NATIONAL INSTITUTE FOR HEALTH CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Dapagliflozin in combination therapy for the treatment of type 2 diabetes

Response to consultee and commentator comments on the provisional matrix of consultees and commentators

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	Boehringer Ingelheim and Lilly Uk should be added as the comparator manufacturer of linagliptin	Boehringer Ingelheim		Added	This organisation has an area of interest directly related to this appraisal and meets the selection criteria to participate in this appraisal. Boehringer Ingelheim and Lilly UK has been added to the matrix of consultees and commentators under 'comparator manufacturers' groups.

2.	This matrix should include: All-Party Parliamentary Group on Diabetes and Yorkshire & Humber Public Health Observatory	Bristol-Myers Squibb & Astra Zeneca		Not included	These organisations do not meet the selection criteria. Organisations are required to be national groups.

National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Dapagliflozin in combination therapy for the treatment of type 2 diabetes

Response to consultee and commentator comments on the draft scope (scope consultation April 2012)

Comment 1: the draft scope

Section	Consultees	Comments	Action
Background Information	Bristol Myers Squibb and AstraZeneca	No comments.	No amendment to the scope required.
	Cochrane Metabolic and Endocrine Disorders Review Group	'Control of disease' is not defined. Given the recent discussion about insecure threshold for 'metabolic control' one could contemplate to refer to this discussion in the background section.	Comment noted. The background section of the scope provides summary information about the disease area and clinical management. A detailed description of glucose control levels is available in NICE clinical guidelines for type 2 diabetes and is not required in the scope.
	CSAS	Information regarding the use of exenatide as a triple therapy is unclear, e.g. fifth paragraph of the background section states 'recommend the use of the twice daily and the prolonged release regimens of exenatide (an incretin mimetic) respectively'.	Comment noted. This has been amended in the scope.
	Merck Sharp and Dohme	No comments.	No amendment to the scope required.

Section	Consultees	Comments	Action
	NHS Gloucestershire	Information regarding the use of exenatide as a triple therapy is unclear, e.g. fifth paragraph of the background section states 'recommend the use of the twice daily and the prolonged release regimens of exenatide (an incretin mimetic) respectively'.	Comment noted. This has been amended in the scope.
	RCGP and PCDS	Good.	Comment noted. No amendment to the scope required.
	Royal College of Nursing	The information appears complete.	Comment noted. No amendment to the scope required.
The technology/ intervention	Bristol Myers Squibb and AstraZeneca	We would like to clarify the settings in which dapagliflozin has been studied. We have therefore separated out the combinations with oral agents from those with insulin. Dapagliflozin has received a positive opinion from the CHMP and awaits full marketing authorisation. It has been studied in clinical trials as monotherapy compared with placebo and metformin XR in adults with type 2 diabetes who have inadequate glycaemic control with diet and exercise. It has also been studied as second line add-on to metformin, glimepiride or pioglitazone. However, given the warnings associated with pioglitazone use, as a precaution we would not recommend dapagliflozin be used in combination with pioglitazone. Dapagliflozin is currently being studied as third-line add-on (+met+su; +met+DPP-4 inhibitor) but these trials have not reported yet. Dapagliflozin has been studied in inadequately controlled patients on insulin (with one or more oral agents) compared with placebo.	Comment noted. The technology section of the scope has been amended to reflect these comments.

Section	Consultees	Comments	Action
	Cochrane Metabolic and Endocrine Disorders Review Group	The description of the technology is accurate.	Comment noted. No amendment to the scope required.
	CSAS	*Question: "Is the description of the technology or technologies accurate?"* Yes	Comment noted. No amendment to the scope required.
	Merck Sharp and Dohme	No comments.	No amendment to the scope required.
	NHS Gloucestershire	The description of the technology is accurate.	Comment noted. No amendment to the scope required.
	RCGP and PCDS	*Question: "Is the description of the technology accurate?"* Yes, as far as I am aware.	Comment noted. No amendment to the scope required.
	Royal College of Nursing	Description appears correct.	Comment noted. No amendment to the scope required.

