National Institute for Health and Care Excellence

Single Technology Appraisal (STA/MTA)

Dapagliflozin in triple therapy regimens for treating type 2 diabetes [ID962]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Astrazeneca	Yes. This topic is appropriate for a NICE appraisal. Background: • Dapagliflozin is an oral anti-diabetic agent; and was the first in the SGLT2 inhibitor class to launch in the UK in November 2012. It is licensed for use in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as monotherapy, add onto metformin, as part of a triple regimen; and as add onto insulin. • The key trial for dapagliflozin use in a triple regimen was not available at the time of the initial NICE assessment. In the absence of this evidence, dapagliflozin gained a NICE recommendation (TA288) for add onto metformin; and add onto insulin use in July 2013. • Dapagliflozin triple data was then incorporated into the licence in December 2013. UK Real World Evidence (RWE) UK RWE demonstrates that dapagliflozin is already being used in triple regimens (representing approximately one third of dapagliflozin use). This indicates a clinical need for NICE guidance regarding dapagliflozin in triple therapy.	Thank you for your comments.

Section	Consultee/ Commentator	Comments [sic]	Action
	Association of British Clinical Diabetologists (endorsed by Royal College of Physicians)	Yes, ABCD is very supportive of this believes that it will help clinicians to make appropriate choices about prescribing about SGLT-2 inhibitors.	Thank you for your comments.
	Diabetes UK	YES	Thank you for your comments.
	Janssen	No Comment	Thanks for your response
Wording	Astrazeneca	We recommend that the remit and appraisal objective are combined as follows to clarify that this assessment is for a single indication only: ***Remit/appraisal objective:*** *To appraise the clinical and cost effectiveness of dapagliflozin triple therapy (dapagliflozin in combination with two other oral anti-diabetic agents) for treating type 2 diabetes.* *This appraisal is a part-review of NICE technology appraisal (TA) 288, dapagliflozin combination treatment. It will only consider recommendation 1.3 in TA288, dapagliflozin triple therapy. The other recommendations in TA288 remain extant.*	Thank you for your comments. The remit and appraisal objective were separated to clarify that the scope will only consider dapagliflozin in triple therapy combination regimens.
	Association of British Clinical Diabetologists (endorsed by Royal College of Physicians)	Yes it does in the broader sense. ABCD does not have any alternatives to add.	Thank you for your comments.

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	Diabetes UK	YES	Thank you for your comments.
	Janssen	No Comment	Thanks for your response
Timing Issues	Astrazeneca	We are conscious of the very high workload currently facing NICE; and would like to offer our support to NICE to explore options for a pragmatic and efficient approach for this assessment, which may release some capacity. Rationale: • This is not a full and complex STA, the assessment is for a single indication only • We expect the assessment to be straightforward given that the other SGLT2 inhibitors (at exactly the same price as dapagliflozin and with similar efficacy and safety as mentioned in previous NICE TAGs) have already been approved by NICE for triple use • Specifically, the evidence considered in the Empagliflozin TA showed that the clinical effectiveness of the SGLT2s is similar (FAD, January 2015) • Committee A with considerable diabetes experience, including the prior SGLT2 inhibitor appraisals, is scheduled to conduct this assessment presenting a strong rationale to consider a more pragmatic and efficient approach. We could accommodate an earlier submission slot if this would support this approach.	Thank you for your comments. Although this is a part review it still requires being conducted through our STA process and therefore submission slot cannot be changed
	Association of British Clinical Diabetologists (endorsed by Royal College of Physicians)	ABCD believes that, this is fairly urgent- as NICE guidance about Type 2 Diabetes treatment is already out.	Thank you for your comments.
	Diabetes UK	This is urgent as it would give more clinicians and patients the confidence to	Thank you for your

Section	Consultee/ Commentator	Comments [sic]	Action
		routinely consider this as another option for triple therapy	comments.
	Janssen	No Comment	Thanks for your response
Additional comments on the draft remit	Association of British Clinical Diabetologists (endorsed by Royal College of Physicians)	ABCD is Supportive of this. What about other Gliflozines.	Thank you for your comments.
	Janssen	No Comment	Thanks for your response

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Astrazeneca	The final sentence should be changed to the below to accurately represent the existing TA288 guidance: *TA288 recommended that dapagliflozin should not be used for triple therapy except as part of a clinical trial; this recommendation will be the subject of this appraisal (because there is new evidence now available about this recommendation).*	Thank you for your comments. This section has now been updated.
	Association of British Clinical Diabetologists (endorsed by Royal College of	We believe this is accurate and comprehensive.	Thank you for your comments.

