NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Dapagliflozin in combination therapy for treating type 2 diabetes

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Bristol Myers-Squibb and AstraZeneca	***Has all the relevant evidence been taken into account?*** When the Appraisal Committee make their decision, they can be confident that all the relevant clinical and economic evidence have been provided throughout the process; as part of the original submission, response to the ERG and DSU reports, and in this document responding to the ACD. With these sources combined, and the additional analysis requested by NICE (including: the revised network meta-analysis, updates to the economic model, and a comparison with the CORE model), the Appraisal Committee should be reassured of the clinical and economic value of dapagliflozin used in combination with metformin or insulin for type 2 diabetes.	Comment noted. The Committee has considered all the evidence submitted, including evidence from clinical trials, patient experts and clinical specialists, the manufacturers' submissions of evidence and the ERG and DSU critiques of these. It also carefully considered the comments received from consultees and commentators in response to the ACD. See responses to individual comments below.
Bristol Myers-Squibb and AstraZeneca	***Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?*** The concerns raised by the committee have been carefully evaluated and addressed in this detailed response document. The Committee made a number of summary conclusions in the ACD relating to the clinical and cost effectiveness evidence. **Evidence for clinical effectiveneness (Section 4, page 51-52 of summary of Appraisal Committee key conclusions)**: • "The Committee concluded that there was significant uncertainty about the validity of the results of the network meta-analyses" • "The Committee concluded that, although dapagliflozin in dual therapy as an add-on to metformin therapy, and as add-on to insulin therapy, appeared to offer benefits in terms of weight loss and a similar effect on glycaemic control compared with other antidiabetic therapies, given their concerns these results should be reproduced in a revised network meta-analysis"	Comments noted. The results of the revised network meta-analyses were considered by the Appraisal Committee at its second meeting. See section 4.5 of the FAD.

Consultee	Comment	Response
Bristol Myers-Squibb and AstraZeneca	**Evidence for cost-effectiveness (Section 4, page 55 of summary of Appraisal Committee key conclusions)**: • "The ICERs for dapagliflozin in combination therapy compared with other antidiabetic drug therapies were all below £20,000 per QALY gained. The ERG's exploratory analyses, which included changes to the utility values associated with weight change and hypoglycaemic events and the annual costs of pioglitazone and diabetic complications, resulted in higher ICERs, although they were all below £30,000 per QALY gained. However, the Committee considered that the ICERs presented by both the manufacturers and the ERG were obtained from an economic model that could not be adequately replicated by the DSU. The Committee also noted that these ICERs were obtained from analyses that did not account for its concerns about the network meta-analysis or the utility values applied to changes in weight, hypoglycaemic events and urinary tract and genital infections" In response to these concerns the Appraisal Committee requests have been fully addressed by BMS/AZ. We have supplied additional evidence in this response document that should reassure the Committee of the robustness and validity of both the network meta analyses and the Dapagliflozin Cost-effectiveness model (DCEM). We have re-run the NMA using the DSU recommended code. We have also reconsidered the utility values relating to weight change and conducted analyses using the ERG preferred values. We have also addressed concerns relating to UTI/GI disutilities and the fear of hypoglycaemia disutility applied. The combined outcome of these revisions has been that we have addressed all the major concerns of the Committee, and produced revised results that continue to demonstrate the cost-effectiveness of dapagliflozin in its use in different parts of the treatment pathway. We have a number of specific comments on parts of the ACD not covered by our additional clarifications and analyses in Part 2 and 3 of the response.	Comments noted. The validity of the revised economic model was considered by the Appraisal Committee at its second and third meetings. See sections 4.12-4.13 of the FAD. The utility values applied to changes in weight, hypoglycaemic events and urinary tract and genital infections were considered by the Appraisal Committee further at its second and third meetings. See sections 4.18-4.20 of the FAD.

Consultee	Comment	Response
Bristol Myers-Squibb and AstraZeneca	***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 (ACD Section 3.33).*** No RCTs between 30 and 46 weeks or greater than 58 weeks were excluded from the NMA on grounds of duration of follow-up. The references for all RCTs identified in the systematic review are provided in Table 7 (metformin) and Table 8 (insulin) of the original submission: ○ Metformin add-on: ▪ No RCTs in the stratum labelled "Duration of study: 12 to 17.9 weeks" were included in the NMA. ▪ In the stratum labelled "Duration of study: >30 weeks", all RCTs involving add-on to metformin were included in a 52 week NMA. ○ Insulin add-on: ▪ As noted by the ERG, a protocol change was implemented to expand the range of the 24 week NMA from 18 to 30 weeks to 16 to 32 weeks; ▪ In the stratum labelled "Duration of study: 12 to 17.9 weeks", only the RCT by Rosenstock *et al*. (16 week RCT) was included in the NMA. All other RCTs in this stratum were excluded on the grounds of: ▪ Duration of follow-up of less than 16 weeks (Wilding 2009; Mudiliar 2010); • Comparator (Strowig 2002; Schiel 2007; Remplio 1998; Osei 1984; Lewitt 1989); or Non-stable insulin (Asnani 2006 [also Mudiliar 2010]).	Comments noted. The relevant sentence in the FAD has been amended to: "The ERG commented that it was not clear whether studies of between 31 and 45 weeks or greater than 58 weeks were also identified in the review. However, in response to clarification, the manufacturers provided a full list of identified trials, none of which were between 31 and 45 weeks' duration." See FAD section 3.29.

Consultee	Comment	Response
Bristol Myers-Squibb and AstraZeneca	***The ERG commented that no attempt was made to adjust the analyses for any other variables (ACD Section 3.34).*** Prior to selecting adjustment factors for the analysis, both a visual assessment of heterogeneity was conducted among key characteristics, and clinical input as to the potential of effect modification was provided. Clinical and patient characteristics considered for model adjustment included: age, sex, duration of diabetes, baseline BMI, duration (leading to the decision to stratify by duration of follow-up), HbA1c (leading to the decision to adjust for HbA1c). Data were provided in tabular format in the submission (Appendix Tables 111 to 123), and key characteristics are presented graphically below **Figure included but not reproduced here**. For any all potential sources of heterogeneity (e.g. outlying data points, wide variation within or across classes), we further investigated: the potential impact of that variable on relative effect sizes; correlation with HbA1c; and feasibility for adjusting the model. *Notes:* The RCT having the highest mean age also had the lowest mean baseline HbA1c; duration of diabetes was negatively correlated with baseline HbA1c; the RCT having the lowest baseline BMI was the only RCT comparing TZD with placebo and no clear impact of baseline BMI could be assessed within other drug classes. NMA models were not fit for all baseline variables to avoid spurious correlations, and to avoid using the same data for model selection and estimation.	Comments noted. The relevant section has been deleted from the FAD.
Bristol Myers-Squibb and AstraZeneca	***The ERG commented that the manufacturers' approach to model selection lacked transparency and that insufficient justification was provided about whether or not adjusted results were presented (ACD Section 3.34).*** The *a priori* selection was to use an adjusted, using treatment-specific coefficients. No network had sufficient data for estimating treatment-specific coefficients (requires approximately 10 data points per comparator); When insufficient evidence was available to reliably estimate a treatment-specific coefficient, then a model using a common coefficient for all treatments vs. the reference was fit. In the 52 week network, the reference treatment was an active control (sulphonylureas) and the assumption that a common coefficient could be	Comments noted. The relevant section has been deleted from the FAD.

