourinary tract infection) • health-related quality of life. 	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> • HbA_{1c} • weight change • total cholesterol, high-density lipoprotein (HDL) cholesterol, systolic blood pressure • incidence of ischaemic heart disease, myocardial infarction, congestive heart failure, stroke, blindness, amputation, end-stage renal disease, non-cardiovascular death • Drug-related outcomes including hypoglycaemic episodes and weight change.

	Final scope issued by NICE	Decision problem addressed in the submission
Economic evaluation	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p>	<p>Cost effectiveness will be expressed in terms of cost per quality-adjusted life year.</p> <p>A lifetime horizon (40 years) will be included in the base case. Shorter modelling time frames will also be included for information.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p>
	Final scope issued by NICE	Decision problem addressed in the submission
Other considerations	<p>If evidence allows, subgroups based on the following criteria will be considered:</p> <ul style="list-style-type: none"> • body mass index • HbA_{1c} • duration of diabetes • dose of insulin. 	<p>Subgroups based on the following criteria will be considered:</p> <ul style="list-style-type: none"> • body mass index <30 and >30 • baseline HbA_{1c}.

The manufacturers stated that subgroup analyses according to dose of insulin and duration of diabetes were not undertaken.

3.2 According to the manufacturer, dapagliflozin would be positioned in the treatment pathway for type 2 diabetes as follows:

- As a dual therapy, dapagliflozin can be added to metformin as an alternative treatment option to sulfonylurea, in people for whom sulfonylurea is not appropriate because of the risk of hypoglycaemia, or in whom weight loss is a treatment goal.
- As an add-on to insulin, dapagliflozin can also be added to insulin with or without metformin in people whose condition is not adequately controlled on insulin and in whom increasing doses

of insulin would result in an increased risk of hypoglycaemia and/or weight gain.

- 3.3 The manufacturers commented that the efficacy and safety of dapagliflozin in triple therapy with metformin and sulfonylurea is still being evaluated in a prospective, randomised controlled trial, which is expected to be finished in late 2013. The manufacturers provided a preliminary assessment of the efficacy and safety of dapagliflozin in triple therapy to fully address the appraisal scope, and recognising that some clinicians may wish to use dapagliflozin in this position.

4 Clinical-effectiveness evidence

- 4.1 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 of which were in patients with type 2 diabetes inadequately controlled on metformin alone (Bailey et al. 2010; Bolinder et al. 2012; Nauck et al. 2011) and 2 in patients with type 2 diabetes inadequately controlled on insulin with or without oral antidiabetic drugs (Wilding et al. 2009 and 2012).

Dual therapy and add-on to insulin

- 4.2 Of the 3 trials of dapagliflozin as an add-on to metformin, 2 were placebo controlled with follow-up of 24 weeks (Bailey et al. 2010; Bolinder et al. 2012) and 1 compared dapagliflozin with a sulfonylurea for up to 52 weeks of follow-up (Nauck et al. 2011). The primary outcomes assessed were change in HbA_{1c} from baseline (Bailey et al. 2010; Nauck et al. 2011) or changes in body weight from baseline (Bolinder et al. 2012). 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. A summary of the baseline patient characteristics of the 3 add-on to metformin trials is presented in table 1.

- 4.3 The 2 trials of dapagliflozin as an add-on to insulin were both placebo controlled with follow-up of 12 weeks (Wilding et al. 2009) or 24 weeks (Wilding et al. 2012). 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. A summary of the baseline patient characteristics from the 2 add-on to insulin trials is presented in table 1.

Table 1. Summary of baseline patient characteristics from 5 dapagliflozin trials

	Bailey et al. (2010) (study 14)	Bolinder et al. (2012) (study 12)	Nauck et al. (2011) (study 4)	Wilding et al. (2009) (study 6)	Wilding et al. (2012) (study 9)
Mean age (Years)					
Dapagliflozin	52.7	60.6	58.1	59.3	55.7
Comparator	53.7	60.8	58.6	58.8	58.4
Sex (% male)					
Dapagliflozin	57	55	55	45	54
Comparator	55	56	55	49	70
Mean HbA_{1c} level (%)					
Dapagliflozin	7.92	7.19	7.69	8.57	8.40
Comparator	8.11	7.16	7.74	8.47	8.40
Mean body weight (kg)					
Dapagliflozin	86.10	92.06	88.44	94.50	103.40
Comparator	87.85	90.91	87.60	94.50	101.80
Mean systolic blood pressure (mmHg)					
Dapagliflozin	126.0	135.9	132.8	140.6	130.7
Comparator	127.7	133.3	133.8	136.1	128.9

4.4 A summary of the key clinical effectiveness results from the 3 trials of dapagliflozin as an add-on to metformin is presented in table 2. Dapagliflozin was associated with a statistically significant reduction in HbA_{1c} compared with placebo at 24 weeks (Bailey et al., Bolinder et al.). It was shown to be non-inferior ($p < 0.0001$) to sulfonylurea at 52 weeks (Nauck et al.). A statistically significantly higher proportion of patients treated with dapagliflozin achieved an HbA_{1c} target of less than 7% (41% versus 26%, $p = 0.006$)

compared with placebo at 24 weeks (Bailey et al.). Dapagliflozin was associated with a statistically significant reduction in body weight compared with placebo at 24 weeks (Bailey et al. Bolinder et al.) and with sulfonylurea at 52 weeks (Nauck et al.). Dapagliflozin was associated with a reduction in systolic and diastolic blood pressure compared with placebo at 24 weeks (Bailey et al. Bolinder et al.) and with sulfonylurea at 52 weeks (Nauck et al.).

Dapagliflozin was not associated with an increased risk of hypoglycaemia compared with placebo at 24 weeks (Bailey et al. Bolinder et al.) and 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 sulfonylurea by 52 weeks (Nauck et al.).

- 4.5 A summary of the key clinical effectiveness results from the 2 trials of dapagliflozin as an add-on to insulin therapy (with or without metformin) is presented in table 2. Dapagliflozin was associated with a statistically significant reduction in HbA_{1c} compared with placebo at 12 weeks (Wilding et al. 2009) and 24 weeks (Wilding et al. 2012). Dapagliflozin was associated with a statistically significant reduction in body weight and systolic blood pressure compared with placebo at 24 weeks (Wilding et al. 2012). A higher proportion of patients treated with dapagliflozin experienced at least 1 hypoglycaemic event (42.3% versus 35.0%) compared with placebo by 24 weeks. However, dapagliflozin was not associated with a statistically significantly higher risk of hypoglycaemic events compared with placebo (odds ratio [OR] 1.36 95% CI 0.91 to 2.05) (Wilding et al. 2012). Dapagliflozin was also associated with a statistically significant reduction in the calculated mean daily insulin dose (-1.16 International Units/day versus 5.08 International Units/day, $p < 0.0001$) compared with placebo at 24 weeks (Wilding et al. 2012).

4.6 The manufacturers conducted pre-planned analyses to determine if there were any variations in the clinical effectiveness of dapagliflozin for the following subgroups: race, ethnicity, baseline HbA_{1c}, age, gender and baseline BMI. Subgroup analyses were conducted on pooled data as well some of the individual studies of dapagliflozin. The manufacturers reported that no significant interactions by subgroup were observed, except for baseline HbA_{1c}. Dapagliflozin treatment was clinically effective across baseline HbA_{1c} subgroups (<8%, ≥8% and <9%, >9%) and generally resulted in greater HbA_{1c} reductions from baseline in people with higher baseline HbA_{1c}.

Table 2: Summary of key clinical effectiveness results of 5 trials of dapagliflozin as dual therapy

Study	Intervention and comparator	Time point used for primary analysis	HbA _{1c} (mean change from baseline) (95% CI) (%)	Weight (mean change from baseline) (95% CI) (kg)	SBP (mean change from baseline) (95% CI) (mmHg)
Metformin add-on studies					
Bailey et al. 2010 (study 14)	Dapagliflozin (n=135)	24 weeks	-0.84 (-0.98, -0.70)	-2.86 (-3.33, -2.39)	-5.1 (-7.7, -2.5)
	Placebo (n=137)		-0.30 (-0.44, -0.16)	-0.89 (-1.35, -0.42)	-0.2 (-2.6, 2.2)
			p<0.0001	p<0.0001	p value not reported
Bolinder et al. 2012 (study 12)	Dapagliflozin (n=91)	24 weeks	-0.39 (-0.48, -0.29)	-2.96 (-3.51, -2.41)	-2.70 (-4.90, -0.60)
	Placebo (n=91)		-0.10 (-0.20, -0.01)	-0.88 (-1.43, -0.34)	0.10 (-2.00, 2.20)
			p<0.0001	p<0.0001	p-value not reported
Nauck et al. 2011 (study 4)	Dapagliflozin (n=406)	52 weeks	-0.52 (-0.60, -0.44)	-3.22 (-3.56, -2.87)	-4.3 (-5.4, -3.2)
	Sulfonylurea (glipizide) (n=408)		-0.52 (-0.60, -0.44)	1.44 (1.09, 1.78)	0.8 (-0.3, 1.9)
			p<0.0001	p<0.0001	p<0.0001
Insulin add-on studies					
Wilding et al. 2009 (study 9)	Dapagliflozin (n=24)	12 weeks	-0.61 (-0.87, -0.36)	-4.51 (-5.48, -3.53)	-7.2 (-12.1, -2.3)
	Placebo (n=23)		0.09 (-0.19, 0.37)	-1.88 (-2.89, -0.88)	2.8 (-4.9, 10.5)
			p value not reported	p value not reported	p value not reported
Wilding et al. 2012 (study 6)	Dapagliflozin (n=194)	24 weeks	-0.96 (NR)	-1.67 (-2.02, -1.31)	-6.9 (-8.7, -5.1)
	Placebo (n=193)		-0.39 (NR)	0.02 (-0.34, 0.38)	-3.9 (-5.7, -2.1)
			p<0.001	p<0.0001	p=0.02
CI, confidence interval					