Section	Consultees	Comments	Action
Population	Boehringer Ingelheim / Eli Lilly	The CHMP positive opinion for dapagliflozin states that treatment is indicated as follows: <u>Monotherapy</u> When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance. <u>Add-on combination therapy</u> In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control	Feedback from clinicians at the scoping workshop held in June 2011 suggested that dapagliflozin would not be used as monotherapy. They therefore recommended that NICE would provide more value to the NHS by focusing an appraisal on the use of dapagliflozin combination therapies. In view of that, this appraisal will consider dapagliflozin in combination therapy only. In light of this comment and others, NICE will further consider whether an additional appraisal of dapagliflozin monotherapy is required through its topic selection processes.

Section	Consultees	Comments	Action
	Bristol Myers Squibb and AstraZeneca	• Dapagliflozin has been evaluated in the 'dual therapy' (or second line setting) as described in the scope • Dapagliflozin has also been evaluated in the 'add-on to insulin' setting as described in the scope As stated above, there are no currently available data for dapagliflozin as third-line add-on to 2 other oral agents. There are no combination studies with GLP-1 analogues.	NICE develops scopes based on the anticipated marketing authorisation for the intervention under consideration and the recommendations received at the scoping workshop. For dapagliflozin, currently the wording of the CHMP opinion does not preclude the use of dapagliflozin in triple combination therapies and clinicians at the workshop considered that dapagliflozin would be predominantly used in dual and triple combination therapies. Therefore, the scope for dapagliflozin includes populations that would be suitable for dapagliflozin in triple combination therapies.
	Cochrane Metabolic and Endocrine Disorders Review Group	In response to the question: "Is the population defined appropriately? Are there groups within this population that should be considered separately?" Yes (with regard to 'inadequate control' see above).	Comment noted. No amendment to the scope required.

Section	Consultees	Comments	Action
	CSAS	In line with the European marketing authorisation when issued, the population could include the use of dapagliflozin 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." Advice received from a GP/CCG prescribing lead is that although diabetologists may not wish to use dapagliflozin as monotherapy it will still be marketed to grass roots GPs as monotherapy (as other drugs have been) and therefore that not including monotherapy in the review seems 'naive'.	Feedback from clinicians at the scoping workshop held in June 2011 suggested that dapagliflozin would not be used as monotherapy, and they therefore recommended that NICE would provide more value to the NHS by focusing an appraisal on the use of dapagliflozin combination therapies. In view of that, this appraisal will consider dapagliflozin in combination therapy only. In light of this comment and others, NICE will further consider whether an additional appraisal of dapagliflozin monotherapy is required through its topic selection processes.

Section	Consultees	Comments	Action
	Merck Sharp and Dohme	As per NICE's guide to the single technology appraisal process, we understand that any review of the new technology will take place within its licensed indications. Information concerning the indications being filed for dapagliflozin was presented during the June 2011 scoping workshop. Based on these discussions, the 'Population' section of this draft scope may require revision to ensure that the populations assessed are only those which are covered by the licensed indication.	In its appraisals of health technologies, NICE is bound by the licensed indication of the intervention under consideration. For dapagliflozin, the population in the scope reflects the current wording of the CHMP opinion for dapagliflozin and the clinical opinion expressed at the scoping workshop. NICE will only make recommendations within the context of the dapagliflozin marketing authorisation.

Section	Consultees	Comments	Action
	NHS Gloucestershire	In line with the European marketing authorisation when issued, the population could include the use of dapagliflozin 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."	Feedback from clinicians at the scoping workshop held in June 2011 suggested that dapagliflozin would not be used as monotherapy, and they therefore recommended that NICE would provide more value to the NHS by focusing an appraisal on the use of dapagliflozin combination therapies. In view of that, this appraisal will consider dapagliflozin in combination therapy only. In light of this comment and others, NICE will further consider whether an additional appraisal of dapagliflozin monotherapy is required through its topic selection processes.
	RCGP and PCDS	The general population of people with Type 2 Diabetes is represented.	Comment noted. No amendment to the scope required.
	Royal College of Nursing	*Question: "Is the population defined appropriately? Are there groups within this population that should be considered separately?"* Yes.	Comment noted. No amendment to the scope required.

