# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Health Technology Appraisal

## Empagliflozin 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.

**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.

## Comments received from consultees

| Consultee | Comment | Response |
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| Boehringer Ingelheim (manufacturer) | The company submitted 2 Word documents in response to consultation which are not reproduced here. Please see the Committee papers for these documents. | Thank you for your response to consultation. The Committee considered the new evidence submitted by the company in response to the ACD. The Committee concluded that the very small differences in costs and QALYs between empagliflozin (10 mg and 25 mg) and its key comparators showed that empagliflozin was a cost-effective use of NHS resources as dual therapy in combination with metformin, triple therapy in combination with metformin and either a sulfonylurea or a thiazolidinedione, and as an add-on treatment to insulin. |
| Royal College of Physicians | We feel this is a reasonable and expected outcome. | Comment noted. |

A “no comment” response was received from the Department of Health, the Royal College of Nursing and the Royal College of Pathologists.

## Comments received from clinical specialists and patient experts

| Nominating organisation | Comment | Response |
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| Association of British Clinical Diabetologists (ABCD) and the Royal College of Physicians (RCP) | There is one section that is either mistaken or confused that I have attached amended below.<br><br>Page 24 4.2 line 8 '…heard from clinical specialists that there may be a small group of people for whom metformin is unsuitable because of intolerance or undesirable effects like weight gain ' is incorrect. Metformin does not cause weight gain (in fact weight loss)<br><br>It should state ' heard from clinical specialists that there may be a small group of people for whom metformin is unsuitable because of gastro-intestinal intolerance.'<br><br>I think the adjudication is fair and I have no additional comment. | Comment noted. Section 4.2 of the FAD has been amended accordingly. |

## Comments received from commentators

| Commentator | Comment | Response |
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| AstraZeneca | Thank you for the opportunity to comment on the above Appraisal Consultation Document (ACD). Our comments are provided below in response to the specific consultation questions.<br><br>**Has all of the relevant evidence been taken into account?**<br>Whilst we agree that all the clinical trial evidence for empagliflozin has been taken into account, we also agree with the ERG's and Appraisal Committees concerns regarding the network meta-analyses and economic model submitted by the company and the need for further information.<br><br>**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**<br>Whilst the current summaries reflect the evidence presented we anticipate that following consideration of the requested validated economic model, the corrected network meta-analyses and the requested sensitivity analyses these will be subject to change.<br><br>**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**<br>Not applicable.<br><br>We have assumed that with new information being submitted a further Appraisal Consultation Document will be issued and we welcome the opportunity to comment on any provisional recommendations issued following the next meeting of the Appraisal Committee. | Comments noted. |

| Commentator | Comment | Response |
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| Janssen | **Section 1: Has all of the relevant evidence been taken into account?**<br>***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)***<br>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:<br>• BMI ≥35 kg/m2 in people of European descent and there are problems associated with high weight, or<br>• BMI <35 kg/m2 and insulin is unacceptable because of occupational implications or weight loss would benefit other comorbidities." [ref. NICE QRG]<br><br>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.<br><br>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.<br><br>**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.** | Thank you for your comment. The Committee was persuaded by the company and the ERG that the GLP-1s are considered at a different point in the treatment pathway and are currently only recommended in specific populations, and so were not considered as comparators (see section 4.2 of the FAD).<br>The limitations of the original network meta-analyses and original health economic model are presented in the FAD. The company has provided a new cost-effectiveness model as part of their response to the ACD. The Committee considered the new evidence submitted by the company in response to the ACD. The Committee concluded that the very small differences in costs and QALYs between empagliflozin (10 mg and 25 mg) and its key comparators showed that empagliflozin was a cost-effective use of NHS resources as dual therapy in combination with metformin, triple therapy in combination with metformin and either a sulfonylurea or a thiazolidinedione, and as an add-on treatment to insulin. |

| Commentator | Comment | Response |
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| | ***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)***<br><br>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. | Thank you for your comment. The disutility for weight gain determined by Bagust and Beale (2005) has been used in the sensitivity analyses of the new cost-effectiveness modelling done by the ERG (see FAD section 3.37). |
| | **Section 2: Are the summaries for clinical and cost-effectiveness reasonable interpretations of the evidence?**<br><br>***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)***<br><br>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." | Thank you for your comment. A new network meta-analysis was provided by the company in response to consultation on the ACD. The results of the company's original network meta-analyses have been replaced with these new network meta-analyses which are presented in tables 2 to 4 of the FAD. |