Network meta-analysis

- 4.7 The manufacturers conducted a number of network meta-analyses to compare the clinical effectiveness of dapagliflozin as an add-on to metformin or insulin with other relevant comparator therapies listed in the scope. The 4 outcomes assessed were: 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 (including major and non-major episodes).
- 4.8 For the comparison of 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 outcomes other than systolic blood pressure, the network included 4 classes of add-on therapy to metformin (dapagliflozin, DPP-4 inhibitors, GLP-1 analogues and thiazolidinediones) and placebo in 15 studies. For the 52-week analysis, the network included 4 classes of add-on therapy (dapagliflozin, DPP-4 inhibitors, thiazolidinediones and sulfonylureas) in 6 studies. For the 24-week analysis of systolic blood pressure, the network included 5 classes of add-on therapy (dapagliflozin, DPP-4 inhibitors, GLP-1 analogues, sulfonylureas, thiazolidinediones) and placebo in 8 studies.
- 4.9 For the comparison of dapagliflozin as an add-on to insulin, the manufacturers conducted a single network meta-analysis for the 4 outcome measures at 24 weeks (± 8 weeks). The network included 3 add-on therapies (dapagliflozin, DPP-4 inhibitors and thiazolidinediones) and placebo in 4 studies. The 12-week study of dapagliflozin (Wilding et al. 2009) and 3 other studies were

excluded from this analysis because they allowed up-titration of insulin in order to maintain glycaemic control.

- 4.10 The manufacturers commented that, because of differences in the design, patient characteristics and duration of follow-up of the studies included in the analyses, variability in the true effect sizes in the included studies was assumed. Therefore, random-effects models were selected over fixed-effects models. Because of the potential modifying effects of baseline HbA_{1c} on changes in HbA_{1c} from baseline, some analyses were adjusted for interaction between treatment and baseline HbA_{1c}.
- 4.11 The results of the network meta-analyses for the add-on to metformin comparisons showed that dapagliflozin was associated with a statistically significant reduction in HbA_{1c} compared with placebo at 24 weeks. No statistically significant differences in the change in HbA_{1c} at 24 weeks or 52 weeks were reported between dapagliflozin and other classes of therapy. Dapagliflozin was associated with a statistically significant reduction in body weight compared with placebo at 24 weeks. Dapagliflozin was also associated with a statistically significant reduction in body weight compared with DPP-4 inhibitors, thiazolidinediones and sulfonylureas at 52 weeks. Dapagliflozin was associated with a statistically significant reduction in systolic blood pressure compared with placebo and sulfonylurea at 24 weeks. However, no statistically significant differences in change in systolic blood pressure at 24 weeks were reported between dapagliflozin and the other 3 drug therapies. No statistically significant differences were reported between dapagliflozin and other drug therapy classes in the risk of hypoglycaemia at 24 weeks. However, dapagliflozin was associated with a statistically significantly lower risk of experiencing a hypoglycaemic event compared with sulfonylurea at 52 weeks.

- 4.12 For the network meta-analyses of add-on therapy to insulin, the 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 manufacturers commented that 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.
- 4.13 The results of the network meta-analyses for the add-on to insulin comparisons showed that dapagliflozin was associated with a statistically significant reduction in HbA_{1c} compared with placebo at 24 weeks. 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 associated with a statistically significant increase in HbA_{1c} compared with thiazolidinediones. Dapagliflozin was associated with a statistically significant reduction in body weight compared with placebo and DPP-4 inhibitors. No numerical data for the differences in changes in body weight were presented by the manufacturers for the comparison of dapagliflozin and thiazolidinediones. However, they were reported in the text to be similar. Dapagliflozin was associated with a statistically significantly lower risk of experiencing a hypoglycaemic event compared with thiazolidinediones at 24 weeks. However, no statistically significant differences were reported for the comparison of dapagliflozin with DPP-4 inhibitors and placebo.

Adverse events

4.14 The manufacturers presented data on the risk of adverse reactions associated with dapagliflozin on the basis of pooled results from a variety of 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 rates of genital and urinary tract infections and volume depletion events (hypotension/hypovolaemia/dehydration) were slightly higher in patients treated with dapagliflozin. Renal impairment or failure events were reported for a small proportion of patients (<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 those who received placebo (1.35%). However, rates of bladder cancer, prostate cancer and breast cancer were higher in patients treated with dapagliflozin. In terms of cardiovascular safety, the manufacturers referred to a pre-specified meta-analysis of 14 randomised controlled trials that was part of their regulatory submission to the US Food and Drug Administration (FDA). The manufacturers reported that there was no evidence that dapagliflozin is associated with an increased cardiovascular risk based on a composite end point of cardiovascular death, myocardial infarction and stroke (hazard ratio [HR] 0.67, 95% CI 0.32 to 1.10).

Dapagliflozin as triple therapy

4.15 The manufacturers submitted 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 sulfonylurea in an addendum to the main submission. The manufacturers pooled data from a subset of patients (██████) who

were treated with metformin and sulfonylurea at baseline from 2 phase III clinical studies which were designed to assess the efficacy and safety of dapagliflozin in older patients (average age 63–64 years) with type 2 diabetes and cardiovascular disease (studies 18 and 19).

4.16 The results of the post hoc analysis of this patient subgroup showed that dapagliflozin was associated with a [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

4.17 The manufacturers did not conduct a systematic review of triple therapy for patients with type 2 diabetes that is inadequately controlled with metformin and sulfonylurea. However, the manufacturers referred to a literature review about add-on therapy to metformin and sulfonyurea for type 2 diabetes produced in 2009 by the Canadian Agency for Drugs and Technologies in Health (CADTH). 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. Thiazolidinediones but not DPP-4 inhibitors and GLP-1 analogues were associated with significant weight gain compared with

metformin and sulfonylureas. The manufacturers noted that since 2009 new data have become available on antidiabetic drugs in the triple therapy setting and specifically highlighted published studies of linagliptin and saxagliptin.

Evidence Review Group Comments

- 4.18 The ERG considered 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 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 30 and 46 weeks or greater than 58 weeks follow-up were identified in the review. The ERG also noted that, for the network meta-analysis of insulin add-on therapies, an amendment was made to the protocol to include studies in the range of 24 weeks \pm 8 weeks instead of \pm 6 weeks to allow studies of 16 weeks follow-up to be included in the analysis. The ERG considered that, although this approach increased the amount of clinical-effectiveness data for the insulin add-on analysis, this was a post hoc amendment to the protocol.
- 4.19 The ERG noted that the network meta-analyses for changes in HbA_{1c} from baseline were adjusted for differences in baseline HbA_{1c} but that no attempt was made to adjust the analyses for any other variables. The ERG considered that the manufacturers' approach to model selection lacked transparency and that insufficient justification was provided about whether or not adjusted results were presented. However, the ERG also noted that the results of the adjusted and unadjusted analyses were reasonably similar.

- 4.20 The manufacturers included dapagliflozin studies only with a dose of 10 mg once daily in the network meta-analyses, although other comparators included a variety of drugs and doses in each class of antidiabetic drug therapy. The ERG commented that the drugs and doses for the insulin add-on analyses were not clearly described in the manufacturers' submission. However, the ERG considered that the assumption that all drugs within each class of antidiabetic drug therapy were considered to be equivalent for the purposes of the network meta-analyses was reasonable. Because of the wide variation in the way that hypoglycaemic events were defined in the clinical trials, the manufacturers included both major and minor hypoglycaemic events in the network meta-analyses. The ERG considered that this approach was reasonable because of the limited data available. The ERG also considered that the exclusion of 2 trials of GLP-1 analogues combined with intensive diet regimes from the network meta-analyses was reasonable because such an intervention would be expected to lead to a much greater body weight loss than the use of a GLP-1 analogue alone.
- 4.21 The manufacturers excluded sulfonylureas from the network meta-analyses of add-on therapies to metformin at 24 weeks, except for the analysis of systolic blood pressure, because of an unstable effect size observed at this time point. The ERG considered that it was unusual to exclude only 1 class of drug therapy from the analyses for this reason and that more justification for this exclusion was needed. The ERG considered that the manufacturers' decision to exclude 3 placebo-controlled trials of thiazolidinediones from the insulin add-on network meta-analyses, because they allowed up-titration of insulin, was acceptable.
- 4.22 The ERG commented that the manufacturers' approach to presenting the clinical effectiveness of dapagliflozin as a triple

therapy add-on to metformin and 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.