Consultee	Comment	Response

	applied for all treatments vs. sulphonylureas was less tenable than in networks involving placebo as the common treatment.
	
	When insufficient evidence was available to reliably estimate a common coefficient, a model having no coefficient was selected.
	
	• 24 week metformin network:
	  ○ The random effects coefficient was estimated to be -0.30 (95% CrI: -0.62 to 0.01), and was included in the final selected model.
	
	• 52 week metformin network:
	  ○ The random effects coefficient was estimated to be 0.02% (95% CrI: -0.23 to 0.24). The magnitude of this coefficient, relative to the uncertainty, led to the decision not to include this adjustment in the final selected model.
	
	• 24 week insulin network:
	  ○ The fixed effect coefficient was estimated to be -5.87% (95% CrI: -17.14 to 6.56). The uncertainty around this coefficient led to the decision not to include this adjustment in the final selected model.
	
	Note: this model was fit using only four RCTs for three comparator agents.
	
	In selecting between the fixed and random effects models, the *a priori* choice was the random effects model, and was selected, unless: i) the fixed effect model offered <u>better</u> model fit according to the DIC (defined as more than 3 units less than the random effects model); or ii) the posterior distribution of the between-studies variance was similar to the prior distribution, indicating that there was insufficient evidence to reliably estimate the between-studies variance (due to a sparse network).	

Bristol Myers-Squibb and AstraZeneca	ACD Section 3.36: It states "… Overall, the ERG considered that the HbA1c threshold levels for switching treatment applied in the model reduced its relevance to UK clinical practice." Please see response xx in Part 2 for further clarification.	Comment noted. The HbA1c threshold levels for switching treatment applied in the model were considered further by the Appraisal Committee at its second meeting. See FAD section 4.16.

Consultee	Comment	Response
Bristol Myers-Squibb and AstraZeneca	ACD Section 3.37: It states "…However, the ERG was unable to validate the adverse event and discontinuation data provided for the dual therapy analyses." AstraZeneca and Bristol-Myers Squibb have already provided additional information to address this perceived gap in the Manufacturer's Submission in the response to ERG's request for further clarification	Comment noted. The relevant section has been deleted from the FAD.
Bristol Myers-Squibb and AstraZeneca	ACD Section 3.39: It states "…The ERG considered that these alternative utility values, which were applied in the manufacturers' scenario analyses, to be more reasonable." However, in Section 3.28 they acknowledge that we had already presented a scenario in which the Bagust utility (0.0061) was used. It should also be acknowledged here.	Comment noted. Section 3.27 of the FAD describes the manufacturers' submission and refers to the range of scenario analyses presented by the manufacturers. It does not refer to the ERG's comments on these analyses. Section 3.33 refers to the ERG's comments on the appropriateness of the utility values applied to weight change and the alternative values explored in the manufacturers' scenario analyses.
Bristol Myers-Squibb and AstraZeneca	ACD Section 4.13: It states "...It noted that the most common adverse events were urinary tract and genital infections." Two sentences later it states "However, the Committee heard from the manufacturers that the recurrence of these events in the clinical trials was low." The focus has been on these AEs specifically because they are related to the mechanism of action, were specifically collected within the trials, and showed greater differences between study arms, but not because they were most frequent. The current Forxiga SmPC states that 'the most commonly reported events leading to discontinuation in patients treated with dapagliflozin 10 mg were increased blood creatinine (0.4%), urinary tract infections (0.3%), nausea (0.2%), dizziness (0.2%), and rash (0.2%)'.	Comments noted. Section 4.11 of the FAD has been amended to state that: "It noted that common adverse events included urinary tract and genital infections and that these events were more common in women than in men."

Consultee	Comment	Response
Bristol Myers-Squibb and AstraZeneca	ACD Section 4.19: It states "The Committee considered that applying the treatment effect on weight loss gradually over the first year would have been more plausible." We believe it would be more plausible for the Committee to consider the speed of weight loss as observed in dapagliflozin's study programme. It states "It considered that it was more plausible that any initial differences in weight change between treatments would converge over time." Our interpretation of this statement is that the Committee believe that patients who receive dapagliflozin will experience greater weight gain that those patients who receive alternatives, following a treatment switch. This statement does not seem plausible and requires revisiting before being updated into the FAD	Comments noted. The manufacturers' approach to modelling changes in body weight was considered further by the Appraisal Committee at its second and third meetings. See FAD section 4.17.

Consultee	Comment	Response
Bristol Myers-Squibb and AstraZeneca	***Are the provisional recommendations a sound and a suitable basis for guidance to the NHS?*** We note that the Appraisal Committee are minded not to recommend dapagliflozin, but have requested the additional clarifications in order to determine a final recommendation. We have provided all the additional analyses requested by NICE within the revised economic model as well as provided clarifications to concerns outlined in the ACD, and this has shown dapagliflozin to be a cost-effective option in combination with oral anti-diabetic drugs, specifically metformin, and in combination with insulin for patients with type 2 diabetes at different points in the patient treatment pathway: • The ICER for dapagliflozin in dual therapy in combination with metformin (after revisions requested by the NICE Appraisal Committee, including the requested ERG changes to utilities for weight change and costs of diabetes without complications) is £7.7k/QALY vs SU and £3.3k vs DPP-4. Even after the revisions requested dapagliflozin has demonstrated cost-effectiveness against these comparators as an add-on to metformin. • The cost-effectiveness results for dapagliflozin in combination with insulin after revisions requested by the NICE Appraisal Committee shows that it dominates DPP-4. Hence, it can be concluded that dapagliflozin represents a cost-effective use of NHS resources as add-on therapy to insulin. • The revised analysis performed for the use of dapagliflozin in triple therapy (in addition to metformin and SU) has also shown it to dominate each relevant comparator (DPP-4, TZD and GLP-1). A summary of the revised DCEM analyses and results are presented in Part 2 of this response (2.3.2), with full disaggregated results in part 3 (3.2.9).	Comments noted. Dapagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if it is used as described for dipeptidyl peptidase-4 (DPP-4) inhibitors in Type 2 diabetes: the management of type 2 diabetes (NICE clinical guideline 87). Dapagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes. Dapagliflozin in a triple therapy regimen in combination with metformin and a sulfonylurea is not recommended for treating type 2 diabetes except as part of a clinical trial. See FAD sections 1.1-1.3. For dapagliflozin dual therapy regimens in combination with metformin, the Committee concluded that because of the small differences in costs and QALYs between dapagliflozin and DPP4 inhibitors, dapagliflozin in a dual therapy regimen in combination with metformin could be recommended. See FAD section 4.22. For dapagliflozin as add-on to insulin all the analyses conducted by the DSU produced an estimate of the ICER for dapagliflozin compared with DPP-4 inhibitors below £20,000 per QALY. See FAD section 4.23.