| Commentator | Comment | Response |
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| | 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:*<br>• *in dual therapy plus metformin or a thiazolidinedione*<br>• *in triple therapy plus metformin and a sulfonylurea*<br>• *in triple therapy plus metformin and a thiazolidinedione*<br>• *as an add-on treatment to insulin."*<br><br>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.<br><br>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."*<br><br>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 <u>in dual therapy. When</u> 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<u>, empagliflozin</u> was statistically inferior to canagliflozin in terms of lowering HbA1c."* | |

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| | 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."*<br><br>Janssen proposes the following change to be made to section 3.21: *"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 <u>in dual therapy</u>."* | |
| | **Section 3: Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**<br><br>No further comments. | Comment noted. |
| | **Section 4: Point to note**<br>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.<br><br>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. | Comment noted. The FAD has been amended accordingly.<br><br>The wording of the FAD has been amended to state '…their anecdotal experience of SGLT-2 inhibitors for treating type 2 diabetes…'. |

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| MSD | **Comments by section number of the ACD**<br><br>**Section 2.5 – the expected annual cost of empagliflozin 10mg and 25mg**<br>The expected annual cost of empagliflozin 10mg and 25mg of £470.30 reported in the ACD appear to be incorrectly calculated, given the cost per 28-tablet pack is £36.59. The annual expected cost of empagliflozin 10mg and 25mg is £476.98 (assuming that there are 365 days per year). | Comment noted. The annual cost has been amended to £477.30, as per the company's submission. |
| | **Section 3.12 to 3.15 – General comment on the manufacturer's network meta-analysis**<br><br>Sections 3.12 to 3.15 describe and present the results from the manufacturer's network meta-analyses and include interpretations of the results. The results from the network meta-analysis should be presented with mean differences with associated 95% credible intervals between all interventions – this has not been done in section 3.15 of the ACD. Statements using "generally comparable", "more likely to result in reductions in body weight and blood pressure" and "showed better reduction in HbA1c levels" are subjective and meaningless. Please present the data using mean differences with associated 95% credible intervals for every drug and dose included in each network meta-analysis for each endpoint in each indication. | Comment noted. The results of the company's original network meta-analyses have been replaced with the company's new network meta-analyses which are presented in tables 2 to 4 of the FAD. |
| | **Section 3.15 – network meta-analysis for urinary tract and genital infections**<br><br>In section 3.15 there is a statement "The incidence of urinary tract and genital tract infections was comparable between empagliflozin and other treatments." Using indirect evidence to compare the incidence of adverse events of treatments is subjective. In the manufacturers submission, page 177, the lack of evidence to infer differences between some comparisons (e.g. between drugs within the same SGLT2 class), and the extremely wide 95% credible intervals indicates there is a great deal of uncertainty in comparing adverse events, and in particular the incidence of urinary tract infections. We believe any results that lead to this degree of uncertainty in the network meta-analysis should be removed from the ACD with a focus on direct evidence. | Comment noted. There was no direct evidence available for the incidence of adverse events with DPP-4 inhibitors and SGLT-2 inhibitors compared with empagliflozin (see section 3.12 of the FAD). In response to consultation on the ACD, the company has updated the network meta-analyses, providing more reliable adverse events data. |

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| | **Section 3.28 – modelling urinary tract and genital infections**<br><br>In this section, it is reported that the manufacturer assumed that "urinary tract infections and genital infections were assumed to happen only in the first cycle after starting treatment". A fixed cycle length of 6 months was used in the manufacturer's cost-effectiveness model. However, as reported earlier, a number of the Phase III randomised clinical trials for empagliflozin had a duration over 6 months, and in some cases, up to 2 years. As such, there is safety data related to urinary tract infections and genital infections for beyond 6 months, and the modelling should reflect the longer-term rates of urinary tract and genital infection rates, along with recurrence rates observed from the full clinical data available. | Comment noted. The new cost effectiveness model provided by the manufacturer has an annual cycle length. The new model was informed by data from the new network meta-analyses provided by the company, which included the relative risk of urinary tract infection at 52 weeks in dual therapy. |

## Comments received from members of the public

No comments were received from members of the public.