- 4.23 The ERG noted that, except for hypoglycaemic events, no formal meta-analyses of data on adverse events were presented by the manufacturer. The ERG commented that the inclusion criteria for the studies included in the pooled analyses of adverse events varied according to the type of event and were not clearly stated, despite further clarification from the manufacturer. The ERG considered that the lack of clarity about the inclusion criteria used made interpretation of the results difficult. The ERG also considered that there was a lack of transparency about how studies had been selected for the analysis of the risk of cancer associated with dapagliflozin.

5 Comments from other consultees

- 5.1 A professional group noted that there is some variation in clinical practice guidelines for diabetes and that the early use of injectable (insulin and GLP-1 analogue) therapy and the relative risks of weight gain and hypoglycaemia compared with the established evidence base for the beneficial impact of glycaemic control with older sulfonylurea agents remain an area of uncertainty.
- 5.2 A professional group commented that a potential advantage of dapagliflozin is that it may improve glycaemic control in people with diabetes but without the weight gain associated with many other treatments. However, it also noted that it has yet to be established

how any repeated adverse effects, including urinary infections, may limit the long-term use of dapagliflozin. It noted that the exclusion in the dapagliflozin studies of patients at higher risk of genito-urinary infections and using diuretics meant that it was unclear whether study patients were representative of wider population with diabetes. The professional group further noted that no additional resources would be needed apart from the costs of educating staff who are responsible for prescribing the drug.

5.3 The patient groups stated that dapagliflozin will provide a further treatment option for people with type 2 diabetes and that any advantages or disadvantages of treatment with dapagliflozin are dependent on how long the person has lived with type 2 diabetes and how well they adhere to treatment. The patient groups stated that dapagliflozin has the potential to reduce the cost to the NHS of hospital admissions caused by complications of diabetes as well as offering improved quality of life. They noted the potential disadvantages of dapagliflozin to be more frequent hypoglycaemic episodes, urinary tract infections and genital infections, and that such adverse effects can cause discomfort and social problems for the patient. One patient group noted that the excretion of glucose through the urine may cause anxiety for some patients who understand an absence of glycosuria to be a sign of good diabetes management.

5.4 The commissioning expert stated that treatment with dapagliflozin would be expected to be initially delivered in a specialist clinical setting before eventually being delivered in primary care. They stated that the likely budget impact of dapagliflozin is currently unknown but will result in additional costs because it is an add-on therapy (to metformin or insulin). They also stated that there would be a need for education and training of NHS staff in delivering the

treatment. It is also expected that patient demand for the treatment will be quite high because of the potential impact on weight loss. The commissioning expert also suggested that NICE should recommend audit criteria for the continued use of dapagliflozin and that it would be helpful to see an algorithm illustrating the impact of lowering HbA_{1c} (as seen in the clinical trials) on mortality.

6 Cost-effectiveness evidence

6.1 A systematic review of the literature did not identify any publications related to the cost effectiveness of dapagliflozin for the treatment of type 2 diabetes. The manufacturers identified 4 UK-based economic evaluations of other antidiabetic drug therapies, as add-on to metformin. No UK-based economic evaluations of add-on therapies to insulin were identified.

Cost effectiveness of dapagliflozin in dual therapy

6.2 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 and for use 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. 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.

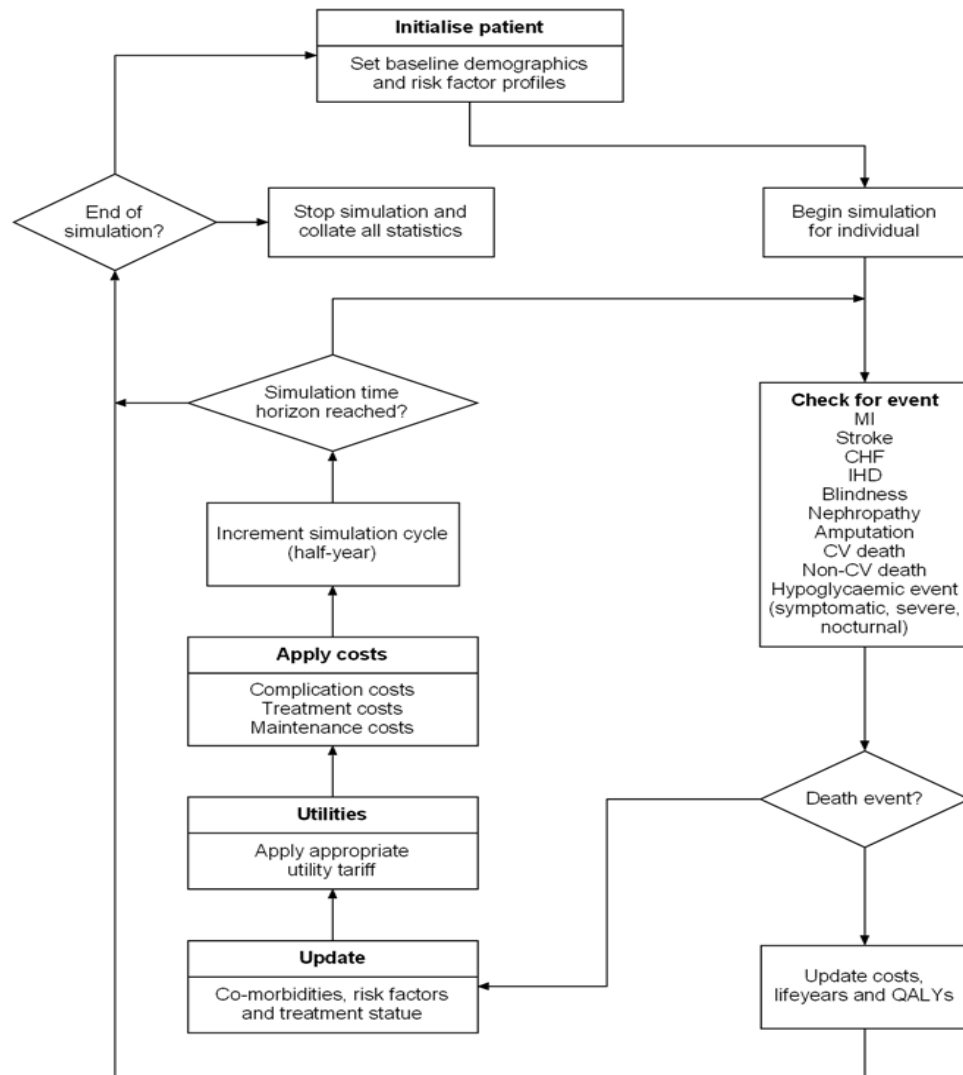
6.3 The manufacturers developed a simulation model run within an Excel front end but with the main calculations performed using C++ programming. The patient cohort entered the model with a set of baseline patient characteristics and modifiable risk factors which

included HbA_{1c}, total body weight, total cholesterol (TC) to high density lipoprotein (HDL) cholesterol ratio (TC:HDL) and systolic blood pressure. The value of these variables changed as the model simulation progressed, as a result of the effects of antidiabetic treatment and through natural progression, calculated from UK Prospective Diabetes Study (UKPDS number 68) risk factor equations. The model then predicted the incidence of 7 specific macro- and micro-vascular events on the basis of the UKPDS 68 event risk equations. Macro-vascular events predicted in the model included ischaemic heart disease, myocardial infarction, congestive heart failure and stroke. Micro-vascular 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. A schematic of the model is presented in figure 1.

- 6.4 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 during which they remained at risk of treatment-related adverse events and long-term macro- or micro-vascular events. Once a diabetes-related death or death from other causes occurred, costs, life years and QALYs were updated and the simulation ended for that patient.

6.5 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). The model included up to 2 additional therapy lines after dapagliflozin and the comparator. For the metformin add-on analysis, 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 in dose from the starting dose). For the insulin add-on analysis, second-line therapy was intensified insulin for the remainder of the simulation. An NHS and personal social services perspective was taken and costs and benefits were discounted at 3.5%.