Section	Consultees	Comments	Action
Comparators	Boehringer Ingelheim / Eli Lilly	Comparators for dapagliflozin monotherapy when metformin is considered inappropriate should be considered in line with the above proposed licensed indication.	Feedback from clinicians at the scoping workshop held in June 2011 suggested that dapagliflozin would not be used as monotherapy, and they therefore recommended that NICE would provide more value to the NHS by focusing an appraisal on the use of dapagliflozin combination therapies. In view of that, this appraisal will consider dapagliflozin in combination therapy only. In light of this comment and others, NICE will further consider whether an additional appraisal of dapagliflozin monotherapy is required through its topic selection precesses.

Section	Consultees	Comments	Action
	Bristol Myers Squibb and AstraZeneca	The comparators listed are the standard treatments currently used in the NHS. Given our comments above, the triple therapy comparators listed in the scope are not considered relevant for this appraisal. **Dual-therapy** For the combination of dapagliflozin and metformin, we will present comparisons with sulfonylureas (with metformin), TZD (with metformin), and DPP-4 inhibitors (with metformin). A comparison with GLP-1 analogues (with metformin) will not be presented because these therapies are recommended by the Institute only where metformin or a sulfonylurea is not tolerated or contraindicated, and a thiazolidinedione and a DPP-4 is contraindicated or not tolerated. The proportion of patients in this setting receiving a GLP-1 analogues is less than 5% and therefore these therapies are not considered routine practice in this setting. For the combination of dapagliflozin and sulfonylurea (SU), whilst this has been studied, we do not consider this combination relevant for this appraisal. SU as monotherapy is not preferred as a first line agent in NICE guidance, SIGN or other international guidelines. Generally, SUs are only recommended if the patient exhibits osmotic symptoms that require rapid control, is not overweight or the patient does not tolerate metformin. In the situations where SU's are initiated as monotherapy, dapagliflozin would generally be considered unsuitable for these patients because of potential exacerbation of osmotic diuresis. **Add-on therapy to insulin** The comparators / context of evaluation noted in the scope is appropriate	The current wording of the CHMP opinion for dapagliflozin does not preclude the use of dapagliflozin in triple combination therapies and clinicians at the workshop considered that dapagliflozin would be predominantly used in dual and triple combination therapies. Accordingly, the comparators in the scopes for triple therapy include combinations that are recommended by NICE or that are routinely used in clinical practice. Similarly, the CHMP opinion covers the use of dapagliflozin in dual therapies; therefore the combination of dapagliflozin and sulfonylurea has been addressed in the scope. GLP-1 analogues have been included as comparators for the combination of dapagliflozin and metformin because NICE has recommended their use for certain people in dual therapy regimens in technology appraisals no. 203 and 248.

Section	Consultees	Comments	Action
	Cochrane Metabolic and Endocrine Disorders Review Group	Combination of dapagliflozin and sulfonylurea: Would it be of interest what kind of sulfonylurea compound is used for combination (e.g. glibenclamide in one arm and glimepiride in another arm), i.e. do combination partners need to be identical? How about repaglinide and nateglinide combination (especially for people with diminished renal function).	When appraising a technology the Committee is able to consider issues related to the specific compounds with which a technology may be combined. Information about the efficacy of the different sulfonylureas should be included in any submission to NICE. No amendments to the scope required. Comments received on the consultation suggest that the use of short acting insulin secretagogues and acarbose is limited to specific subgroups of patients. The manufacturer has suggested that dapagliflozin is unlikely to be used in patients with renal impairment because of its mechanism of action. No amendments to the scope required.