Consultee	Comment	Response
	By providing the clarifications to concerns raised by the DSU, and additional analyses based on revisions to the DCEM, and by demonstrating the reproducibility of the results using the CORE model, we have reduced the level of uncertainty concerning the ICERs reported. The results/conclusions from the DCEM and the CORE Model continues to support the cost-effectiveness of dapagliflozin and provides added assurance that dapagliflozin remains within acceptable bounds of cost-effectiveness with sufficient certainty in appropriate positions within type 2 diabetes treatment pathway. Hence, the ICER results we have generated and reported in this response provide a strong basis for a positive recommendation by NICE for dapagliflozin in final NICE guidance.	Dapagliflozin in a triple therapy regimen is currently being studied as an add-on to 2 other oral agents. The Committee considered that the cost-effectiveness analyses should be considered as exploratory in nature. See FAD section 4.24.
Bristol Myers-Squibb and AstraZeneca	***Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?*** There are no particular aspects of the current recommendation or of a potential positive recommendation for dapagliflozin that are likely to result in unlawful discrimination issues against any group of people.	Comment noted. No actions requested.
Department of Health	I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation**.**	Comment noted. No actions requested.
National Diabetes Nurse Consultant Group	***Has all the relevant evidence been taken into account?*** Yes	Comment noted. No actions requested.
National Diabetes Nurse Consultant Group	***Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?*** ACD Section 3.48: Dapagliflozin dominate DPPIV inhibitors in terms of cost-unclear why the recommendations is being made not to recommend as the analysis shows that it dominates DPPIV inhibitors for a cost perspective and as not as expensive as GLP-1 or some insulin options therefore will not be of any greater expense than many current therapy choices.	Comment noted. Dapagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if it is used as described for dipeptidyl peptidase-4 (DPP-4) inhibitors in Type 2 diabetes: the management of type 2 diabetes (NICE clinical guideline 87). See FAD section 1.1

Consultee	Comment	Response
National Diabetes Nurse Consultant Group	***Are the provisional recommendations a sound and a suitable basis for guidance to the NHS?*** No. ACD Section 1.1: Unclear why the recommendations not to recommend has been made as this new class of medication gives another option for people with type 2 diabetes who are refusing an injectable therapy and it has proven benefits as an add on to people with type 2 diabetes on insulin	Comment noted. Dapagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if it is used as described for dipeptidyl peptidase-4 (DPP-4) inhibitors in Type 2 diabetes: the management of type 2 diabetes (NICE clinical guideline 87). Dapagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes. See FAD sections 1.1 and 1.2
National Diabetes Nurse Consultant Group	***Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?*** No	Comment noted no action required
NHS Tees	We are in agreement with the... comments submitted by the Commissioning Support Appraisals Service;	Comment noted. Please see responses to the Commissioing Support Appraisals Service.
Royal College of Nursing	Nurses working in this area of health have reviewed the Appraisal Consultation Document of the technology appraisal of Dapagliflozin in combination therapy for the treatment of type 2 diabetes. There are no further comments to submit at this stage on behalf of the Royal College of Nursing.	Comment noted no action required

Comments received from commentators

Commentator	Comment	Response
Commissioning Support Appraisals Service	We are in agreement with the recommendation in the ACD not to recommend dapagliflozin due to considerable uncertainties regarding the clinical and cost effectiveness of this drug in real life clinical practice. • **Combination therapy dapagliflozin (as either a metformin or insulin add-on) appears to offer weight loss benefits and to have similar effects as comparators in terms of glycaemic control.** However, the committee concluded that there are significant uncertainties regarding the selection of outcomes and the validity of the network meta-analyses used to assess the effectiveness of dapagliflozin versus UK relevant comparators. • **Evidence on the effects of the licensed dose and treatment combinations for dapagliflozin comes from five clinical trials and three network meta-analysis.** The clinical trials included three metformin 'add-on' and two insulin 'add-on' studies, in which dual therapy was used. Effectiveness data for dapagliflozin as an add-on to sulfonylurea was not provided, despite the availability of such evidence. Evidence is less robust for triple therapy (dapagliflozin + metformin + suphonylurea) or other combinations with two oral drugs, as clinical trials were older or had not been completed for the relevant combinations. • **There is significant uncertainty regarding the cost effectiveness of dapagliflozin**. There are concerns over the credibility and reproducibility of the economic model, e.g. the QALY gains were related to weight change rather than diabetic complications or other adverse events associated with any of the treatments. Removing the impact of BMI on utility increased the ICER of dapagliflozin plus insulin compared to DPP-4 inhibitors plus insulin from £19,094 per QALY gained to £105,511 per QALY gained. • **NICE have requested further information from the manufacturer regarding their modelling.** Additional information has been requested regarding the network meta-analysis and cost-effective models submitted by the manufacturer as the Decision Support Unit (DSU) at NICE could not replicate the model. • **The safety profile of dapagliflozin differs from other oral diabetic drugs.** The most common adverse events were urinary tract and genital infections, which were more common in women than men. The committee concluded that the manner in which these adverse events were accounted for in the economic model required consideration and adjustment.	Comments noted. The manufacturers provided further analyses in response to the ACD. As a result of the additional evidence and reviews of this by the ERG and DSU, the Committee made the following recommendations: Dapagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if it is used as described for dipeptidyl peptidase-4 (DPP-4) inhibitors in Type 2 diabetes: the management of type 2 diabetes (NICE clinical guideline 87). Dapagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes. Dapagliflozin in a triple therapy regimen in combination with metformin and a sulfonylurea is not recommended for treating type 2 diabetes except as part of a clinical trial. See FAD sections 1.1-1.3.

Commentator	Comment	Response
	• **The annual cost of dapagliflozin per patient is estimated at £476.92.** This is based on a patient receiving a daily dose of 10mg dapagliflozin. • **In England and Wales the incremental cost of adding dapagliflozin could total £10.8 million in the fifth year after implementation.** This cost assumes about 2.5 million patients being eligible for dapagliflozin and 4.3% of them receiving it in year five.	
Merck Sharpe and Dohme	**General comment on the ACD:** As acknowledged by the ERG and the DSU, there are significant concerns over the reproducibility of the economic model. It appears the that the model submitted does not comply with the requirements of the NICE Guide to Methods of Technology Appraisals, which states that the model should follow accepted guidelines, and full documentation and justification of structural assumptions and data inputs should be provided. Until these concerns are resolved satisfactorily and the manufacturer can provide a robust model in which both the ERG and DSU have confidence, we feel it would be inappropriate for a positive recommendation to be made on the use of dapagliflozin.	Comments noted. The validity of the manufacturers' revised economic model was considered by the Appraisal Committee at its second and third meetings. See FAD sections 4.12-4.13.
Merck Sharpe and Dohme	**Section 3.15 - Dapagliflozin in triple therapy** The ACD confirms that the assessment of clinical effectiveness of dapagliflozin compared with DDP-4 inhibitors, GLP-1 analogues and thiazolidinediones was based on indirect evidence. The manufacturer has referred to a literature review concerning add-on therapy to metformin and sulfonylurea produced in 2009 from the Canadian drugs agency. However new data is available since then including studies of the newer DPP-4 inhibitors (linagliptin and saxagliptin). This newer data has not been captured in the analysis as the manufacturers did not conduct an up-to-date systematic review of triple therapy for people with type 2 diabetes inadequately controlled with metformin and sulfonylurea. Consequently we do not consider that any robust conclusions can be drawn from the indirect evidence presented in the submission for triple therapy.	Comments noted. The Committee concluded that significant caution should be taken when interpreting the results of the manufacturers' preliminary analyses on the clinical effectiveness of dapagliflozin in the triple therapy setting. See FAD section 4.10.