Figure 1. Economic model schematic

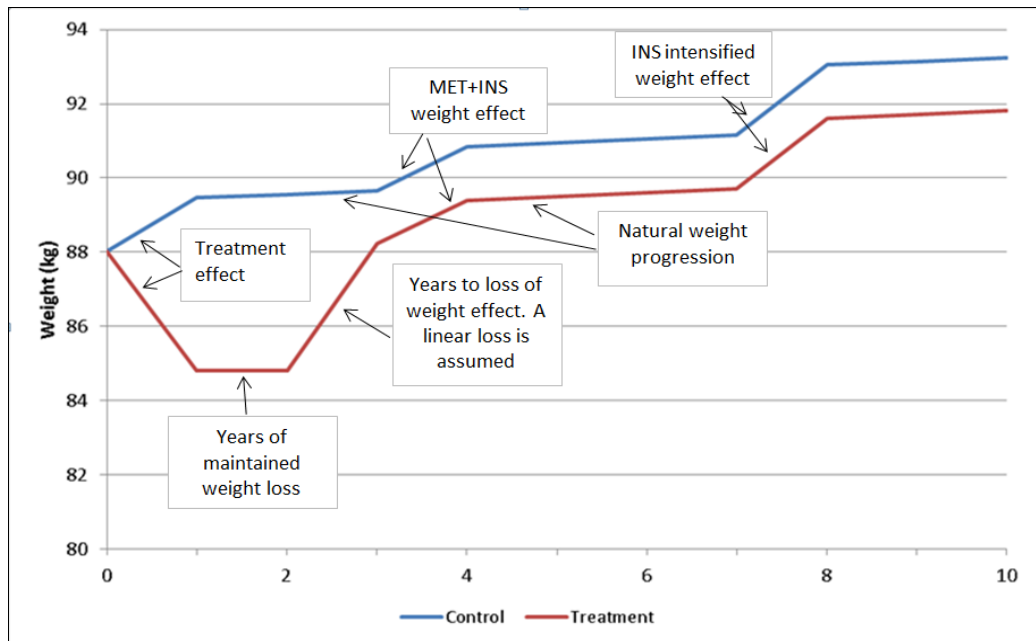


6.6 The baseline patient characteristics, modifiable risk factors and adverse event rates in the model were derived from the study by Nauck et al. (2011) for the comparison of dapagliflozin and sulfonylurea as add-on therapies to metformin and from the manufacturer network meta-analyses (at 24 weeks) for all of the other comparisons. The probability of treatment discontinuation because of adverse events was not available for the insulin add-on analysis, so this was assumed to be 0 for both dapagliflozin and DPP-4 inhibitors. 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% was used for the comparison of dapagliflozin and sulfonylurea (based on Nauck et al.) and a value of 8.17% was used for the comparison of dapagliflozin with DPP-4 inhibitors and thiazolidinediones (based on the metformin add-on network meta-analyses). In the insulin add-on analysis, a threshold value of 8.90% was used based on the insulin add-on network meta-analyses.

- 6.7 The economic model included changes in weight associated with treatment. Where 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 sulfonylurea as add-on to metformin (Del Prato et al. 2011). After year 2, weight was assumed to return to its baseline value until treatment switch 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 modelled as a change for the first year only, after which a natural progression in weight gain of 0.1 kg per year was assumed. The impact of treatment on in weight change in the model is illustrated in figure 2.

Figure 2. Impact of treatment on weight change in manufacturers' model (taken from page 212 of the manufacturer submission)



x-axis: years

6.8 The model estimated the impact of macro- and micro-vascular 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 EQ-5D data from a Department of Health Survey for England (2003) of patients with no major complications. 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 UKPDS patients with type 2 diabetes in 1996 to estimate the impact of diabetes-related complications on health-related quality of life. The impact of end-stage renal disease on health-related quality of life was taken from the Health Outcomes Data Repository (HODaR), a database of diabetic inpatients treated at Cardiff and Vale National Health Service Hospitals Trust by (Currie et al. 2005). The impact of change in body weight on health-related quality of life was taken from a study commissioned by the manufacturers of 100 Canadian

patients with type 2 diabetes who completed a time trade-off exercise (Lane et al. 2012). Regression modelling was used to estimate the association between respondents' body mass index and health-related quality of life. This resulted in separate values for the changes in health-related quality of life caused by a 1 unit decrease or increase in BMI. The impact of hypoglycaemic events on health-related quality of life was taken from a separate study by Currie et al. (2006), which estimated separate EQ-5D utility decrements for symptomatic, nocturnal and severe events in UK patients with type 2 diabetes. The impact of urinary tract infections on health-related quality of life was taken from a study of urinary tract infections in ambulatory women (Barry et al. 1997). In the absence of any other available data, the same utility values were used for genital infections. A summary of all utility values used in the model is presented in table 3.

Table 3. Summary of utility values used in the manufacturers' model

Health state or event	Utility value or decrement	Source
Baseline utility	Age dependent	DH Health Survey for England (2003)
Diabetes-related complications		
Ischaemic heart disease	-0.090	UKPDS 62 (Clarke et al. 2002)
Myocardial infarction	-0.055	
Congestive heart failure	-0.108	
Stroke	-0.164	
Amputation	-0.280	
Blindness	-0.074	
End-stage renal failure	-0.263	Currie et al. 2005
Hypoglycaemic events		
Symptomatic	-0.042	Currie et al. 2006
Nocturnal	-0.008	
Severe	-0.047	
Adverse events		
Urinary tract infection	-0.00283	Barry et al. 1997
Genital infection	-0.00283	
BMI changes		
per unit increase	-0.0472	Lane et al. 2012
per unit decrease	+0.0171	

6.9 The economic model included the acquisition costs of antidiabetic drugs, taken from England and Wales drug tariff (February 2012). In the base-case analysis, the daily costs of sulfonylureas and DPP-4 inhibitors were based on the most frequently prescribed drug therapies in these respective drug classes in the UK (gliclazide and sitagliptin). The daily cost of thiazolidinediones (pioglitazone) was calculated as a weighted average (based on UK prescription data) of the daily cost of 15 mg, 30 mg and 45 mg doses. The lowest cost for generic metformin and the lowest cost available human neutral protamine Hagedorn insulin regimen was

applied (Insuman Basal). 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 during 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. A summary of the drug acquisition costs applied in the model is presented in table 4.

- 6.10 The annual costs of macro and micro-vascular diabetic complications, except for end-stage renal failure, were taken from a UKPDS sub-study (UKPDS 65) of 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 (see table 4). The costs of end-stage renal failure were based on the average annual costs of automated peritoneal dialysis taken from a UK-based study by Baboolal et al. (2008). The costs of severe hypoglycaemic events (£390) were taken from a study by Hammer et al (2009), which 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.

Table 4. Costs of drug therapies and diabetic complications

Drug therapy	Price per tablet	Dose per tablet	Daily dose	Annual cost (£)
Dapagliflozin	£1.31	10 mg	10 mg	£476.92
SU (gliclazide)	£0.04	80 mg	160 mg	£27.90
DPP-4 (sitagliptin)	£1.19	100 mg	100 mg	£433.57
TZD (non-proprietary pioglitazone)	£1.13	28.8 mg	28.8 mg	£414.07
GLP-1 analogue (exenatide 55%; liraglutide 45%)	NA	NA	NA	£886.90
Metformin	£0.02	500 mg	2000 mg	£23.46
Insulin (Insuman basal) – add-on to metformin	£0.0053 per kg/day			
Intensified insulin – add-on to metformin	£0.0080 per kg/day			
Insulin (Insuman basal) – add-on to insulin	£0.0096 per kg/day			
Intensified insulin – add-on to insulin	£0.0120 per kg/day			
Annual medical costs of diabetic complications				
Event	Fatal	Non-fatal	Maintenance	
Ischaemic heart disease	-	£3,479	£1,149	
Myocardial infarction	£2,244	£6,709	£1,105	
Congestive heart failure	£3,880	£3,880	£1,360	
Stroke	£5,658	£4,103	£776	
Amputation	£13,359	£13,359	£771	
Blindness	-	£1,752	£742	
End-stage renal failure		£34,806	£34,806	
DPP-4, dipeptidyl peptidase-4; SU, sulfonylurea; TZD, thiazolidinedione.				

6.11 The manufacturers' base-case deterministic cost-effectiveness results for the add-on to metformin analyses are presented in table 5. The comparison between dapagliflozin and sulfonylurea resulted in an incremental cost-effectiveness ratio (ICER) of £2671 per QALY gained (incremental costs £1246, incremental QALYs

0.467). The comparisons between dapagliflozin and DPP-4 inhibitors and between dapagliflozin and thiazolidinediones showed 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.

6.12 The manufacturers’ base-case deterministic cost-effectiveness results for the add-on to insulin analysis are presented in table 5. The comparison between dapagliflozin and DPP-4 inhibitors resulted in an ICER of £4358 per QALY gained (incremental costs £517, incremental QALYs 0.119).

Table 5. Base-case deterministic cost-effectiveness results for the dual therapy analyses

Drug	Total			Incremental			ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	Incremental cost per QALY gained
Add-on to metformin							
Dapagliflozin versus sulfonylurea							
SU	£ 11,658	14.71	11.28	-	-	-	-
Dapagliflozin	£ 12,904	14.76	11.74	£ 1,246	0.050	0.467	£ 2,671
Dapagliflozin versus DPP-4, thiazolidinedione							
Dapagliflozin	£ 14,733	15.67	12.62				
Thiazolidine-dione	£ 14,793	15.67	12.20	£60	-0	-0.42	Dominated by dapagliflozin
DPP-4	£ 14,882	15.64	12.60	£149	-0.03	-0.02	Dominated by dapagliflozin
Add-on to insulin							
Dapagliflozin versus DPP-4							
DPP-4	£ 17,298	15.41	12.21	-	-	-	
Dapagliflozin	£ 17,815	15.41	12.33	£ 517	0.007	0.119	£ 4,358
DPP-4, dipeptidyl peptidase-4; LYG, life year gained; QALY, quality-adjusted life year; SU, sulfonylurea.							