Section	Consultees	Comments	Action
	CSAS	For the dual therapy ‘combination of dapagliflozin and sulfonylureas’; metformin (with sulfonulurea) could be added as a comparator. Comparators for monotherapy, if considered, could include metformin and sulfonylureas.	As per NICE clinical guidelines no. 66 and no. 87, metformin would normally be considered first and it may be used second line to first-line sulfonylurea only when a rapid therapeutic response is required because of hyperglycaemic symptoms. As such, metformin (with a sulfonylurea) is not considered a relevant comparator for the combination of dapagliflozin and sulfonylurea.
	Merck Sharp and Dohme	Please see our above comments concerning the 'Population' section of the draft scope. Similarly, revisions to the 'Comparators' section of the draft scope may be required to ensure that this section only includes comparators against the combination therapy regimes for which dapagliflozin is licensed.	Comment noted. See response to comment by Merck Sharp and Dohme about the population.
	NHS Gloucestershire	For the dual therapy ‘combination of dapagliflozin and sulfonylureas’; metformin (with sulfonulurea) could be added as a comparator. Comparators for monotherapy, if considered, could include metformin and sulfonylureas.	As per NICE clinical guidelines no. 66 and no. 87, metformin would normally be considered first and it may be used second line to first-line sulfonylurea only when a rapid therapeutic response is required because of hyperglycaemic symptoms. As such, metformin (with a sulfonylurea) is not considered a relevant comparator for the combination of dapagliflozin and sulfonylurea.

Section	Consultees	Comments	Action
	RCGP and PCDS	All are reasonable alternatives to which this new agent should be compared.	Comment noted. No amendment to the scope required.
	Royal College of Nursing	*Question: "Is this (are these) the standard treatment(s) currently used in the NHS with which the technology should be compared? Can this (one of these) be described as 'best alternative care'?"* Yes all treatment currently used in clinical practice and the combinations they are used in are covered	Comment noted. No amendment to the scope required.
Outcomes	Bristol Myers Squibb and AstraZeneca	The outcome measures listed will capture the most important health related benefits (and harms) of the technology	Comment noted. No amendment to the scope required.
	Cochrane Metabolic and Endocrine Disorders Review Group	*Question: "Will these outcome measures capture the most important health related benefits (and harms) of the technology?"* Apart from some surrogate outcomes, yes. Maybe, cancer should be included as an outcome as well.	The outcomes section of the scope includes adverse effects of treatment. Data for cancer may be included in submissions to NICE as part of this outcome.
	CSAS	Consider adding fasting plasma glucose (FPG) which was used as a secondary outcome in five of the phase III trials 'Dapadliflozin for type 2 diabetes mellitus – add on therapy'.	The outcomes section of the scope includes glycaemic control. Fasting plasma glucose is a component of glycaemic control, and such data may be included in a submission to NICE. No amendment to the scope is therefore required.
	Merck Sharp and Dohme	No comments.	No amendment to the scope required.

Section	Consultees	Comments	Action
	NHS Gloucestershire	Consider adding fasting plasma glucose (FPG) which was used as a secondary outcome in five of the phase III trials 'Dapadliflozin for type 2 diabetes mellitus – add on therapy'.	The outcomes section of the scope includes glycaemic control. Fasting plasma glucose is a component of glycaemic control, and such data may be included in a submission to NICE. No amendment to the scope is therefore required.
	RCGP and PCDS	*Question: "Will these outcome measures capture the most important health related benefits (and harms) of the technology?"* Yes.	Comment noted. No amendment to the scope required.
	Royal College of Nursing	*Question: "Will these outcome measures capture the most important health related benefits (and harms) of the technology?"* Yes.	Comment noted. No amendment to the scope required.
Economic analysis	Bristol Myers Squibb and AstraZeneca	Cost effectiveness will be expressed in terms of cost per quality-adjusted life year. The time horizon for modelling in diabetes needs to be sufficiently long to include diabetic complications and therefore a lifetime horizon (40 years) will be included in the base case. Shorter modelling time frames will also be included for information. Costs will be considered from an NHS and Personal Social Services perspective.	Comment noted. No amendment to the scope required.
	Cochrane Metabolic and Endocrine Disorders Review Group	None.	Comment noted. No amendment to the scope required.