Commentator	Comment	Response
Merck Sharpe and Dohme	**3.16 Cost effectiveness** The economic model should be updated to reflect the safety issues associated with pioglitazone, as acknowledged in section 4.3 of the ACD. The incremental dapagliflozin associated renal monitoring cost (as required in line with the marketing authorisation for Dapagliflozin) should also be incorporated into the economic model.	Comments noted. When considering the cost effectiveness of dapagliflozin as dual therapy in combination with metformin, the Committee considered that on the basis of clinical specialist opinion that suggested that the use of pioglitazone in UK clinical practice was decreasing, therefore a thiazolidinedione was not a key comparator in the dual therapy setting. See FAD section 4.22. The costs of renal monitoring (£39), based on a GP visit and urine sample, were included in the first year of the manufacturers' model only for the dapagliflozin treatment group. See FAD section 3.25.
Merck Sharpe and Dohme	**Sections 3.21, 3.36 and 4.18 – HbA_{1c} thresholds applied in the model** MSD agrees with the concerns raised by the ERG and the NICE Appraisal Committee regarding the inconsistencies in the HBA_{1c} thresholds applied in the manufacturer's cost-effectiveness model, which were not consistent with the NICE Clinical Guideline for Type 2 Diabetes (NICE CG87). The base-case analyses should use HBA_{1c} thresholds that are consistent with the NICE Clinical Guidelines for Type 2 Diabetes.	Comment noted. The manufacturers' assumptions about the HbA_{1c} threshold levels used to switch or intensify treatment in the economic model were discussed further by the Committee at its second and third meetings. See FAD section 4.16.

Commentator	Comment	Response
Merck Sharpe and Dohme	**Section 3.22 – modelling patient weight over time** The manufacturers have stated that in their modelling the weight reduction for dapagliflozin was assumed to be maintained for two years, based on 2-year extension data. This assumption raises two concerns. Firstly, extension data is self-selecting in nature and therefore, making any assumptions about the potential of dapagliflozin to provide sustained weight loss benefit versus the comparators based on this is highly speculative, at best. Secondly, the manufacturers appear to have modelled that patients treated on dapagliflozin have a lower weight than patients treated on the comparators for the whole time horizon of the model (i.e. 40 years), as highlighted below by Figure 27 from the manufacturer's submission. Figure 27 from the manufacturer's submission, shows that the weight of patients on both treatments converge to the original weight of the patient at treatment initiation between year 2 and 3 (as the manufacturer state). However, after 3 years, Figure 27 shows that the patients on treatment (i.e. dapagliflozin) continue to have a lower weight compared to the patients on the 'control' (i.e. comparator). This assumption is not based on any evidence. **Figure included but not reproduced here** Additionally, the weight loss due to dapagliflozin is not uniform for all T2DM patients, and therefore weight loss has to be adjusted for a patient's baseline body weight and/or their BMI. The weight loss assumption for dapagliflozin is the key driver of the cost-effective model. The approach used by the manufacturer brings into question the reliability and robustness of their cost-effectiveness results. Amendments to these assumptions regarding weight change after 52 weeks do not appear to have been requested as part of the Committee's recommendation for further analyses from the manufacturer.	Comments noted. The manufacturers' approach to modelling changes in body weight was discussed further by the Committee at its second and third meetings. See FAD section 4.17.

Commentator	Comment	Response
Merck Sharpe and Dohme	**Section 3.25 – ERG's estimated cost of a severe hypoglycaemic event** The ERG estimated the direct costs of a severe hypoglycaemic event from the Hammer et al. study to be £320 compared to the manufacturer's estimate of £390 (section 5.3.2, ERG Report). MSD believes that the manufacturer has correctly calculated the direct cost of a severe hypoglycaemic event as £390. The total UK direct costs for patients with type 2 diabetes reported in Table 5 of Hammer et al. (2009) for three groups of patients that were categorised based on the way their hypoglycaemic event was managed were £33, £231 and £862 (in 2007 prices). Hammer et al. reported that the prevalence of the three treatment groups in the general population was 47.4%, 18.4% and 34.2%, respectively (based on Table 2 & 7 in the Hammer et al. publication). By applying these weightings, the average direct cost of a hypoglycaemic event is £353 in 2007 prices. Inflating this price (using the Hospital and Community Health Services Pay and Prices Index[5]) by 10.48% to 2011 prices equates to £390, as calculated by the manufacturer. In the ERG's estimated cost of £320, they based their weightings on the percentage of participants that were recruited in each treatment group in the study. As stated by the authors of the Hammer et al., study recruitment used a "non-random selection process". Therefore, it is more appropriate to apply the prevalence of the three treatment groups in the general population reported by Hammer et al. (as the manufacturer did) rather than the weightings of study participants, which are not representative of the general population.	Comments noted. The ERG's estimated cost of £320 for a severe hypoglycaemic event was not applied in any further exploratory analyses conducted by the ERG on the manufacturers' original economic model or in subsequent analyses conducted by the manufacturers or DSU on the revised model.

Commentator	Comment	Response
Merck Sharpe and Dohme	**Section 3.25 – costs of managing urinary tract infections (UTIs) and genital infections** The manufacturer assumed that the cost of treating a UTI or genital infection is only associated with the cost of one GP visit (£36). MSD believes this is an underestimate of the NHS resource and cost associated with treating UTIs and genital infections. UTIs and genital infections increase the risk of patients requiring GP visits, prescriptions and potentially hospital visits. Health Protection Agency guidance recommends treatment with antibiotics in severe cases or if the patient has ≥ 3 symptoms, and in mild cases depending on the results of the dipstick test and the presence of cloudy urine. It is therefore likely that additional drug therapies would need to be considered in some cases if a patient were to develop a UTI or genital infection as an adverse reaction to dapagliflozin therapy.	Comments noted. The Committee heard from the manufacturers that, because of the mechanism of action of dapagliflozin, the clinical trials had actively looked for urinary tract and genital infections and that only a small proportion of these infections needed treatment. See FAD section 4.11.
Merck Sharpe and Dohme	**Section 3.32 – ERG comments on scope of appraisal** The ACD states: "*Overall, the ERG considered that DPP-4 inhibitors are the key comparators for dapagliflozin in both the dual therapy and triple therapy settings*." This statement is inconsistent with the algorithms for dual therapy in the NICE Clinical Guideline 87 for Type 2 Diabetes[2]. For add-on to metformin, sulfonylureas, DPP-4 inhibitors and thiazolidinediones are recommended in the NICE Guidelines. While the use of pioglitazone (the only thiazolidinedione available in the UK) is in decline because of concerns about safety, sulfonylureas are commonly used. As such, both DPP-4 inhibitors and sulfonylureas are both key comparators for the dual therapy setting.	NICE does not respond to comments made about documents prepared by independent academic groups. The key comparators for dapagliflozin in the dual therapy setting in combination with metformin were discussed by the Committee in its second and third meetings. See FAD section 4.22.