- 6.13 The manufacturers conducted a number of one-way sensitivity analyses on various model input parameters, which included varying the lower and upper 95% confidence limits for the effect of antidiabetic drug therapies on modifiable risk factors, varying the utility decrement associated with adverse events by 10%, and varying the costs associated with adverse events by 25%. The manufacturers also presented a range of scenario analyses, which included: varying the HbA_{1c} threshold switch values, alternative BMI-related utility values, assuming no impact of hypoglycaemic events on utility, varying the duration of treatment effect on body weight, applying results of the 52 week network meta-analyses (for the add-on to metformin comparisons only), assuming no treatment discontinuation, and applying alternative baseline patient characteristics. For the metformin add-on comparisons, the ICERs for the comparison of dapagliflozin with sulfonylurea and thiazolidinediones were fairly robust to changes in all input parameters. For the comparison of dapagliflozin with DPP-4 inhibitors, dapagliflozin resulted in lower QALYs and higher costs when the upper 95% confidence limit for systolic blood pressure associated with dapagliflozin and the lower 95% confidence limit for systolic blood pressure associated with DPP-4 inhibitors were applied. When the upper 95% confidence limit for HbA_{1c} associated with dapagliflozin was applied, it resulted in lower costs and QALYs compared with DPP-4 inhibitors (an ICER of £3764 per QALY yielded).
- 6.14 The manufacturers presented 2 scenario analyses using alternative utility values for weight change. In the first of these scenarios a utility of ± 0.0061 was applied for a ± 1 unit change in BMI and in the second ± 0.0038 was applied for a ± 1 unit change in BMI. Both were taken from a study by Bagust et al. evaluating the impact of BMI on EQ-5D utility in patients with type 2 diabetes, and had been

used in previous health technology assessments. For the metformin add-on comparisons the ICERs for the comparison of dapagliflozin with sulfonylurea were £8,863 and £10,514 per QALY gained respectively. Dapagliflozin remained dominant for the comparison of dapagliflozin with DPP-4s and thiazolidinediones. For the comparison of dapagliflozin with DPP-4 inhibitors as add-on to insulin, the ICERs were sensitive to changes to the BMI-related utility values. When changes in, the ICERs increased to £21,171 and £32,409 per QALY gained respectively.

- 6.15 Results of the probabilistic sensitivity analyses for the metformin add-on comparisons showed that, at a cost-effectiveness threshold of £20,000 per QALY gained, the probability of dapagliflozin being cost effective was 100% compared with sulfonylurea, 66% compared with DPP-4 inhibitors and 100% compared with thiazolidinediones. Results of the probabilistic sensitivity analysis for the insulin-add on comparison with DPP-4 inhibitors showed that, at a cost-effectiveness threshold of £20,000 per QALY gained, the probability of dapagliflozin being cost effective was 99.6%.

Cost effectiveness of dapagliflozin in triple therapy

- 6.16 In an addendum to the main submission the manufacturers provided an assessment of the cost effectiveness of dapagliflozin in triple therapy for people with type 2 diabetes that is inadequately controlled with metformin and sulfonylurea. The model structure was identical to that used for the economic evaluation of dual therapies in the main submission. The comparator therapies as add-on to metformin and sulfonylurea were DPP-4 inhibitors, thiazolidinediones and GLP-1 analogues. Clinical effectiveness data were drawn from a pooled analysis of a subset of patients treated with dapagliflozin in studies 18 and 19 and the CADTH review of oral antidiabetic drugs as triple therapy. All comparator

triple therapies were assumed to be preceded by first-line dual therapy with metformin and sulfonylurea. The manufacturers assumed that after triple therapy, all patients would receive metformin and insulin. 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 based on the study by Nauck et al. (2011) of patients with type 2 diabetes inadequately controlled on metformin alone. The HbA_{1c} threshold for switching treatment was 7.72% based on the study comparing dapagliflozin with sulfonylurea as add-on to metformin (Nauck et al., 2011).

6.17 The manufacturers' base-case deterministic cost-effectiveness results for the triple therapy analyses as add-on to metformin and sulfonylurea are presented in table 6. The comparisons of dapagliflozin with DPP-4 inhibitors, thiazolidinediones and GLP-1 analogues showed that dapagliflozin dominated the 3 comparator drug therapies, resulting in lower costs and higher QALYs.

Table 6. Base-case deterministic cost-effectiveness results for triple therapy comparisons

Drug	Total			Incremental			ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	Incremental cost per QALY gained
Dapagliflozin	£11,865	14.69	11.71				
DPP-4 inhibitors	£11,974	14.70	11.47	£109	0.01	-0.24	Dominated by dapagliflozin
Thiazolidinediones	£11,951	14.70	11.09	£86	0.01	-0.62	Dominated by dapagliflozin
GLP-1 analogues	£13,244	14.70	11.69	£1,380	0.01	-0.02	Dominated by dapagliflozin

DPP-4, dipeptidyl peptidase-4; GLP: glucagon-like peptide; ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.

- 6.18 The manufacturers conducted a limited number of scenario analyses for the triple therapy analyses. These included reducing the impact of BMI on health-related quality of life by 10%, 50% and 100% and applying a utility loss of -0.0061 for 1 unit increase in BMI. For all analyses, dapagliflozin continued to dominate the comparator drugs except for the scenario that involved removing the impact of BMI on health-related quality of life. This resulted in an ICER of £2,358,369 per QALY gained (incremental costs: $-\text{£}109$, incremental QALYs 0.000) for the comparison with DPP-4 inhibitors, although dapagliflozin continued to dominate thiazolidinediones and GLP-1 analogues. Results of the probabilistic sensitivity analyses showed that, at a cost-effectiveness threshold of £20,000 per QALY gained, the probability of dapagliflozin being dominant was 75% compared with DPP-4 inhibitors, 72% compared with thiazolidinediones and 80% compared with GLP-1 analogues.

Decision Support Unit comments

- 6.19 The Decision Support Unit (DSU) was commissioned by NICE to examine the economic model submitted by the manufacturer. The DSU was asked to report on whether the model functioned as described in the manufacturer 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.
- 6.20 The DSU identified several differences between the economic model described in the submission and the executable model provided by the manufacturer. There were some differences between the macro- and micro-vascular 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.

6.21 The DSU identified several aspects of the executable model that were not described in the manufacturers' submission. The probability of an event occurring during a 6-month cycle was calculated as the difference between the output of the event equation for the current time and the output of the event equation at 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.

6.22 The DSU commented that it was unable to reproduce the results of the probabilistic sensitivity analyses reported in the manufacturer

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 manufacturer 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.

Evidence Review Group comments

- 6.23 The ERG noted that the decision to switch or intensify treatment in the model was based on HbA_{1c} levels above the threshold of 7.5% that is currently recommended in NICE clinical guideline 87. When the manufacturers changed these HbA_{1c} 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 reduced the relevance of the model to UK clinical practice.
- 6.24 The ERG commented that it was able to validate the majority of the clinical effectiveness data used in the economic model by the manufacturer. The ERG requested further detail from the

manufacturers on the sources of the treatment-related adverse events and discontinuation rates, which were provided in appendices to the main submission. However, the ERG was unable to validate the adverse event and discontinuation data provided for the dual therapy analyses.

- 6.25 The ERG commented that the utility values used for hypoglycaemic events, taken from Currie et al. (2004) may have been too large. 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 suggested that the loss in utility associated with hypoglycaemic events reported in Currie et al. (2004) should have been halved when applied within a 6-month cycle in the model.
- 6.26 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 sulfonylurea (£946.26 as opposed to £886.90). The ERG noted that when a reduced cost of pioglitazone was included in the model the ICERs changed from dapagliflozin dominating thiazolidinedione (pioglitazone) to having ICERs of £3980 and £1409 for the dual therapy and triple therapy comparisons respectively.
- 6.27 In regard to the costs of macro and micro-vascular 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 costs should have been applied in the model for patients who did not experience a diabetic complication.

6.28 The ERG estimated a lower cost of a severe hypoglycaemic event (£320 rather than £390) from the study by Hammer et al. (2007). In addition, the ERG considered that the 50% of patients in the study sample in Hammer et al. (2007) who needed medical attention for their severe hypoglycaemic event may have been too high. The ERG noted that in NICE clinical guideline 87, it was assumed that only 25% of severe hypoglycaemic events would need medical attention. When the ERG reduced the proportion of patients seeking medical attention from 50% to 25%, this reduced the cost of a severe hypoglycaemic event further from £320 to £178.

6.29 The ERG noted that, although the model cycle length was 6 months, the probabilities of macro and micro-vascular 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 micro-vascular events were not halved to correspond with the 6 month cycle length used in the model but were applied in full immediately upon 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.

6.30 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 following 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.