Section	Consultees	Comments	Action
	CSAS	The time horizon is appropriate.	Comment noted. No amendment to the scope required.
	Merck Sharp and Dohme	No comments.	No amendment to the scope required.
	NHS Gloucestershire	The time horizon is appropriate.	Comment noted. No amendment to the scope required.
	RCGP and PCDS	No comment.	No amendment to the scope required.
	Royal College of Nursing	*Question: "Comments on aspects such as the appropriate time horizon."* Yes.	Comment noted. No amendment to the scope required.
Equality and Diversity	Bristol Myers Squibb and AstraZeneca	The NICE Clinical Guideline 87 (NICE, 2009) states that for patients of non-European descent (African, South Asian or Caribbean), the body mass index (BMI) threshold for treatment with GLP-1 agonists is adjusted downward, as they are at higher risk of developing type 2 diabetes. A similar adjustment is recommended for these ethnic groups in the NICE guidance for liraglutide (TA203) and exenatide prolonged release (TA248). A separate economic analysis for South Asian, African or Caribbean patients will not been presented in the submission. However, in view of their increased risk and consequent increased opportunity to gain benefit from treatment at lower BMIs, a lower BMI threshold should still apply.	Issues relating to BMI threshold for groups of non-European descent may be considered in an appraisal where recommendations are made relating to BMI. This information is important to include in any submission to NICE. No amendments to the scope required.
	Cochrane Metabolic and Endocrine Disorders Review Group	None.	No amendment to the scope required.

Section	Consultees	Comments	Action
	CSAS	There were no equality issues identified.	Comment noted. No amendment to the scope required.
	Merck Sharp and Dohme	No comments.	No amendment to the scope required.
	NHS Gloucestershire	There were no equality issues identified.	Comment noted. No amendment to the scope required.
	RCGP and PCDS	There are some differences in prevalence across populations, but poorer data concerning treatment differences. We are not aware that particular differences in efficacy, acceptability or usage would arise with this agent.	Comment noted. No amendment to the scope required.
	Royal College of Nursing	None.	No amendment to the scope required.
Other considerations	Boehringer Ingelheim / Eli Lilly	We suggest that subgroup analysis based on presence of co-morbid hypertension be performed given the importance of this risk factor on cardiovascular complications for this patient population.	Co-morbid hypertension is one of a number of risk factors for cardiovascular complications. Cardiovascular complications of diabetes are included in the outcomes section of the scope and these data could be included in a submission to NICE where considered relevant. No amendment to the scope required.
	Bristol Myers Squibb and AstraZeneca	Sub-groups considered in the clinical programme include: baseline HbA1c; ethnicity; race; body mass index; age and gender. While not formally considered a sub-group, those patients included in the trial programme for the add-on to insulin indication will have been diagnosed with Type 2 diabetes longer than patients from the add-on to metformin indication.	Comment noted. No amendment to the scope required.

Section	Consultees	Comments	Action
	Cochrane Metabolic and Endocrine Disorders Review Group	I think age and gender subgroups should be included as well (the latter especially with regard to urogential infection risk).	NICE would not normally make recommendations on the basis of age or gender. The social value judgements document provides specific guidance about the circumstances in which recommendations based on age and gender can be made. No amendment to the scope required.
	CSAS	No comments.	No amendment to the scope required.
	Merck Sharp and Dohme	No comments.	No amendment to the scope required.
	NHS Gloucestershire	No comments.	No amendment to the scope required.
	RCGP and PCDS	None.	No amendment to the scope required.
	Royal College of Nursing	None.	No amendment to the scope required.
Questions for consultation	Bristol Myers Squibb and AstraZeneca	*Questions:* *"Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?* *Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* *Please identify the nature of the data which you understand to be available to*	Comment noted. The Committee will consider the innovative nature of dapagliflozin during the course of the appraisal. No amendment to the scope required.