Commentator	Comment	Response
Merck Sharpe and Dohme	**Section 3.40 – Price of DPP-4 inhibitors** The revised annual cost of DPP-4 inhibitors of £450.51 estimated by the ERG and reported in the ACD is not appropriate. The appropriate cost for DPP-4 inhibitors (based on sitagliptin) to use in this analysis is £433.57, which is the same as that used by the manufacturer. The most commonly used DPP-4 inhibitor in England is sitagliptin 100mg (Prescription Cost Analysis Data, 2011[7]), which has an annual cost of £433.57 (Drug Tariff, February 2013[8]). Regarding the cost of DPP-4 inhibitors, the dapagliflozin ERG report states the following: *"Note that sitagliptin in combination with a metformin total daily dose of 1g is available at an annual cost of £450.51"* There are two issues if this price is used in the analyses for DPP-4 inhibitors: firstly, sitagliptin 100mg rather than the sitagliptin/metformin combination product accounts for the majority of sitagliptin and DPP-4 inhibitor usage (Table 1)[7]. Therefore, the cost of DPP-4 inhibitors should either be based on the cost of the most commonly prescribed DPP-4 inhibitor (sitagliptin 100mg, £433.57 per patient/per year) or on a weighted average cost taking into account the level of usage of each DPP-4 inhibitor and DPP-4 inhibitor/metformin combination product; **Table included but not reproduced here** Secondly, the cost of metformin is inputted separately in the cost-effectiveness analyses. If the cost for this combination product of sitagliptin and metformin (£450.51) is applied for DPP-4 inhibitors, it is necessary to remove the cost of metformin (£23.46, Table 62, Dapagliflozin manufacturer's submission[3]) to avoid double counting the costs associated with metformin. In the ERG's re-analyses, it is not clear as to whether this was accounted for.	Comments noted. The ERG's alternative estimate of the annual costs of DPP-4 inhibitors were not applied in any further exploratory analyses conducted by the ERG on the manufacturers' original economic model or in subsequent analyses conducted by the manufacturers or DSU on the revised model.

Commentator	Comment	Response
Merck Sharpe and Dohme	**Section 3.40 – Price of pioglitazone** As noted by the ERG, the price of pioglitazone has fallen compared with that reported in the manufacturer's submission for dapagliflozin (which was based on the February 2012 Drug Tariff). This is because pioglitazone was added to Category M in the Drug Tariff in April 2012. While the ERG noted that the Drug Tariff price of pioglitazone was "£139.16" in the November 2012 Drug tariff (Dapagliflozin ERG Report), the price has fallen significantly since then. Table 2 below summarises the weighted average cost of pioglitazone compared to the Drug tariff in February 2012 (the source used by the manufacturer), November 2012 (the source used by the ERG) and February 2013 (the latest price available), based on the weightings that were reported in the manufacturer's submission. Between November 2012 and February 2013, the weight average cost of pioglitazone has fallen from £112.18 to £69.06 (a 38.4% price reduction). **Table 2 included but not reproduced here.**	Comments noted. The Committee noted that pioglitazone is now off-patent and that the latest acquisition costs are substantially lower than those presented in the manufacturers' submission. The Committee acknowledged that the manufacturers were unable to provide this estimate in their submission, but considered that the estimate of £69.09 was reasonable. See FAD section 4.21.
Merck Sharpe and Dohme	**Section 4.2 – clinical effectiveness of dapagliflozin in triple therapy** MSD do not consider that sufficiently robust evidence has been submitted by the manufacturers to allow a recommendation to be made for use of dapagliflozin as part of a triple therapy regime.	Comments noted. The Committee concluded that significant caution should be taken when interpreting the results of the manufacturers' preliminary analyses on the clinical effectiveness of dapagliflozin in the triple therapy setting. See FAD section 4.10.
Merck Sharpe and Dohme	**Section 4.9, 4.11 and 4.12 – network meta-analysis** The network meta-analyses submitted by the manufacturer provided most of the clinical effectiveness data for the comparison of dapagliflozin and other anti-diabetic therapies. However we are concerned by the level of uncertainty surrounding the validity of the results of the network meta-analyses. This therefore makes any results presented questionable, and until the issues with the programme code which has been used to run the network meta-analyses are resolved, we believe that the results presented cannot be considered as robust. Consequently the weight loss benefit claimed to be shown by dapagliflozin is yet to be proven conclusively.	The manufacturers revised network meta-analyses were considered by the Appraisal Committee at its second meeting. See FAD section 4.5.

Commentator	Comment	Response
Merck Sharpe and Dohme	**Section 4.10 – comparative clinical-effectiveness data at 24-weeks and 52-weeks** The ACD states: "*The Committee also heard from the manufacturers that 2-year follow-up data were available for the clinical trials of dapagliflozin but that, because most of the trials of other antidiabetic drug therapies were of 24-week duration, it was necessary that the clinical-effectiveness data used in the cost-effectiveness analysis were based on the results of the clinical trials and network meta-analyses at 24 weeks.*" There is clinical-effectiveness data available from the manufacturer's network meta-analysis at 52-weeks for the add-on to metformin analysis for the following outcomes: ➢ HbA1c ➢ Weight change ➢ Hypoglycaemic event Given the long-term time horizon of the model, the NICE Appraisal Committee need to consider the cost-effectiveness results based on the 52-week data for these endpoints (presented as a scenario analysis by the manufacturer) in addition to the base case analysis using 24-week data, as part of their deliberations.	Comments noted. The Committee discussed the clinical effectiveness data that were applied in the economic models further at its second and third meetings. See FAD section 4.15.
Merck Sharpe and Dohme	**Section 4.13 – Adverse events** The ACD confirms that the Committee has heard from patient groups that adverse events are a concern for patients with type 2 diabetes if they result in the need for additional drug therapies. The most common adverse events for dapagliflozin were urinary tract infections (UTIs) and genital infections. UTIs and genital infections increase the risk of patients requiring GP visits, prescriptions and potentially hospital visits. Health Protection Agency guidance recommends treatment with antibiotics in severe cases or if the patient has ≥ 3 symptoms, and in mild cases depending on the results of a dipstick test and the presence of cloudy urine. It is therefore likely that additional drug therapies would need to be considered in some cases if a patient were to develop a UTI or genital infection as an adverse reaction to dapagliflozin therapy.	Comments noted. The Committee heard from the manufacturers that, because of the mechanism of action of dapagliflozin, the clinical trials had actively looked for urinary tract and genital infections and that only a small proportion of these infections needed treatment. See FAD section 4.11.