Section	Consultee/ Commentator	Comments [sic]	Action
	Physicians)		
	Diabetes UK	The background information is accurate and references to other guidelines and TAs are useful	Thank you for your comments.
	Janssen	No Comment	Thanks for your response
The technology/ intervention	Astrazeneca	Yes. The description is accurate.	Thank you for your comments.
	Association of British Clinical Diabetologists (endorsed by Royal College of Physicians)	Yes	Thank you for your comments.
	Diabetes UK	YES	Thank you for your comments.
	Janssen	No Comment	Thanks for your response
Population	Astrazeneca	Yes. The population is defined appropriately. A potential sub-group of the population inadequately controlled on dual therapy with metformin with a DPP4-inhibitor is the following: • Patients who are inadequately controlled after all appropriate oral options (i.e. Met, SU, TZD & DPP4s) have been trialled; and who require an additional oral option before injectables.	Thank you for your comments. Possible subgroups may be considered as part of the full appraisal.

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		However, it should be noted that the evidence base is very limited for patients inadequately controlled on dual therapy with metformin with a DPP4-inhibitor, as described below (comparators section).	
	Association of British Clinical Diabetologists (endorsed by Royal College of Physicians)	Yes, and No	Thank you for your comments.
	Diabetes UK	People with higher HbA1c (69 to 86mmol/mol)	Thank you for your comments. Possible subgroups may be considered as part of the full appraisal.
	Janssen	No Comment	Thanks for your response
Comparators	Astrazeneca	For the combination dapagliflozin, metformin and a sulfonylurea, we propose a comparison only against the other SGLT2 inhibitors and DPP4s in line with the approach taken within the recent empagliflozin STA appraisal. We agree with the exclusion of the following comparators for the reasons below (as per the empagliflozin manufacturer submission): • Pioglitazone: TZDs are currently used very rarely and their use is currently falling • Insulin is considered irrelevant: as an injectable it is considered at a different point in the treatment pathway For the combination dapagliflozin, metformin and a DPP4, we have conducted a systematic review, which has identified only four relevant RCTs; and shows that a robust NMA/indirect comparison is not feasible against any of the proposed	Thank you for your comments. For the purposes of the scope it is appropriate for the comparator section to remain broad and inclusive. The company for dapagliflozin will consider the availability of evidence as part of the full appraisal.

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		comparators in this draft scope. There is unmet need for an additional oral option before injectables (after MET, DPP4 & other appropriate OADs including SUs and pioglitazone have failed). Dapagliflozin is the only SGLT2 inhibitor with RCT evidence in combination with MET + DPP4. We therefore welcome discussions with NICE concerning any pragmatic options to assess dapagliflozin for such patients in the absence of a robust NMA.	
	Association of British Clinical Diabetologists (endorsed by Royal College of Physicians)	Yes, these are. But see comments below as well	Thank you for your comments.
	Diabetes UK	YES	Thank you for your comments.
	Janssen	In line with the recently published NICE guidelines NG28, Janssen believes that GLP-1 agonists should also be considered as a comparator in triple therapy, as part of this technology appraisal.	Thank you for your comments. For consistency with previous scopes considering SGLT2 inhibitor combination treatment for type 2 diabetes, GLP-1 agonists have been added to the comparator section of the scope.
Outcomes	Astrazeneca	Dapagliflozin provides the clinical benefits of weight loss and blood pressure reduction in addition to HbA1C lowering.	Thank you for your

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		Change from baseline in total body weight; and change from baseline in SBP should therefore be added to the outcomes listed.	comments. The outcomes section is intended to provide a broad overview of possible outcomes to be considered. More detailed specific outcomes may be considered by the company for dapagliflozin as part of the full appraisal.
	Association of British Clinical Diabetologists (endorsed by Royal College of Physicians)	Yes	Thank you for your comments.
	Diabetes UK	YES	Thank you for your comments.
	Janssen	No Comment	Thanks for your response
Economic analysis	Astrazeneca	The time horizon planned is 40 years as used within most type 2 diabetes economic analyses including those within the recent canagliflozin STA; dapagliflozin STA and SGLT2 inhibitors as monotherapy MTA.	Thank you for your comments.
	Association of British Clinical	Yes	Thank you for your comments.

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	Diabetologists (endorsed by Royal College of Physicians)		
	Diabetes UK	N/A	Thank you for your comments.
	Janssen	No Comment	Thanks for your response
Equality and Diversity	Astrazeneca	AstraZeneca has no comments.	Thanks for your response
	Association of British Clinical Diabetologists (endorsed by Royal College of Physicians)	No comments	Thank you for your comments.
	Diabetes UK	Not aware of any	Thank you for your comments.
	Janssen	No Comment	Thanks for your response
Other considerations	Astrazeneca	AstraZeneca has no comments.	Thanks for your response
	Association of	None	Thanks for your