- 6.31 The ERG noted that, within 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 arms in the model. It noted that using different treatment-specific baseline HbA_{1c} values results in the risk factor curves for both treatment arms not converging over time, whereas if the baseline HbA_{1c} values had been the same for both treatment arms, the curves would have converged. 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.
- 6.32 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.

- 6.33 The ERG commented on the appropriateness of the utility values applied to weight change in the model, noting 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 Bolinder et al. (2012) 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 Bolinder et al. the dapagliflozin treatment arm 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. (2005) involved a multivariate analysis of EQ-5D utility values that controlled for the complications of diabetes and estimated a smaller loss in utility (-0.0061) associated with a unit increase in BMI. This alternative utility decrement was used in the manufacturers' sensitivity analyses.
- 6.34 The ERG noted that the study by Lane et al. was commissioned not only to examine impact of weight change on health-related quality of life, but also the impact of urinary tract infections and genital infections on health-related quality of life. However, these data were not presented in the manufacturers' submission.

- 6.35 In the triple therapy analyses, the ERG considered that it was unnecessary for the model to include a dual therapy of metformin and 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.
- 6.36 The ERG did not conduct any exploratory sensitivity analyses. It noted that the majority of concerns raised related to the model structure, choice of risk equations and implementation of risk equations in the model. Because of the inter-related nature of Excel, Visual Basic and C++, these could not be resolved by the ERG. The ERG considered that the key inputs around which there was uncertainty were the health-related quality of life impacts of weight changes and severe hypoglycaemic events, and the costs of severe hypoglycaemic events. It also noted that the majority of any cost savings associated with dapagliflozin (in the metformin add-on analyses) arose from the lower rates of end-stage renal failure.

7 Equalities issues

- 7.1 During scoping consultation, 1 consultee suggested that dapagliflozin works through elimination via the kidneys and may therefore have an impact on renal function. It was also noted that there is a higher prevalence of established renal failure in people of African Caribbean and South Asian family origin. However, the summary of product characteristics for dapagliflozin states that it is not recommended for use in people with moderate to severe renal impairment.

8 Innovation

- 8.1 The manufacturers consider dapagliflozin to be a step-change in the treatment of type 2 diabetes because, unlike other antidiabetic drug therapies that move glucose from the circulation to various compartments, it actively removes glucose via the kidneys. The manufacturers stated that the action of dapagliflozin is independent of insulin, which means that it maintains its efficacy beyond the 6 months observed in the phase III trials. Dapagliflozin is also associated with weight loss, as a result of calorie loss caused by glucose excretion, whereas other oral antidiabetic drugs are often associated with weight gain (thiazolidinediones and sulfonylureas) or are weight neutral (DPP-4 inhibitors).

9 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes. NICE technology appraisal guidance 248 (2012). Available from <http://www.nice.org.uk/guidance/TA248>
- Liraglutide for the treatment of type 2 diabetes. NICE technology appraisal guidance 203 (2010). Available from www.nice.org.uk/guidance/TA203
- Type 2 diabetes: newer agents for blood glucose control in type 2 diabetes (partial update of CG66) NICE clinical guideline 87 (2009) Available from www.nice.org.uk/guidance/CG87
- Type 2 diabetes: the management of type 2 diabetes (partially updated by CG87). NICE clinical guideline 66 (2008). Available from www.nice.org.uk/guidance/CG66
- Diabetes in pregnancy: management of diabetes and its complications from pre-conception to the postnatal period. NICE clinical guideline 63 (2008). Available from www.nice.org.uk/guidance/CG63
- Continuous subcutaneous insulin infusion for the treatment of diabetes (review). NICE technology appraisal guidance 151 (2008). Available from www.nice.org.uk/guidance/TA151
- Type 2 diabetes: prevention and management of foot problems. NICE clinical guideline 10 (2004). Available from www.nice.org.uk/guidance/CG10

NICE pathways

- There is a NICE pathway on diabetes, which is available from <http://pathways.nice.org.uk/pathways/diabetes>

Appendix B: Previous NICE recommendations

Type 2 diabetes: the management of type 2 diabetes

NICE clinical guideline 87 (partial update of CG 66)

1.5 Oral glucose control therapies (1): metformin, insulin secretagogues and acarbose

1.5.1 Metformin

- 1.5.1.1 Start metformin treatment in a person who is overweight or obese (tailoring the assessment of body-weight-associated risk according to ethnic group⁶) and whose blood glucose is inadequately controlled (see 1.3.1) by lifestyle interventions (nutrition and exercise) alone.
- 1.5.1.2 Consider metformin as an option for first-line glucose-lowering therapy for a person who is not overweight.
- 1.5.1.3 Continue with metformin if blood glucose control remains or becomes inadequate (see 1.3.1) and another oral glucose-lowering medication (usually a sulfonylurea) is added.
- 1.5.1.4 Step up metformin therapy gradually over weeks to minimise risk of gastrointestinal side effects. Consider a trial of extended-absorption metformin tablets where gastrointestinal tolerability prevents continuation of metformin therapy.
- 1.5.1.5 Review the dose of metformin if the serum creatinine exceeds 130 micromol/litre or the estimated glomerular filtration rate (eGFR) is below 45 ml/minute/1.73-m².

⁶ See 'Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children' (NICE clinical guideline 43) (www.nice.org.uk/guidance/CG43).

- Stop the metformin if the serum creatinine exceeds 150 micromol/litre or the eGFR is below 30 ml/minute/1.73-m².
- Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those at risk of eGFR falling below 45 ml/minute/1.73-m².

1.5.1.6 The benefits of metformin therapy should be discussed with a person with mild to moderate liver dysfunction or cardiac impairment so that:

- due consideration can be given to the cardiovascular-protective effects of the drug
- an informed decision can be made on whether to continue or stop the metformin.

1.5.2 Insulin secretagogues

1.5.2.1 Consider a sulfonylurea as an option for first-line glucose-lowering therapy if:

- the person is not overweight
 - the person does not tolerate metformin (or it is contraindicated)
- or**
- a rapid response to therapy is required because of hyperglycaemic symptoms.

1.5.2.2 Add a sulfonylurea as second-line therapy when blood glucose control remains or becomes inadequate (see 1.3.1) with metformin.

1.5.2.3 Continue with a sulfonylurea if blood glucose control remains or becomes inadequate (see 1.3.1) and another oral glucose-lowering medication is added.

1.5.2.4 Prescribe a sulfonylurea with a low acquisition cost (but not glibenclamide) when an insulin secretagogue is indicated (see 1.5.2.1 and 1.5.2.2).

1.5.2.5 When drug concordance is a problem, offer a once-daily, long-acting sulfonylurea.

1.5.2.6 Educate a person being treated with an insulin secretagogue, particularly if renally impaired, about the risk of hypoglycaemia.

1.5.3 Rapid-acting insulin secretagogues

1.5.3.1 Consider offering a rapid-acting insulin secretagogue to a person with an erratic lifestyle.

1.5.4 Acarbose

1.5.4.1 Consider acarbose for a person unable to use other oral glucose-lowering medications.

1.6 Oral glucose control therapies (2): other oral agents and exenatide

The recommendations in this section were updated by the short clinical guideline 'Type 2 diabetes: newer agents for blood glucose control in type 2 diabetes' (www.nice.org.uk/CG87shortguideline). The guideline gives details of the methods and the evidence used to develop the recommendations.

1.6.1 DPP-4 inhibitors (sitagliptin, vildagliptin)

1.6.1.1 Consider adding a DPP-4 inhibitor (sitagliptin, vildagliptin) instead of a sulfonylurea as second-line therapy to first-line metformin when control of blood glucose remains or becomes inadequate ($HbA_{1c} \geq 6.5\%$, or other higher level agreed with the individual) if:

- the person is at significant risk of hypoglycaemia or its consequences (for example, older people and people in certain jobs [for example, those working at heights or with heavy machinery] or people in certain social circumstances [for example, those living alone]), or
- the person does not tolerate a sulfonylurea or a sulfonylurea is contraindicated. **[new 2009]**

1.6.1.2 Consider adding a DPP-4 inhibitor (sitagliptin, vildagliptin) as second-line therapy to first-line sulfonylurea monotherapy when control of blood glucose remains or becomes inadequate ($HbA_{1c} \geq 6.5\%$, or other higher level agreed with the individual) if:

- the person does not tolerate metformin, or metformin is contraindicated. **[new 2009]**

- 1.6.1.3 Consider adding sitagliptin⁷ as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate ($\text{HbA}_{1c} \geq 7.5\%$ or other higher level agreed with the individual) and insulin is unacceptable or inappropriate⁸. **[new 2009]**
- 1.6.1.4 Only continue DPP-4 inhibitor therapy (sitagliptin, vildagliptin) if the person has had a beneficial metabolic response (a reduction of at least 0.5 percentage points in HbA_{1c} in 6 months). **[new 2009]**
- 1.6.1.5 Discuss the potential benefits and risks of treatment with a DPP-4 inhibitor (sitagliptin, vildagliptin) with the person to enable them to make an informed decision.

