MSD Comments: Consultation on ACD – Canagliflozin in combination therapy for treating type 2 diabetes

General comment on the ACD:

The clinical effectiveness data that has been considered in the technology appraisal for canagliflozin versus the sulphonylurea comparator has relied on glimepiride data. However, in England and Wales, gliclazide is the most commonly used sulphonylurea.

Comments by section number of the ACD

- **Section 2.4 – the expected annual cost of canagliflozin 100mg and 300mg**

The expected annual cost of canagliflozin 100mg and 300mg reported in the ACD of £477.36 and £608.83, respectively, appear to be incorrectly calculated if the cost of a 30-tablet pack is £39.20 and £49.99 for canagliflozin 100mg and 300mg, respectively. The annual expected cost of canagliflozin 100mg, based on a 30-tablet pack cost of £39.20 is £476.93 (assuming there are 365 days per year). The annual expected cost of canagliflozin 300mg, based on a 30-tablet pack cost of £49.99 is £608.21 (assuming there are 365 days per year).

- **Section 3.13 – Dual therapy with a metformin background**

In this section, the results from the manufacturer's network meta-analysis for HbA_{1c} change at 52 weeks are reported for dual therapy with a metformin background. The source of the data is not clear in this section. For clarification, we would recommend that the initial text is updated to state that this is sourced from the manufacturer's network meta-analysis (bold text added):
"*The manufacturer presented differences in HbA_{1c} change for canagliflozin 100mg and 300mg compared with the different comparators as dual therapy with a metformin background* ***from the network meta-analysis they conducted***"

- **General comment on the manufacturer's network meta-analysis**

Sections 3.13 to 3.23 present the results from the manufacturer's network meta-analyses and include interpretations of the results. When interpreting the results, the mean results and any numerical differences should be considered alongside the 95% credible intervals – however, this has not been done consistently in sections 3.13 to 3.23 of the ACD. Ideally, the mean results with the 95% confidence intervals should be presented for every drug and dose included in each network meta-analysis for each endpoint in each indication without any interpretation to reflect the limitation of network meta-analyses. It should be noted that network meta-analyses need to be interpreted with caution, however, should an interpretation be included, then the 95% credible intervals must be reported throughout and considered as part of the interpretation. The following comments below outline our recommended changes.

- **Section 3.13 – Dual therapy with a metformin background**

The text in this section states that "*canagliflozin 100mg produced a greater reduction in HbA_{1c} than sitagliptin 100mg (-0.01% [-0.48 to 0.44]) and dapagliflozin 10mg (-0.14% [-0.81 to 0.47])*". This conclusion is incorrect as the 95% credible intervals for both drugs cross the line of no effect. The interpretation stated for the network meta-analysis results for canagliflozin 100mg versus liraglutide 1.2mg, canagliflozin 300mg, pioglitazone 30mg, exenatide 10µg or glimepiride is not appropriately

phrased in this section, as these results only show non-inferiority. As such, the text should be updated to either:

- Report the mean results and 95% credible intervals for each drug and dose with no interpretation
- Or, updated to the following: "*canagliflozin 100mg produced a **non-inferior** reduction in HbA_{1c} versus sitagliptin 100mg (-0.01% [-0.48 to 0.44]), dapagliflozin 10mg (-0.14% [-0.81 to 0.47]), liraglutide 1.2 mg (0.40% [-0.33 to 1.11]), canagliflozin 300 mg (0.13% [-0.25 to 0.52]), pioglitazone 30 mg (0.11% [-0.44 to 0.84]), exenatide 10 micrograms (0.02% [-0.65 to 0.55]) or glimepiride (0.00% [-0.45 to 0.46]).*" and remove the text referring to "greater reduction".

The text in this section also states that "*canagliflozin 300mg produced a greater reduction in HbA_{1c} than pioglitazone 30mg (-0.02% [-0.57 to 0.72]), exenatide 10µg (-0.11% [-0.78 to 0.42]), glimepiride (-0.13% [-0.58 to 0.33]), canagliflozin 100 mg (−0.13% [−0.52 to 0.25]), sitagliptin 100 mg (−0.14% [−0.61 to 0.31]) and dapagliflozin 10 mg (−0.27% [−0.94 to 0.34])*". This conclusion is incorrect as the 95% credible intervals for both drugs crosses the line of no effect. The interpretation from the network meta-analysis for canagliflozin 300mg compared with liraglutide 1.2mg is also inappropriately phrased in this section. As such, the text should be updated to either:

- Report the mean results and 95% credible intervals for each drug and dose with no interpretation
- Or, updated the text to the following: "*canagliflozin 300mg produced a **non-inferior** reduction in HbA_{1c} versus pioglitazone 30 mg (-0.02% [-0.57 to 0.72]), exenatide 10 micrograms (-0.11% [-0.78 to 0.42]), glimepiride (-0.13% [-0.58 to 0.33]), canagliflozin 100 mg (−0.13% [−0.52 to 0.25]), sitagliptin 100 mg (−0.14% [−0.61 to 0.31]), dapagliflozin 10 mg (−0.27% [−0.94 to 0.34]) and liraglutide 1.2 mg (0.27% [−0.46 to 0.98]*" and remove the text referring to "greater reduction"

- **<u>Section 3.14, 3.15 and 3.16 – Dual therapy with a metformin background</u>**

No 95% credible intervals have been reported for the network meta-analysis results for change in weight, systolic blood pressure or hypoglycaemia risk, and therefore it is not possible to verify if the conclusions such as "greater weight reduction" are appropriate. The mean results for each drug and dose must be reported along with the 95% credible intervals and the conclusions reflecting the 95% credible intervals and whether they demonstrate statistically significant or non-inferior differences.

In section 3.14, the results have been interpreted as "at least similar" – this is an inappropriate way to interpret the results. Any differences seen should be interpreted as whether they are statistically significant or non-inferior.

In section 3.14, the phrase "gave a lesser weight reduction" should be corrected to state "gave a smaller weight reduction".

- **<u>Section 3.17 – Triple therapy with a metformin plus sulphonylurea background</u>**

No 95% credible intervals have been reported for the network meta-analysis results for change in HbA_{1c}, weight, systolic blood pressure or hypoglycaemia risk, and therefore it is not possible to verify if the conclusions such as "greater weight reduction" are appropriate. The mean results for each drug and dose must be reported along with the 95% credible intervals. Should an interpretation be included, the conclusions need to reflect the 95% credible intervals and state whether they are statistically significant or non-inferior differences. The current interpretations included in this

section, such as "produced a similar reduction" or "slightly greater" should be removed, as these statements are subjective and do not take into consideration the 95% credible intervals.

- **Section 3.18 – Triple therapy with a metformin plus thiazolidinedione background**

No 95% credible intervals have been reported for the network meta-analysis results for change in HbA_{1c}, weight, systolic blood pressure or hypoglycaemia risk, and therefore it is not possible to verify if the conclusions are appropriate. The mean results for each drug and dose must be reported along with the 95% credible intervals. Should an interpretation be included, the conclusions need to reflect the 95% credible intervals and state whether they are statistically significant or non-inferior differences. The current interpretations included in this section, such as "smaller reduction" should be removed, as these statements are subjective and do not take into consideration the 95% credible intervals.

- **Section 3.19 and 3.20 – add-on to insulin with or without an antihyperglycaemic background**

No 95% credible intervals have been reported for the network meta-analysis results for change in HbA_{1c}, weight or systolic blood pressure, and therefore it is not possible to verify if the conclusions such as "the reduction in HbA_{1c} at 26 weeks with canagliflozin 100 mg and 300 mg was greater than sitagliptin 100 mg" are appropriate. The mean results for each drug and dose must be reported along with the 95% credible intervals and the conclusions reflecting the 95% credible intervals and whether they demonstrate statistically significant or non-inferior differences. The current interpretations included in this section, such as "greater reduction" should be removed unless this can be substantiated by statistically significant differences.

- **Section 3.22 and 3.23 – adverse events**

This section reports numerical differences for adverse events observed between different therapy groups. However, there are no p-values reported and it is unclear if any statistical analysis was conducted. If the conclusions in this section are purely based on numerical differences, no subjective interpretation stating if the percentages are numerically higher or lower should be included. For example, the text:

- "*The incidence of adverse events leading to discontinuation in the broad dataset was higher in the canagliflozin 300 mg group (7.3%) than the canagliflozin 100 mg (5.6%) and non-canagliflozin (5.0%) groups*" should be updated to state the findings removing any interpretation: "*The incidence of adverse events leading to discontinuation rate in the broad dataset was 7.3%, 5.6% and 5.0% in the canagliflozin 300 mg, canagliflozin 100 mg and non-canagliflozin groups, respectively*".
- "*The incidence of adverse events considered related to the study drug by the investigator was slightly higher in the canagliflozin 100 mg and 300 mg groups (33.6% and 29.4% respectively) than the non-canagliflozin group (21.8%)*" should be updated to state the findings removing any interpretation: "*The incidence of adverse events considered related to the study drug by the investigator was 33.6%, 29.4% and 21.8% in the canagliflozin 100 mg, 300 mg and non-canagliflozin groups, respectively*"
- "*the incidence of genital mycotic infection adverse events in women was higher in those receiving canagliflozin 100 mg (14.7%) and canagliflozin 300 mg (13.9%) than in those taking placebo (3.1%)*" should be updated to state the findings removing any interpretation "*the incidence of genital mycotic infection adverse events in women was 14.7%, 13.9% and 3.1% in those receiving canagliflozin 100 mg, canagliflozin 300 mg (13.9%) and placebo, respectively*"