Section	Consultees	Comments	Action
	Bristol Myers Squibb and AstraZeneca (continued)	*enable the Appraisal Committee to take account of these benefits."* We consider dapagliflozin to be a highly innovative agent in the treatment of type 2 diabetes for the following reasons: • Dapagliflozin is a first-in-class agent. Unlike other therapies it actively removes glucose via the kidney. In contrast, other agents move glucose from the circulation to various compartments (muscle, fat etc,). The action of dapagliflozin is insulin independent, meaning it does not rely on underlying beta-cell function to exert its effect. In diabetes, beta-cell function wanes over time and therefore exogenous insulin (insulin injections) is/are eventually required. This means that dapagliflozin maintains its efficacy well beyond the initial 6 months investigated in the trials. Data at 2 years will be presented in this submission for 3 pivotal studies. • Dapagliflozin can be added to insulin and exerts a clinically meaningful insulin sparing effect while reducing HbA1c and weight. • Dapagliflozin is associated with weight loss, as a result of the calorie loss induced by glucuresis (glucose excretion). Other oral agents are often associated with weight gain (TZD or SU) or are weight neutral (DPP-4 inhibitors) Dapagliflozin is also associated with moderate blood pressure reductions. *Question: "Please answer any of the questions for consultation if not covered in the above sections. If appropriate, please include comments on the proposed process this appraisal will follow (please note any changes made to the process are likely to result in changes to the planned time lines)."* • The most appropriate comparators for dapagliflozin for the treatment of Type 2 diabetes have been included in the scope although the list of potential comparators is greater than the evidence base for dapagliflozin at this time (see comments above).	Comment noted. Comments received on the consultation suggested that the use of short acting insulin secretagogues and acarbose

Section	Consultees	Comments	Action
	Bristol Myers Squibb and AstraZeneca (continued)	• Dapagliflozin is not considered a relevant comparator to the rapid-acting insulin secretagogues given the specific recommendations for these therapies made in CG87 – these agents are recommended for patients with erratic lifestyles. Given their mechanism of action and the need to take them 2-4 times a day, prior to a meal, they are not widely used in the UK. • Dapagliflozin is not considered a relevant comparator to acarbose given the specific recommendation for this therapy made in CG87 – acarbose is only recommended by NICE for persons unable to use other agents. Due mainly to its side effect profile, acarbose is not widely used in the UK.	is limited to specific subgroups of patients. Therefore no amendments to the scope have been made.
	Cochrane Metabolic and Endocrine Disorders Review Group	*Questions: "Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?* *Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* *Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits."* Repaglinide and nateglinide would be relevant comparators (see above). Subgroups (see above). Innovative potential is limited. No separate technology appraisal necessary. *Question: "Please answer any of the questions for consultation if not covered in the above sections. If appropriate, please include comments on the proposed process this appraisal will follow (please note any changes made to the process are likely to result in changes to the planned time lines)."* None.	Comment noted. Comments received on the consultation suggested that the use of short acting insulin secretagogues and acarbose is limited to specific subgroups of patients. Therefore no changes to the scope have been made made.

Section	Consultees	Comments	Action
	CSAS	Dapagliflozin has a novel therapeutic target and may have a differing adverse event profile to existing treatments. Higher rates of breast and bladder cancer have been seen in some of the phase III trials. Some publications also suggest that urinary tract and genital infections may be more common with dapagliflozin.	Comment noted. As part of its deliberations on clinical and cost effectiveness, the Committee may consider adverse event data where these are considered relevant. Adverse events of treatment are included as an outcome in the scope. No amendment to the scope required.
	Merck Sharp and Dohme	*Question: "Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?"* The benefit of dapagliflozin on the underlying components of diabetes (insulin resistance, beta cell function and hepatic glucose output) is unknown. Therefore we do not believe that dapagliflozin can be considered as innovative. *Question: "Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?"* No comments *Question: "Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits."* No comments *Question: "Please answer any of the questions for consultation if not covered in*	Comment noted. The Committee will consider the innovative aspect of dapagliflozin during the course of the appraisal. No amendment to the scope required.