A DPP-4 inhibitor (sitagliptin, vildagliptin) may be preferable to a thiazolidinedione (pioglitazone) if:

- further weight gain would cause or exacerbate significant problems associated with a high body weight, or
- a thiazolidinedione (pioglitazone) is contraindicated, or
- the person has previously had a poor response to, or did not tolerate, a thiazolidinedione (pioglitazone).

There may be some people for whom either a DPP-4 inhibitor (sitagliptin, vildagliptin) or a thiazolidinedione (pioglitazone) may be suitable and, in this case, the choice of treatment should be based on patient preference. **[new 2009]**

⁷ At the time of publication, sitagliptin was the only DPP-4 inhibitor with UK marketing authorisation for use in this combination.

⁸ Because of employment, social or recreational issues related to putative hypoglycaemia, injection anxieties, other personal issues or obesity.

1.6.2 Thiazolidinediones (pioglitazone)⁹

1.6.2.1 Consider adding a thiazolidinedione (pioglitazone) instead of a sulfonylurea as second-line therapy to first-line metformin when control of blood glucose remains or becomes inadequate ($\text{HbA}_{1c} \geq 6.5\%$, or other higher level agreed with the individual) if:

- the person is at significant risk of hypoglycaemia or its consequences (for example, older people and people in certain jobs [for example, those working at heights or with heavy machinery] or people in certain social circumstances [for example, those living alone]), or
- a person does not tolerate a sulfonylurea or a sulfonylurea is contraindicated. **[new 2009]**

1.6.2.2 Consider adding a thiazolidinedione (pioglitazone) as second-line therapy to first-line sulfonylurea monotherapy when control of blood glucose remains or becomes inadequate ($\text{HbA}_{1c} \geq 6.5\%$, or other higher level agreed with the individual) if:

- the person does not tolerate metformin or metformin is contraindicated. **[new 2009]**

1.6.2.3 Consider adding a thiazolidinedione (pioglitazone) as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate ($\text{HbA}_{1c} \geq 7.5\%$, or other higher level agreed with the individual) and insulin is unacceptable or inappropriate¹⁰. **[new 2009]**

⁹ The recommendations in this section replace 'Guidance on the use of glitazones for the treatment of type 2 diabetes' (NICE technology appraisal guidance 63).

¹⁰ Because of employment, social or recreational issues related to putative hypoglycaemia, injection anxieties, other personal issues or obesity.

- 1.6.2.4 Do not commence or continue a thiazolidinedione (pioglitazone) in people who have heart failure, or who are at higher risk of fracture. **[new 2009]**
- 1.6.2.5 When selecting a thiazolidinedione (pioglitazone), take into account up-to-date advice from the relevant regulatory bodies (the European Medicines Agency and the Medicines and Healthcare products Regulatory Agency), cost, safety and prescribing issues (see 1.6.2.8). **[new 2009]**
- 1.6.2.6 Only continue thiazolidinedione therapy (pioglitazone) if the person has had a beneficial metabolic response (a reduction of at least 0.5 percentage points in HbA_{1c} in 6 months). **[new 2009]**
- 1.6.2.7 Consider combining pioglitazone with insulin therapy¹¹ for a person:
- who has previously had a marked glucose-lowering response to thiazolidinedione therapy (pioglitazone), or
 - who is on high-dose insulin therapy and whose blood glucose is inadequately controlled. **[new 2009]**
- 1.6.2.8 Discuss the potential benefits and risks of treatment with a thiazolidinedione (pioglitazone) with the person to enable them to make an informed decision.
- A thiazolidinedione (pioglitazone) may be preferable to a DPP-4 inhibitor (sitagliptin, vildagliptin) if:
- the person has marked insulin insensitivity, or
 - a DPP-4 inhibitor (sitagliptin, vildagliptin) is contraindicated, or
 - the person has previously had a poor response to, or did not tolerate, a DPP-4 inhibitor (sitagliptin, vildagliptin).

¹¹ At the time of publication pioglitazone was the only thiazolidinedione with UK marketing authorisation for use with insulin.

There may be some people for whom either a thiazolidinedione (pioglitazone) or a DPP-4 inhibitor (sitagliptin, vildagliptin) may be suitable and, in this case, the choice of treatment should be based on patient preference. *[new 2009]*

1.6.3 GLP-1 mimetic (exenatide)

1.6.3.1 Consider adding a GLP-1 mimetic (exenatide) as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate ($\text{HbA}_{1c} \geq 7.5\%$, or other higher level agreed with the individual), and the person has:

- a body mass index (BMI) $\geq 35.0 \text{ kg/m}^2$ in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight, or
- a BMI $< 35.0 \text{ kg/m}^2$, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities. *[new 2009]*

1.6.3.2 Only continue GLP-1 mimetic (exenatide) therapy if the person has had a beneficial metabolic response (a reduction of at least 1.0 percentage point in HbA_{1c} and a weight loss of at least 3% of initial body weight at 6 months). *[new 2009]*

1.6.3.3 Discuss the potential benefits and risks of treatment with a GLP-1 mimetic (exenatide) with the person to enable them to make an informed decision. *[new 2009]*

1.7 Glucose control: insulin therapy

1.7.1 Oral agent combination therapy with insulin

1.7.1.1 When starting basal insulin therapy:

- continue with metformin and the sulfonylurea (and acarbose, if used)
- review the use of the sulfonylurea if hypoglycaemia occurs.

1.7.1.2 When starting pre-mixed insulin therapy (or mealtime plus basal insulin regimens):

- continue with metformin
- continue the sulfonylurea initially, but review and discontinue if hypoglycaemia occurs.

1.7.2 Insulin therapy

The recommendations in this section were updated by the short clinical guideline 'Type 2 diabetes newer agents for blood glucose control in type 2 diabetes' (www.nice.org.uk/CG87shortguideline). The guideline gives details of the methods and the evidence used to develop the recommendations.

1.7.2.1 Discuss the benefits and risks of insulin therapy when control of blood glucose remains or becomes inadequate ($HbA_{1c} \geq 7.5\%$ or other higher level agreed with the individual) with other measures. Start insulin therapy if the person agrees. **[new 2009]**

1.7.2.2 For a person on dual therapy who is markedly hyperglycaemic, consider starting insulin therapy in preference to adding other drugs to control blood glucose unless there is strong justification¹² not to. **[new 2009]**

1.7.2.3 When starting insulin therapy, use a structured programme employing active insulin dose titration that encompasses:

- structured education
- continuing telephone support

¹² Because of employment, social or recreational issues related to putative hypoglycaemia, injection anxieties, other personal issues or obesity.

- frequent self-monitoring
- dose titration to target
- dietary understanding
- management of hypoglycaemia
- management of acute changes in plasma glucose control
- support from an appropriately trained and experienced healthcare professional.

1.7.2.4 Initiate insulin therapy from a choice of a number of insulin types and regimens.

- Begin with human NPH insulin injected at bed-time or twice daily according to need.
- Consider, as an alternative, using a long-acting insulin analogue (insulin detemir, insulin glargine) if:
 - the person needs assistance from a carer or healthcare professional to inject insulin, and use of a long-acting insulin analogue (insulin detemir, insulin glargine) would reduce the frequency of injections from twice to once daily, or
 - the person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes, or
 - the person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs, or
 - the person cannot use the device to inject NPH insulin.
- Consider twice-daily pre-mixed (biphasic) human insulin (particularly if $HbA_{1c} \geq 9.0\%$). A once-daily regimen may be an option.
- Consider pre-mixed preparations that include short-acting insulin analogues, rather than pre-mixed preparations that include short-acting human insulin preparations, if:

- a person prefers injecting insulin immediately before a meal,
or
- hypoglycaemia is a problem, or
- blood glucose levels rise markedly after meals. **[new 2009]**

1.7.2.5 Consider switching to a long-acting insulin analogue (insulin detemir, insulin glargine) from NPH insulin in people:

- who do not reach their target HbA_{1c} because of significant hypoglycaemia, or
- who experience significant hypoglycaemia on NPH insulin irrespective of the level of HbA_{1c} reached, or
- who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to a long-acting insulin analogue were made, or
- who need help from a carer or healthcare professional to administer insulin injections and for whom switching to a long-acting insulin analogue would reduce the number of daily injections. **[new 2009]**

1.7.2.6 Monitor a person on a basal insulin regimen (NPH insulin or a long-acting insulin analogue [insulin detemir, insulin glargine]) for the need for short-acting insulin before meals (or a pre-mixed insulin preparation). **[new 2009]**

