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**Janssen's Response to the Appraisal Consultation Document**

**Type 2 Diabetes Mellitus (T2DM) - empagliflozin (combination therapy)**

Please find below Janssen's response to the revised Appraisal Consultation Document (ACD) for empagliflozin issued in August 2014. We are pleased to have had the opportunity to provide our comments in relation to the interpretation of the cost-effectiveness evidence within the ACD.

Our detailed response to the ACD is split into four sections. In section 1 we highlight our response with respect to the evidence base used in this appraisal. Commentary is focused on the data used by the manufacturer to inform the indirect comparisons between empagliflozin and other anti-diabetic therapies. In section 2 and 3 we summarise Janssen's position regarding the current ACD recommendation. Lastly, in section 4 we remark on a few typographical errors within the ACD.

## Section 1: Has all of the relevant evidence been taken into account?

### *1.1 The Indirect comparison presented by the manufacturer does not utilise all the appropriate data (Section 3.12, 3.18 and 4.2 of the ACD)*

The company's submission considered DPP-4 inhibitors and other SGLT-2 inhibitors (dapagliflozin and canagliflozin) to be the comparators for empagliflozin. Clinical opinion suggests that there may be a place for empagliflozin as part of dual therapy as well as triple therapy. In the UK, the current NICE guidelines explicitly state: "Consider adding exenatide to metformin and a sulfonylurea if:

• BMI ≥35 kg/m$^2$ in people of European descent and there are problems associated with high weight, or

• BMI <35 kg/m$^2$ and insulin is unacceptable because of occupational implications or weight loss would benefit other comorbidities." [*ref. NICE QRG*]

Currently, there GLP-1 agonist are used in specific patient groups, namely patients who would benefit from weight loss. These patients could benefit from an SGLT2 inhibitor in place of a GLP-1 agonist. Therefore, Janssen suggests that GLP-1 agonists should be considered as an appropriate comparator as part of this submission for patients currently on a background therapy of metformin + SU/TZD or insulin ± SoC.

As a result of the above, Janssen believes that several key studies may have been omitted from this indirect comparison network and submission overall due to the omission of other potentially relevant comparators. In building a robust evidence network for an indirect comparison, studies should have been included that were not considered in the eventual

economic comparison, such as the GLP-1 studies, as they add to the weight of evidence within the network and increase the robustness of any conclusions drawn from the indirect comparisons.

**As per the concerns already raised within Sections 3.39 to 3.41 of the ACD, Janssen believes that a number of assumptions made in the manufacturer's submission, including major errors in the model structure largely invalidate the economic analysis of the submission; potentially leading to a significant overestimation in cost-effectiveness of empagliflozin relative to other anti-diabetic therapies. Janssen requests that the limitations of the flawed indirect comparisons as well as economic modelling approach undertaken by the manufacturer be taken into consideration in the FAD and that the caution warranted interpretation of the ACD should emphasise much more clearly the limitations of the approach taken and the potential biases in favour of empagliflozin.**

### *1.2 The assumptions made by the manufacturer about weight change in the economic analysis are subject to significant uncertainty (Section 3.31 of the ACD)*

Within the ACD, change in body weight from baseline is considered as an important secondary outcome, remarking that empagliflozin was more likely to result in reductions in body weight and blood pressure when compared with DPP-4 inhibitors in both dual and triple therapy. However, within the economic modelling of weight changes, when considering the QALY adjustment related to weight changes, the submission assumes that weight loss did not have an impact on utilities while weight gain would result in a decrease of utility. The ERG suggests that this might be a rather conservative assumption, which disadvantages the SGLT2 inhibitor class. Janssen agrees that there is a value associated with weight loss as well as weight gain but, in order to compare fairly across all previously submitted technology appraisals for the SGLT2 inhibitor class, Janssen believes that base case simulations should follow these modelling assumptions. We propose that the guidance should consider recognising that a higher utility used in the manufacturer's submission (-0.0159) may considerably overestimate the impact of weight gain achieved with empagliflozin and biases against comparators such as DPP-4 inhibitors and SU. We suggest that base case simulations should use the disutility for weight gain determined by Bagust and Beale (2005). This study reports a disutility per increased unit of BMI (-0.0061), a figure used in the economic modelling of the two prior SGLT-2 STAs, canagliflozin (TA315) and dapagliflozin (TA288). Therefore, Janssen suggests that a re-analysis should consider inclusion of such a parameter.