- **Section 3.25 – comparative clinical-effectiveness data at 26-weeks and 52-weeks**

The ACD states that the ERG identified the following uncertainty:

"*It was not convinced by the manufacturer's justification for network meta-analysis for triple therapy assessing effects at 26 weeks, rather than at 52 weeks.*"

Given the long-term time horizon of the model and the uncertainty noted by the clinical specialists on the long-term efficacy and safety data of the newer treatment options (section 4.3), the NICE Appraisal Committee need to consider the cost-effectiveness results based on the 52-week data in addition to the analysis using 26-week data, as part of their deliberations even if these includes data for fewer comparators.

- **Section 3.30 – cost-effectiveness data and the use of annual 'drift' values**

The ACD states:

"The manufacturer explained that diabetes treatments have an initial effect followed by annual 'drift', where the effect lessens over time. Biomarker values after the first cycle were estimated using annual drift values for each treatment. Based on published values, HbA_{1c} drift was assumed to be 0.14% for canagliflozin, dapagliflozin, DPP-4 inhibitors and GLP-1 analogues, 0.07% for thiazolidinediones, 0.24% for sulfonylureas and 0.15% for insulin."

The manufacturer has sourced HbA_{1c} drift values from the ADOPT study, which analysed metformin, TZD and SU and demonstrated different drift values for each therapy. The manufacturer assumed that the HbA_{1C} drift values for canagliflozin, dapagliflozin, DPP-4 inhibitors and GLP-1 were the same as metformin. However, the deterministic sensitivity analyses demonstrated that the HbA_{1c} drift values was the key driver of the cost-utility model (section 3.39, ACD) and therefore it is important to adequately understand the implications of this assumption. It seems likely that the HbA_{1c} drift values for canagliflozin, dapagliflozin, DPP-4 inhibitors and GLP-1 would vary between different treatments and exploratory analyses looking at different scenarios are required.

- **Section 4.12 – clinical and cost-effectiveness of canagliflozin dose escalation strategy**

The recommended starting dose for canagliflozin is 100mg. The summary of product characteristics states that the dosage can be increased to 300mg if tighter glycaemic control is needed. However, there is no clinical trial evidence for canagliflozin based on dose escalation from 100mg to 300mg.

In section 4.12, the ACD states that "The committee concluded that there was uncertainty about the precise clinical effectiveness of canagliflozin when escalating the dose in clinical practice". The expected annual cost of canagliflozin 300mg (£608.83, stated in section 2.4) is significantly higher than 100mg (£477.26, , stated in section 2.4), costing £131.57 more per patient than canagliflozin 100mg. Given the lack of clinical trial data for the dose escalation and the significant drug acquisition cost difference between the two canagliflozin doses, the cost-effectiveness of the dose escalation strategy for canagliflozin is unknown – therefore the NICE Committee cannot conclude with sufficient confidence that a dose escalation strategy is more cost-effective than canagliflozin 100mg.

- **Section 4.13 – Adverse events associated with canagliflozin**

The ACD confirms that the Committee has considered the clinical specialist perspective on the rate of genital infections and management of these occurrences with canagliflozin. However, it does not

appear that the committee has considered the perspective of patients. The most common adverse events for canagliflozin are genital infections. Genital infections increase the risk of patients requiring GP visits, prescriptions and potentially hospital visits and many patients will fear the risk associated with such infections. The Committee should consider the patient perspective on the risk of GIs associated with canagliflozin and consider this as part of their deliberations.

Furthermore, evidence associated with canagliflozin related to bone fractures does not to appear to have been considered. The EPAR included the following table on incidence of bone fractures (all and low trauma):

	Non-CANA	CANA 100mg	CANA 300mg
Total no. of subjects with adverse events n(%)	47 (1.4)	58 (1.9)	54 (1.8)
Low Trauma	31 (1.0)	41 (1.3)	39 (1.3)

The EPAR states "The Kaplan-Meier plot indicates a questionable increase in low-trauma fractures with CANA (both doses). The difference became obvious very early in treatment (after around 6 weeks). Thus, it remains unclear whether this effect could be caused by CANA. Usually bone changes (e.g. noticeable decrease in bone density) need more time to develop. On the other hand, the increase in fractures (if true) may be due to increased falls related to CANA-induced dizziness or hypotension". The committee should consider this adverse event when assessing the adverse event profile of canagliflozin.