Commentator	Comment	Response
Merck Sharpe and Dohme	**Section 4.17 – Interpretation of cost-effectiveness results for add-on to metformin (dual therapy)** The manufacturer sourced the clinical effectiveness data for the metformin add-on analyses from different sources. The Committee has acknowledged that it "*would have been preferable to use clinical-effectiveness data from the same source for all comparators*". However, MSD is concerned about the impact this has the interpretation of the cost-effectiveness results for the add-on to metformin scenario. For the 'dual therapy ' add-on to metformin analyses, it is not appropriate to directly compare the incremental cost-effectiveness ratio (ICER) obtained from the dapagliflozin versus SU analysis to the ICERs obtained from the dapagliflozin, DPP-4 inhibitors, glitazones analysis because the clinical-effectiveness estimates have been derived from different sources. As a consequence, the cost-effectiveness results for the add-on to metformin cannot be directly compared and incrementally analysed to identify situations of simple or extended dominance across all the comparators. The NICE Guide to Methods of Technology Appraisals states the requirement to assess dominance in cost-effectiveness analyses: "*Standard decision rules should be followed when combining costs and QALYs. These should reflect any situation in which dominance or extended dominance exists.*" As such, the approach used by the manufacturer poses further uncertainty in the cost-effectiveness results for the metformin add-on analysis. **References included but not reproduced here**	Comments noted. The Committee considered that, on the basis of clinical specialist opinion that suggested that the use of pioglitazone in UK clinical practice was decreasing, a thiazolidinedione was not a key comparator in the dual therapy setting. The Committee also noted the evidence from the clinical specialists supported by the manufacturers that, in clinical practice, dapagliflozin would predominantly be used in combination with metformin when a sulfonylurea is not appropriate. Therefore, the Committee also considered that sulfonylurea was not a relevant comparator in the dual therapy setting. See FAD section 4.22.
Boehringer Ingelheim	ACD Section 1.2: Given the complexity of the analysis it may have been pertinent for the Committee to specify what additional information it would like to see presented to improve the transparency of the analysis besides reporting more clinical outcomes.	Comment noted.
Boehringer Ingelheim	ACD Section 3.8: While it is understandable why the manufacturer did not conduct a NMA for adverse events, it would have improved the coherence of the analysis and accounted for potential biases in different baselines and so on. Its impact on results could be explored as a sensitivity analysis.	Comments noted. The manufacturers' network meta-analyses included hypoglycaemic events but not other adverse events such as urinary tract or genital infections. See FAD section 3.8.

Commentator	Comment	Response
Boehringer Ingelheim	ACD Section 3.25: *"The cost of end-stage renal failure of was based on the average annual costs of automated peritoneal dialysis taken from a separate UK-based study"* This is incorrect the costs are from a study of both haemodialysis and peritoneal dialysis with the final cost being weighted according to current UK usage.	Comment noted. The relevant sentence in section 3.25 of the FAD has been amended to state: "The annual cost of end-stage renal failure (£34,806) was based on the weighted average cost of automated peritoneal dialysis, continuous ambulatory peritoneal dialysis, hospital haemodialysis and satellite unit based haemodialysis, taken from a separate UK-based study".
Boehringer Ingelheim	ACD Section 3.25: It is inappropriate to consider UTIs and GTIs to be the same in terms of costs and HRQoL. While it's agreed that GTIs could receive local treatment, UTIs should receive initial oral antibiotics (after eventual culture and antibiogram). In particular in men UTI can be difficult to manage and when not managed appropriately can lead to potential complications including pyelonephritis. A further complication is that in people with various co morbidities the diagnosis is often missed and could lead to rapid hospitalisation with corresponding increased health costs. The study used by the manufacturer (Turner et al 2010) was in non-pregnant women with suspected uncomplicated urinary tract infection (where antibiotic use was not mandatory) and patients were excluded if immediate antibiotic treatment was necessary (if they were pregnant, if they had pyelonephritis, nausea, vomiting, or other severe systemic symptoms). Therefore, its applicability to this adverse event is uncertain and needs to be accounted for in interpretation of the cost effectiveness results.	Comments noted. The Committee heard from the manufacturers that, because of the mechanism of action of dapagliflozin, the clinical trials had actively looked for urinary tract and genital infections and that only a small proportion of these infections needed treatment. See FAD section 4.11. The Committee noted that in scenario analyses the manufacturers had applied a range of estimates for the loss in utility associated with urinary tract and genital infections. It was also aware that the results of the revised analyses were not sensitive to changes in these utility values. See FAD section 4.20.

Commentator	Comment	Response
Boehringer Ingelheim	ACD Section 3.26: The manufacturer's model predicts that patients gain just over 11 QALYs over a life time after treatment. In all the models previously reviewed by the manufacturer on pg198 of their submission none of the models report QALY gains over 9. Even considering variation in the baseline characteristics it seems unreasonable that the total QALY gains per patient should vary this much, given that the same clinical equations underpin the majority of the models. The reason for this difference should be explored and explained.	Comments noted. The Committee discussed the validation report provided by the manufacturers which compared the results from the revised model with the results that would have been obtained using the CORE diabetes model. The Committee noted that the results generated from the CORE diabetes model were comparable to those obtained from the manufacturers' original and revised economic models for the dual therapy and insulin add-on therapy analyses. See FAD section 4.13.
Boehringer Ingelheim	ACD Section 3.33: It would make sense to use the data from the longest time period possible to reflect the long term effectiveness of the treatment.	Comment noted. The manufacturers revised network meta-analyses were considered by the Appraisal Committee at its second meeting. See FAD sections 4.5 and 4.15.
Boehringer Ingelheim	ACD Section 4.9: On p150 table 41 of the manufacturer's submission there appears to be inconsistency between the direct estimate of effectiveness with TZDs (0.37 (0.03-1.48)) and the indirect (3.15 (0.13 – 78.32)) while the direct estimate does lie within the credible estimate of the indirect the difference is sufficient to cast doubt on the robustness of the analysis. Did the Committee want a rationale or explanation for variation between the code used in the analysis and the Technical Support Document?	Comments noted. The Committee noted that, although the WinBUGs programme code used to run the original network meta-analyses provided in the manufacturers' submission differed from the code recommended by the NICE DSU, the manufacturers had also provided revised network meta-analyses that were based on the recommended code. The Committee also noted that the results of the manufacturers' revised network meta-analyses were similar to those from the original analyses. See FAD section 4.5.
Boehringer Ingelheim	ACD Section 4.10: Does the Committee mean that there is uncertainty in extrapolating all intermediate outcomes to long-term diabetic complications, or only linking HbA1c to cardiovascular events? This link is the only one mentioned explicitly as being of unknown significance; others have been accepted in the past.	Comment noted. The Committee concluded that, despite some uncertainty about the impact of HbA_{1c} reduction on longer-term macrovascular complications, it was prepared to accept the link between intermediate outcomes collected in the clinical trials and longer-term clinical outcomes.. See FAD section 4.6.

