Comments on Appraisal Consultation Document

Dapagliflozin in combination therapy for the treatment of type 2 diabetes [ID427]

Dear consultees and commentators

You are invited to comment on the attached appraisal consultation document (ACD) for the above appraisal.

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

Equality Issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:

- could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;
- could have any adverse impact on people with a particular disability or disabilities.

Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.

Order number *(For internal use only)*	**Section Number** Indicate **number** or **'general'** if your comment relates to the whole document	**Page Number** Indicate **number** or **'general'** if your comment relates to the whole document	**Comments** **Please insert each new comment in a new row.** **Please do not paste other tables into this table, as your comments could get lost – type directly into this table.**
Example	3.4.6	45	Our comments are as follows ……
1.	1.2	3	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.
2.	3.8	10	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.
3.	3.25	19	*"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.
4.	3.25	19	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.
5.	3.26	20	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.
6.	3.33	23	It would make sense to use the data from the longest time period possible to reflect the long term effectiveness of the treatment.
7.	4.9	37	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
8.	4.9	38	Did the Committee want a rationale or explanation for variation between the code used in the analysis and the Technical Support Document?
9.	4.10	38	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.
10.	4.14	41	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).
11.	4.16	42	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.
12.	4.17	43	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.
13.	4.21	45	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.
14.	4.26	48	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.
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