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	British Clinical Diabetologists (endorsed by Royal College of Physicians)		response
	Diabetes UK	In view of the current EMA report, there is a need to consider the issues around DKA risks	Thank you for your comments. Adverse events will be considered in more detail as part of the full appraisal.
	Janssen	No Comment	Thanks for your response
Innovation	Astrazeneca	Dapagliflozin is an oral anti-diabetic agent; and was the first in the SGLT2 inhibitor class to launch in the UK in November 2012. Two further SGLT2 inhibitors have launched in the UK since this time (canagliflozin and empagliflozin). The SGLT2 inhibitor class has provided an alternative oral treatment option for adults with type 2 diabetes class. The SGLT2 inhibitor class has a mechanism of action, which acts independently of insulin to remove excess glucose and its associated calories in the urine. The SGLT2 inhibitors deliver meaningful reductions in glucose with the additional secondary benefits of weight loss and blood pressure lowering.	Thank you for your comments. Innovation will be considered in more detail as part of the full appraisal.
	Association of British Clinical Diabetologists (endorsed by	No,	Thank you for your comments. Innovation will be considered in more detail as part of

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	Royal College of Physicians)		the full appraisal.
	Diabetes UK	NO Our understanding is that, in practice, depagliflozin is already used in triple therapy regimens just like the other SGLT-2 inhibitors Not if the QALY calculation takes all of the outcomes and the impact of potential weight loss into account	Thank you for your comments. Innovation will be considered in more detail as part of the full appraisal.
	Janssen	No Comment	Thanks for your response
Questions for consultation	Astrazeneca	*Should GLP-1 analogues be included as a comparator?* For the combination dapagliflozin, metformin and a sulfonylurea, we do not think that GLP1 analogues are an appropriate comparator in line with the approach taken within the recent empagliflozin STA manufacturer submission. Rationale: GLP1s are considered irrelevant: as an injectable they are considered at a different point in the treatment pathway For the combination dapagliflozin, metformin and a DPP4, we have conducted a systematic review, which has identified only four relevant RCTs; and shows that a robust NMA/indirect comparison is not feasible against GLP1 analogues. *Where do you consider dapagliflozin in triple therapy regimens will fit into the existing NICE pathway, diabetes?* We see dapagliflozin; and the other SGLT2 inhibitors fitting into the NICE pathway under the second intensification with metformin combination therapy section. The bold text below should be added to bring the NICE pathway in line with the NICE	For consistency with previous scopes considering SGLT2 inhibitor combination treatment for type 2 diabetes, GLP-1 agonists have been added to the scope. Thank you for your comments.

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		guideline (NG28)*:*
		In adults with type 2 diabetes, if dual therapy with metformin and another oral drug (see first intensification with metformin combination therapy in this pathway) has not continued to control HbA1c to below the person's individually agreed threshold for intensification, consider either:
		• *triple therapy with:*
		  • *metformin, a DPP-4 inhibitor and a sulfonylurea or*
		  • *metformin, pioglitazone and a sulfonylurea or*
		  • ***metformin, pioglitazone or an SU, and an SGLT2i***
		• *starting insulin-based treatment (see insulin-based treatments in this pathway)*	

	Association of British Clinical Diabetologists (endorsed by Royal College of Physicians)	Have all relevant comparators for dapagliflozin in triple therapy regimens been included in the scope? ***Yes*** · Which treatments are considered to be established clinical practice in the NHS for type 2 diabetes? **All stated in NICE T"2guidance** · Should GLP 1 analogues be included as a comparator? **Yes** · Is it appropriate to compare adding dapagliflozin to dual therapy with a switch to insulin? **Unlikely in clinical practice** · Is pioglitazone (in combination with metformin and a DPP-4 inhibitor) routinely used in clinical practice in the NHS? **It may be more used now following NICE T2 guidance** Are the outcomes listed appropriate?	Thank you for your comments. For consistency with previous scopes considering SGLT2 inhibitor combination treatment for type 2 diabetes GLP-1 agonists have been added as comparators to the scope.

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		Yes Are there any subgroups of people in whom dapagliflozin is expected to be more clinically effective and cost effective or other groups that should be examined separately? **Those with liver disease where explicit licensed role?** **Those with Obesity?** **Quadruple therapy?** Where do you consider dapagliflozin in triple therapy regimens will fit into the existing NICE pathway, diabetes? As with other SGLT2 Is - SU-metf-Pio (dula from these options) + add on dapa	Possible subgroups may be considered as part of the full appraisal
	Diabetes UK	• GLP-1 could possibly be used as a comparator • Using insulin as a comparator is less appropriate • The use of pioglitazone (with metformin and DPP-4 inhibitor is not routine practice, and numbers are varied across the country. It could be a useful option for specific patient groups.	Thank you for your comments. For consistency with previous scopes considering SGLT2 inhibitor combination treatment for type 2 diabetes, GLP-1 agonists have been added to the scope.
	Janssen	No Comment	Thanks for your response

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft scope	Astrazeneca	As described above regarding timing, we are conscious of the very high workload currently facing NICE; and would like to offer our support to NICE to explore options for a pragmatic and efficient approach for this assessment of a single indication only, which may release some capacity. We could accommodate an earlier submission slot if this would support this approach.	Thank you for your comments. Although this is a part review it still requires being conducted through our STA process and therefore submission slot cannot be changed.
	Association of British Clinical Diabetologists (endorsed by Royal College of Physicians)	None	Thanks for your response
	Janssen	N/A	Thanks for your response

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

Department of Health

Novo Nordisk