## Section 2: Are the summaries for clinical and cost-effectiveness reasonable interpretations of the evidence?

### *2.1 Janssen believes the conclusion drawn that clinical-effectiveness between SGLT-2 inhibitors is equal, is unsupported by the data presented within the submission. (Section 3.15, 3.21 and 4.4 of the ACD)*

In Section 3.15 of the ACD it summarises that the revised results of the NMA submitted by the manufacturer demonstrate comparable clinical effectiveness of dapagliflozin, canagliflozin and empagliflozin in dual therapy. Also, it states: "when empagliflozin (either dose) was compared with canagliflozin 300 mg as triple therapy (on background metformin and a sulfonylurea) or when empagliflozin 10 mg was compared with canagliflozin 300 mg as an add-on to insulin therapy, empagliflozin was statistically inferior to canagliflozin in terms of lowering HbA1c."

Seemingly unsupported by these results in Section 4.4 of the ACD it has been concluded that canagliflozin, dapagliflozin and empagliflozin have similar clinical effectiveness across all treatment lines. Specifically, in section 4.4 of the ACD it states: "*The Committee discussed the network meta-analyses which reported the relative effectiveness of empagliflozin with the relevant comparators in the absence of head-to-head trials. The Committee noted the results of the network meta-analyses, which suggested that empagliflozin could be considered to have similar clinical effectiveness to canagliflozin, dapagliflozin and sitagliptin when used:*

- *in dual therapy plus metformin or a thiazolidinedione*
- *in triple therapy plus metformin and a sulfonylurea*
- *in triple therapy plus metformin and a thiazolidinedione*
- *as an add-on treatment to insulin.*"

Janssen believes there to be two inaccuracies within this conclusion. As suggested above, it is inappropriate to generalise comparable efficacy for SGLT2 inhibitors across all treatment lines based on the network meta-analysis presented in this submission. In addition, there is no direct head-to-head or indirect clinical evidence available to compare the efficacy of canagliflozin in combination with thiazolidinedione at dual therapy. Therefore, we propose the conclusion adequately reflect the differences in clinical evidence available for each product and only draws comparisons where clinical evidence is available.

Mindful of this, Janssen would like to suggest the following changes to the ACD. In section 3.15 of the ACD it states: "*Results from the indirect comparison showed that empagliflozin*

*was generally comparable to the other SGLT-2 inhibitors. However, the exception was when empagliflozin (either dose) was compared with canagliflozin 300 mg as triple therapy (on background metformin and a sulfonylurea) or when empagliflozin 10 mg was compared with canagliflozin 300 mg as an add-on to insulin therapy. In these comparisons, empagliflozin was statistically inferior to canagliflozin in terms of lowering HbA1c*."

Janssen proposes the following change to be made to section 3.15: "*Results from the indirect comparison showed that empagliflozin was generally comparable to the other SGLT-2 inhibitors in dual therapy. When empagliflozin (either dose) was compared with canagliflozin 300 mg as triple therapy (on background metformin and a sulfonylurea) or when empagliflozin 10 mg was compared with canagliflozin 300 mg as an add-on to insulin therapy, empagliflozin was statistically inferior to canagliflozin in terms of lowering HbA1c*."

In section 3.21 it states "*The ERG had access to an independent, academic, unpublished network meta-analysis comparing the clinical effectiveness of dapagliflozin, canagliflozin and empagliflozin in dual therapy, which found no clinically significant differences between empagliflozin and canagliflozin. After validating some of the company's revised results at the clarification stage, the ERG largely agreed with the company's conclusion that empagliflozin's clinical effectiveness is comparable to that of canagliflozin, dapagliflozin and sitagliptin.*"

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## Section 3: Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

No further comments.

## Section 4: Point to note

Janssen believes that there is a typographical mistake within the ACD (see Section 2.5). It states that the annual cost of empagliflozin is estimated to be £470.30. Given that the price of empagliflozin (excluding VAT) is £36.59 per pack of 28 tablets for both 10 mg and 25 mg doses. Janssen calculates the annual cost of empagliflozin to be £477.30 per annum, similar to the annual cost of canagliflozin 100 mg, at £477.26.

Janssen believes that there is a second typographical mistake within the ACD (see Section 4.3) in reference to the quotes form the clinical expert regarding the clinical experience of SGLT-2 inhibitors in the UK. It reads: "The Committee also heard from the clinical specialists about their anecdotal experience of empagliflozin for treating type 2 diabetes in the trials." Janssen had noted that this clinical experience was in reference to experience using dapagliflozin not empagliflozin.