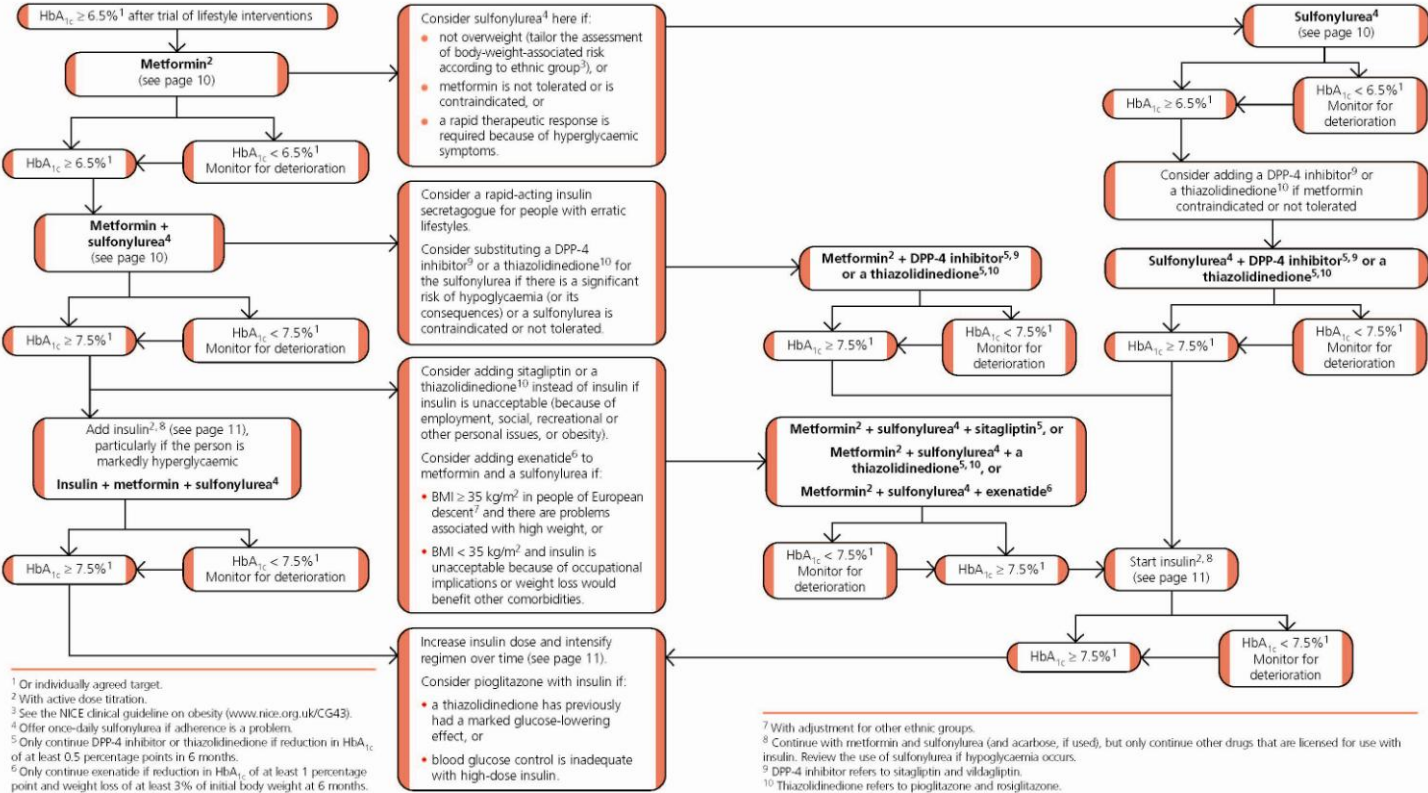
1.7.2.7 Monitor a person who is using pre-mixed insulin once or twice daily for the need for a further injection of short-acting insulin before meals or for a change to a regimen of mealtime plus basal insulin, based on NPH insulin or long-acting insulin analogues (insulin detemir, insulin glargine), if blood glucose control remains inadequate. **[new 2009]**

1.7.3 Insulin delivery devices

- 1.7.3.1 Offer education to a person who requires insulin about using an injection device (usually a pen injector and cartridge or a disposable pen) that they and/or their carer find easy to use.
- 1.7.3.2 Appropriate local arrangements should be in place for the disposal of sharps.
- 1.7.3.3 If a person has a manual or visual disability and requires insulin, offer a device or adaptation that:
- takes into account his or her individual needs
 - he or she can use successfully.

Care pathway from short clinical guideline 87 (page numbers refer to the quick reference guide for CG87)

Blood-glucose-lowering therapy



¹ Or individually agreed target.
² With active dose titration.
³ See the NICE clinical guideline on obesity (www.nice.org.uk/CG43).
⁴ Offer once-daily sulfonylurea if adherence is a problem.
⁵ Only continue DPP-4 inhibitor or thiazolidinedione if reduction in HbA_{1c} of at least 0.5 percentage points in 6 months.
⁶ Only continue exenatide if reduction in HbA_{1c} of at least 1 percentage point and weight loss of at least 3% of initial body weight at 6 months.

⁷ With adjustment for other ethnic groups.
⁸ Continue with metformin and sulfonylurea (and acarbose, if used), but only continue other drugs that are licensed for use with insulin. Review the use of sulfonylurea if hypoglycaemia occurs.
⁹ DPP-4 inhibitor refers to sitagliptin and vildagliptin.
¹⁰ Thiazolidinedione refers to pioglitazone and rosiglitazone.

Liraglutide for the treatment of type 2 diabetes mellitus***NICE technology appraisal guidance 203***

- 1.1 Liraglutide 1.2 mg daily in triple therapy regimens (in combination with metformin and a sulphonylurea, or metformin and a thiazolidinedione) is recommended as an option for the treatment of people with type 2 diabetes, only if used as described for exenatide in 'Type 2 diabetes: the management of type 2 diabetes' (NICE clinical guideline 87); that is, when control of blood glucose remains or becomes inadequate (HbA1c \geq 7.5%, or other higher level agreed with the individual), and the person has:
- a body mass index (BMI) \geq 35 kg/m² in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight, **or**
 - a BMI < 35 kg/m², and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.
- 1.2 Treatment with liraglutide 1.2 mg daily in a triple therapy regimen should only be continued as described for exenatide in 'Type 2 diabetes: the management of type 2 diabetes' (NICE clinical guideline 87); that is, if a beneficial metabolic response has been shown (defined as a reduction of at least 1 percentage point in HbA1c and a weight loss of at least 3% of initial body weight at 6 months).

- 1.3 Liraglutide 1.2 mg daily in dual therapy regimens (in combination with metformin or a sulphonylurea) is recommended as an option for the treatment of people with type 2 diabetes, only if:
- the person is intolerant of either metformin **or** a sulphonylurea, or treatment with metformin **or** a sulphonylurea is contraindicated, **and**
 - the person is intolerant of thiazolidinediones **and** dipeptidyl peptidase-4 (DPP-4) inhibitors, or treatment with thiazolidinediones **and** DPP-4 inhibitors is contraindicated.
- 1.4 Treatment with liraglutide 1.2 mg daily in a dual therapy regimen should only be continued if a beneficial metabolic response has been shown (defined as a reduction of at least 1 percentage point in HbA1c at 6 months).
- 1.5 Liraglutide 1.8 mg daily is not recommended for the treatment of people with type 2 diabetes.
- 1.6 People with type 2 diabetes currently receiving liraglutide who do not meet the criteria specified in section 1.1 or 1.3, or who are receiving liraglutide 1.8 mg, should have the option to continue their current treatment until they and their clinicians consider it appropriate to stop.

Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes

NICE technology appraisal guidance 248

- 1.1 Prolonged-release exenatide in triple therapy regimens (that is, in combination with metformin and a sulphonylurea, or metformin and a thiazolidinedione) is recommended as a treatment option for people with type 2 diabetes as described in '[Type 2 diabetes: the management of type 2 diabetes](#)' (NICE clinical guideline 87); that is, when control of blood glucose remains or becomes inadequate ($\text{HbA}_{1c} \geq 7.5\%$ [59 mmol/mol] or other higher level agreed with the individual), and the person has:
- a body mass index (BMI) $\geq 35 \text{ kg/m}^2$ in those of European family origin (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight **or**
 - a BMI $< 35 \text{ kg/m}^2$, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.
- 1.2 Treatment with prolonged-release exenatide in a triple therapy regimen should only be continued as described in '[Type 2 diabetes: the management of type 2 diabetes](#)' (NICE clinical guideline 87); that is, if a beneficial metabolic response has been shown (defined as a reduction of at least 1 percentage point in HbA_{1c} [11 mmol/mol] and a weight loss of at least 3% of initial body weight at 6 months).

- 1.3 Prolonged-release exenatide in dual therapy regimens (that is, in combination with metformin or a sulphonylurea) is recommended as a treatment option for people with type 2 diabetes, as described in '[Liraglutide for the treatment of type 2 diabetes mellitus](#)' (NICE technology appraisal 203); that is, only if:
- the person is intolerant of either metformin **or** a sulphonylurea, or a treatment with metformin **or** a sulphonylurea is contraindicated, **and**
 - the person is intolerant of thiazolidinediones and dipeptidyl peptidase-4 (DPP-4) inhibitors, **or** a treatment with thiazolidinediones **and** DPP-4 inhibitors is contraindicated.
- 1.4 Treatment with prolonged-release exenatide in a dual therapy regimen should only be continued as described in '[Liraglutide for the treatment of type 2 diabetes mellitus](#)' (NICE technology appraisal guidance 203); that is, if a beneficial metabolic response has been