Commentator	Comment	Response
Boehringer Ingelheim	ACD Section 4.14: The sentence *"The Committee also expressed concern that the DSU was unable to reproduce the results of the probabilistic sensitivity analyses reported in the manufacturers' submission."* is not complete. In 3.54 it's stated that the DSU were unable to reproduce the results for the deterministic and probabilistic analyses. Plus it states that the two models were not consistent with each other (i.e. when mean estimates are used they are not the same).	Comment noted. This sentence has been amended to reflect the revised model provided by the manufacturer. The Committee noted that the manufacturers had provided a revised economic model in order to address concerns raised by the DSU about the original model and that the DSU considered that their concerns had been addressed. However, it also noted that the DSU and the ERG had identified a number of errors in the revised model which were subsequently addressed by the DSU in its exploratory analyses. The Committee concluded that the manufacturers' revised economic model with the subsequent amendments made by the DSU was acceptable for assessing the cost effectiveness of dapagliflozin in combination therapy for treating type 2 diabetes. See FAD section 4.12.
Boehringer Ingelheim	ACD Section 4.16: Given the number of new treatments and the ongoing update of the type 2 diabetes in adults guideline it would seem more appropriate to include as many of the options outlined in the scope as possible. Otherwise it would be good to see the reasoning of why certain treatments were/were not considered appropriate to help inform future appraisals in diabetes.	Comment noted. The key comparators for dapagliflozin in the dual therapy setting in combination with metformin were discussed further by the Committee in its second and third meetings. See FAD section 4.22.
Boehringer Ingelheim	ACD Section 4.17: The presentation and rationale for choosing clinical data from NMAs or head-to-head trials was unclear and should be clarified. A single coherent analysis of all the data is preferable and then any concerns around the estimates can be explored deliberatively afterwards.	Comments noted. The Committee discussed the clinical effectiveness data that were applied in the economic models further at its second and third meetings. See FAD section 4.15.

Commentator	Comment	Response
Boehringer Ingelheim	ACD Section 4.21: Could a rationale be given as to why the estimates from Bagust 2005 were chosen rather than any of the alternatives quoted in the manufacturer's submission pg 59 table 217. There are alternatives also collected with EQ-5D which may be plausible and the Committee's rationale for choosing Bagust should be clear.	Comments noted. The Committee noted that the loss in utility associated with a 1-unit increase in BMI (−0.0472) was similar to the loss in utility associated with a myocardial infarction (−0.055), which may not be credible. The Committee concluded that the utility values associated with changes in weight may have been too large and that the values (±0.0061 per BMI unit decrease or increase) applied in the manufacturers' scenario analyses and DSU analyses were more reasonable. See FAD section 4.18.
Boehringer Ingelheim	ACD Section 4.26: It would be useful to add here that the incremental QALY gains between the treatments are relatively small. Therefore, any uncertainty over how HRQoL has been captured could result in the ICERs changing significantly.	Comments noted. The Committee noted that the DSU analyses showed that DPP-4 inhibitors were associated with higher costs and QALYs than dapagliflozin, but that these differences were small. It noted further that in the DSU probabilistic sensitivity analysis these differences were even smaller. The Committee noted that the differences in QALYs were largely explained by the changes in health-related quality of life (utility) associated with changes in weight (BMI). See FAD section 4.22.
Eli Lilly and Company	Eli Lilly and Company Ltd appreciates the opportunity to review and comment on the ap-praisal consultation document (ACD) for Dapagliflozin in combination therapy for the treatment of type 2 diabetes. Eli Lilly supports the development of new technologies which provide individual treatment choices and a patient-centred approach to diabetes management. With regard to the specific questions posed in the ACD, we have no comments to make.	Comment noted. No actions required.

Commentator	Comment	Response
Novo Nordisk	***Has all of the relevant evidence been taken into account?*** Novo Nordisk note from the evidence presented for triple therapy that the manufacturer has relied on an existing network meta-analysis that was conducted by the Canadian Agency for drugs and technologies in health (CADTH). It should be noted that this review excluded some studies that may have been relevant to the decision problem outlined by NICE. We are aware of one such study from the liraglutide clinical development programme that could have contributed further evidence to the GLP1 group. This has not been considered in the current analysis. **Reference included but not reproduced here**	Comments noted. The Committee concluded that significant caution should be taken when interpreting the results of the manufacturers' preliminary analyses on the clinical effectiveness of dapagliflozin in the triple therapy setting. See FAD section 4.10.
Novo Nordisk	***Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?*** Based on our review of the network meta-analysis and the use of these results in the cost effectiveness model, it is difficult for Novo Nordisk to comment whether these are reasonable interpretations of the evidence due to the way the information has been presented by the manufacturer. Much of the analysis is presented as confidential and it is not always possible to cross check which figures were being used for which analysis. Novo Nordisk would however like to comment on the approach taken to the analysis of dapagliflozin as triple therapy. In this analysis post-hoc evidence for dapagliflozin was compared with an existing published network meta-analysis that did not include dapagliflozin. The manufacturer has used this data in an economic model to show that dapagliflozin dominates all of the possible comparators, GLP-1, DPP-4 and glitazone. We would like to point out that this analysis is based on an unadjusted comparison between dapagliflozin and the relevant comparators, that does not preserve randomisation and therefore this cannot be considered a robust basis on which to make a recommendation on the use of dapagliflozin in triple therapy.	Comments noted. The Committee concluded that significant caution should be taken when interpreting the results of the manufacturers' preliminary analyses on the clinical effectiveness of dapagliflozin in the triple therapy setting. See FAD section 4.10. The Committee noted that the clinical-effectiveness data applied in the triple therapy model were based on an indirect comparison of pooled data of 2 trials of dapagliflozin and a separate systematic review of other antidiabetic drug therapies conducted in 2009. The Committee was also aware that dapagliflozin is currently being studied as a triple therapy add-on to 2 other oral agents. The Committee considered that the cost-effectiveness analyses should be considered as exploratory in nature. See FAD section 4.24.