Section	Consultees	Comments	Action
	Merck Sharp and Dohme (continued)	*the above sections. If appropriate, please include comments on the proposed process this appraisal will follow (please note any changes made to the process are likely to result in changes to the planned time lines).”* • In response to the consultation question: "Are there other relevant comparators not currently in the scope that should be added? In particular, are rapid-acting insulin secretagogues and acarbose relevant comparators? Please note that sitagliptin is also licensed as triple oral therapy in combination with a PPARγ agonist and metformin when use of a PPARγ agonist is appropriate and when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control. However use of sitagliptin in this indication is very low compared to its use in its other licensed indications. • In response to the consultation question: "Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately? We suggest it is also important for NICE to consider any subgroups of people in whom the technology may be less clinically and cost effective. Based on the clinical data for dapagliflozin and its mode of action, it is likely that this drug will be less effective in patients with renal insufficiency. As the product licence for dapagliflozin has not yet been granted, it is unclear whether the licence will include restrictions on the use of dapagliflozin in patients with renal insufficiency. Nevertheless we feel it appropriate to raise this point at this time for NICE's consideration.	The scope has been amended to reflect this comparator. Comments noted. At the scoping workshop, the manufacturer indicated that dapagliflozin would not be licensed for use in people who had renal failure and that these people were not included in the clinical trials. It is therefore not considered an equality issue and needs not be reflected in the scope.

Section	Consultees	Comments	Action
	NHS Gloucestershire	Dapagliflozin has a novel therapeutic target and may have a differing adverse event profile to existing treatments. Higher rates of breast and bladder cancer have been seen in some of the phase III trials. Some publications also suggest that urinary tract and genital infections may be more common with dapagliflozin.	Comment noted. As part of its deliberations on clinical and cost effectiveness, the Committee may consider adverse event data where this is considered relevant. Adverse events of treatment are included as an outcome in the scope. No amendment to the scope required.
	RCGP and PCDS	• None of the existing treatments are entirely adequate and there is clearly the requirement for further improvements in the efficacy, durability and acceptability of Type 2 Diabetes treatments. Thus this agent may have the potential to be a valuable addition to current options, if its efficacy, tolerability and safety profile can be satisfactorily demonstrated. • We are happy with the draft scope. All relevant comparators appear to have been included. The use of short acting insulin secretagogues is small-scale, as is that of acarbose, and their exclusion is not a significant omission. The issue of a separate appraisal as 'add-on' to insulin is one which we would regard as one of practicality, for NICE to decide.	Comment noted. No amendment to the scope required.
	Novo Nordisk	We note that dapagliflozin will be appraised as a Single Technology Appraisal (STA) however NICE are also in the process of reviewing the Type 2 Clinical Guidelines (CG87). As this is likely to include a review of all of the available treatments we would recommend the review of dapagliflozin is incorporated within the NICE Clinical Guidelines rather than as a separate STA.	Comment noted. To provide timely guidance to the NHS, dapagliflozin has been referred to the Institute as a Single Technology Appraisal.

Section	Consultees	Comments	Action
	Royal College of Nursing	The technology being reviewed is different to any other treatment option currently available as it influences a different pathway in managing diabetes control potentially, it could have positive benefits on weight management for patients with type 2 diabetes which many other oral options do not offer.	Comment noted. The Committee will consider the innovative aspect of dapagliflozin during the course of the appraisal. No amendment to the scope required.
Additional comments on the draft scope.	ABCD and RCP	The ABCD/RCP are grateful for the opportunity to comment on the draft scope. Our experts are happy with the draft scope.	
	Cochrane Metabolic and Endocrine Disorders Review Group	None.	No amendment to the scope required.
	RCGP and PCDS	None.	No amendment to the scope required.
	Royal College of Physicians	The RCP is grateful for the opportunity to comment on the draft scope. We have liaised with the Association of British Clinical Diabetologists who we believe have responded separately and are happy with the scope. We support their comments in this respect.	Comment noted. No amendment to the scope required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health
Healthcare Improvement Scotland
Novartis Pharmaceuticals UK