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional 1	4	'Newer' glucose-lowering agents such as dapagliflozin are vital to the continuous clinical effort in reducing the burden of diabetes and its complications, especially hypoglycaemia and weight gain. The benefits of the agent, rather than the perceived risks should be strongly considered. The evidence of benefit is strong, and more notice should be given to the clinician, striving to reduce the clinical and financial burden of diabetes and its complications.	Comments noted. Dapagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if it is used as described for dipeptidyl peptidase-4 (DPP-4) inhibitors in Type 2 diabetes: the management of type 2 diabetes (NICE clinical guideline 87). Dapagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes. Dapagliflozin in a triple therapy regimen in combination with metformin and a sulfonylurea is not recommended for treating type 2 diabetes except as part of a clinical trial. See FAD sections 1.1-1.3.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
NHS Professional 2	4	Although further clarification of the evidence may be useful, the current evidence as it stands is enough to make this treatment available to certain groups of patients on trial basis. Withdrawing treatment from patients who do not show adequate response in terms of HbA1c reduction is likely to maximise cost-effectiveness. Patients who might benefit from this treatment include those who are poorly controlled on oral therapy but in whom all other possible add-on therapies are either contraindicated or have been ineffective; i.e. Dapagliflozin should be considered as a pre-insulin option if all other agents have failed including GLP-1 based therapies. Dapagliflozin is also expected to be useful in patients who are poorly controlled on insulin and in who intensifying insulin therapy is not considered appropriate due to risk of hypoglycaemia and/or weight gain. The use of Dapagliflozin with insulin is expected to be more cost-effective given the cost savings associated with reduction in insulin dose or the avoidance of an increase in insulin dose.	Comments noted. Dapagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if it is used as described for dipeptidyl peptidase-4 (DPP-4) inhibitors in Type 2 diabetes: the management of type 2 diabetes (NICE clinical guideline 87). Dapagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes. See FAD sections 1.1 and 1.2.
NHS Professional 3	1	One must not underestimate the social, financial and health impact of hypoglycaemia. Whilst cost-effective, SUs will always cause hypoglycaemia albeit to varying extents. Potentially vulnerable groups such as those over age 65 are particularly at risk of hypoglycaemia. Hospital admissions for these groups can be lengthy costly and overal l detrimental to ongoing quality of life I do not think the QALYs associated with hypoglycaemia should be adjusted.	Comments noted. Dapagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if it is used as described for dipeptidyl peptidase-4 (DPP-4) inhibitors in Type 2 diabetes: the management of type 2 diabetes (NICE clinical guideline 87). Dapagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes. Dapagliflozin in a triple therapy regimen in combination with metformin and a sulfonylurea is not recommended for treating type 2 diabetes except as part of a clinical trial. See FAD sections 1.1-1.3.

Role*	Section	Comment	Response
NHS Professional 3	3	Pioglitazone should no longer be considered an alternative 2nd or third line option due to significant concerns of adverse effects in particular hip fracture in both men and women I feel it should not be included as a comparator.	Comment noted. The Committee considered that, on the basis of clinical specialist opinion that suggested that the use of pioglitazone in UK clinical practice was decreasing, a thiazolidinedione was not a key comparator in the dual therapy setting. See FAD section 4.22.
NHS Professional 4	1	I agree with the queries above that should be provided by the manufacturer. Cost-benefit anlysis is extremely complex for diabetes; I think is worth highlighting that sGLT2 inhibitors are new tools that could significantly help clinicians in the treatment of patients with type 2 diabetes.	Comment noted. The Committee understood that a new treatment providing an additional option would be valued by clinicians. See FAD section 4.2.
NHS Professional 4	2	In patients with reduced renal function the sGLT2 transporters are downregulated and therefore sGLT2 inhibitors loose in their effectiveness. Hypoglycaemia is not an adverse reaction driven by sGLT2 inhibitors; hypoglycaemia occurs only when combination therapy is made with hypoglycaemic agents such as sulphonylurea and insulin. SGLT2 inhibitors promote a minor loss of fluids and I would see the combination with ppar-gamma agonists (which promote fluids retention) ideal. I am not sure whether there is any clear evidence to refuse this combination, but I can see where is coming from; possibly because of the “noise” in bladder cancer attributed to Pioglitazone. I do not see, for the moment, any issue related to the use of sGLT2 inhibitors and neoplasia of the urinary tract. Patients with familial glycosuria and patients with diabetes (and recurrent glycosuria) do not appear to have higher incidence of neoplastic disease in the urinary tract. Nethertheless, I guess there might be a call for caution in this respect.	Comments noted. Section 2 of the FAD provides a summary of adverse reactions described in the summary of product characteristics.
NHS Professional 4	4	I agree on all the point raised by the committee. In relation to the Committee note that the majority of the QALY gains associated with dapagliflozin arise from the direct impact of weight change on health-related quality of life rather than diabetic complications and other adverse events is true within the time the drug has been used to date. Weight loss provides, in the long term, significant benefit in the diabetes-associated chronic complication; I wonder if this can be extrapolated or modelled.	Comments noted. The manufacturers’ approach to modelling changes in body weight was considered further by the Appraisal Committee at its second and third meetings. See FAD section 4.17.

Role*	Section	Comment	Response
NHS Professional 5	1	We believe that this agent will deliver acceptable HbA1c reductions and weight reductions.	Comments noted. Dapagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if it is used as described for dipeptidyl peptidase-4 (DPP-4) inhibitors in Type 2 diabetes: the management of type 2 diabetes (NICE clinical guideline 87). Dapagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes. Dapagliflozin in a triple therapy regimen in combination with metformin and a sulfonylurea is not recommended for treating type 2 diabetes except as part of a clinical trial. See FAD sections 1.1-1.3.
NHS Professional 5	2	We have patients with significant issues that will benefit. Patients who would otherwise have a GLP1 or have failed to remind to GLP1 therapy or are becoming increasingly resistant to insulin and are putting weight on.	Comment noted. No actions requested.

Role*	Section	Comment	Response
NHS Professional 5	5	We have a number of patients with significant issues that will benefit from this technology. The price is low enough that extra insulin, GLP1 and weigh loss drugs will be avoided. The CCG feels that we will DVD money by using dapagliflozin in the identify patient groups as well as potentially avoiding a number of referrals for increased insulin resistance and to our primary care diabetes service for GLP1 initiation.	Comments noted. Dapagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if it is used as described for dipeptidyl peptidase-4 (DPP-4) inhibitors in Type 2 diabetes: the management of type 2 diabetes (NICE clinical guideline 87). Dapagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes. Dapagliflozin in a triple therapy regimen in combination with metformin and a sulfonylurea is not recommended for treating type 2 diabetes except as part of a clinical trial. See FAD sections 1.1-1.3.

Role*	Section	Comment	Response
NHS Professional 6	4	We must be looking at combined benefits of this drug including modest reduction to HbA1c AND weight loss for around 66% of clinical trial participants. I feel that drugs that both address glycaemic and weight issues are an invaluable new addendum to our diabetes drugs armoury. Forxiga is being priced at around half the cost of GLP1 therapy and I believe NICE should be fully supporting the use of this drug in Type 2 Diabetes as 2nd or 3rd line glucose lowering therapy after Metformin. The weight loss we see with Forxiga and GLP1 therapy is for many patients their first recent success and weight management and changes to confidence and beliefs about their own ability to lose weight should be supported and maximised by health professionals support and behavioural intervention.	Comments noted. Dapagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if it is used as described for dipeptidyl peptidase-4 (DPP-4) inhibitors in Type 2 diabetes: the management of type 2 diabetes (NICE clinical guideline 87). Dapagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes. Dapagliflozin in a triple therapy regimen in combination with metformin and a sulfonylurea is not recommended for treating type 2 diabetes except as part of a clinical trial. See FAD sections 1.1-1.3.