NICE National Institute for Health and Care Excellence

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Single Technology Appraisal (STA)

Canagliflozin in combination therapy for treating type 2 diabetes [ID554]

[redacted]

The Evidence Review Group, Southampton Health Technology Assessment Centre (SHTAC), and the technical team at NICE have now had an opportunity to take a look at the submission received on the 15 October 2013 by Janssen-Cilag. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm on 21st November 2013**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

[redacted]

Yours sincerely

Janet Robertson
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

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Section A: Clarification on effectiveness data

Literature review

A1. In section 6.2.2 on page 54 and figure 1 in Amaris 2013, ref 72 (PRISMA flow diagram, page 26), it is stated that 208 citations were identified for data extraction. It is unclear how the 12 potentially relevant canagliflozin RCTs listed in section 6.2.4 on page 56 were selected from these 208 citations. Please clarify how these 12 RCTs were selected and please provide reasons for why others were excluded, along with the number of studies excluded for each reason at this stage.

A2. In figure 1 in Amaris 2013, ref 72 (PRISMA flow diagram, page 26) the number of references that did not meet the inclusion criteria for the network meta-analysis sums to 123 (in box titled 'Discarded from the NMA as did not meet inclusion criteria'). Please provide a list of these references.

A3. In figure 1 in Amaris 2013, ref 72 (PRISMA flow diagram, page 26) a total of 648 full texts were screened for eligibility, and the total number of references 'discarded as did not meet the inclusion criteria' sums to 434. This should leave 214 publications for inclusion in the narrative review, rather than the 208 publications as specified. Please explain this discrepancy.

A4. Please provide reference number 57 '*CEGEDIM. Patient Data Report: Diabetes Treatment Combinations - Report AH [JAN2364513_ADH.DN2]. 2013*'.

Clinical effectiveness

A5. It is stated on page 107 that there were no differences in change in HbA1c over time according to baseline BMI. However, data from the sub-group analyses by baseline BMI have not been reported. Please provide these results.

A6. The DIA3008 insulin sub-study compares canagliflozin plus standard of care (SoC) compared with placebo plus SoC in subjects with T2DM.

- Please clarify whether SoC is analogous to other terms used in the submission for this study, such as 'AHA medications'?
- Please clarify whether there is a specific definition of SoC in this study?
- Please provide data showing which AHA medications were being taken in addition to insulin and canagliflozin/placebo in that trial.

A7. On page 112, in reference to the network meta-analysis, it is stated ***"****According to clinical experts, background therapies are an important treatment effect modifier. Therefore, analyses were conducted by background therapy. Trials assessing treatments on top of a "mixed" background were therefore excluded from the NMA.*" Please explain what is meant by 'mixed background'.

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A8. On page 112, in reference to the network meta-analysis, it is stated *"Treatments not recommended in the UK (i.e. by NICE or the SMC) were excluded from the NMA (e.g. insulin degludec and liraglutide 1.8 mg)"*. Please provide a list of all treatments which were excluded from the NMA.

A9. On page 123 it is stated *"SAS and WinBUGS programs are reported in Appendix 7 in section 10.7.10 (Clinical SRL – Winbugs and SAS programs)".* In the appendix there only appears to be Winbugs code. Please clarify whether the SAS code should have been included here too? If so please provide the SAS code or a summary of what the code does.

Section B: Clarification on cost-effectiveness data

B1. In table 33 on page 176 the economic model chooses one comparator within each class of treatment. Please clarify whether other treatments in each class were examined in scenario analyses?

B2. On page 179 it states for some treatments BMI was estimated by weight using a weighted average of male and female heights in the UK general population.

- Please clarify for which treatments did this estimation occur?
- Please clarify whether this was tested in sensitivity analysis?
- Please clarify what happened if there was neither BMI nor weight data?

B3. Please clarify how and why the CODE-2 study for HRQoL data was chosen from the 80 included HRQoL studies reported on page 194.

B4. On page 175, it is stated that *"The relationship between hypoglycaemic event rate and HbA1c is described by a user-defined hazard ratio for event rates corresponding to each 1% point decrease in HbA1c, defined by the user. In an analysis based on DCCT data, the multivariate regression estimate of the RR was 1.43."* Please confirm whether a hazard ratio or a relative risk (RR) was applied to model the relationship between hypoglycaemic event rate and HbA1c?

B5. On page 175, the economic model input data sheet does not appear to contain profiles for some of the dual therapy comparisons shown in table 32. Please provide the profiles for the canagliflozin dual therapy comparisons with TZD, GLP-1-a and dapagliflozin, and the profiles which concern its use as an add-on to insulin (or advise where these are located if already supplied).

B6. On page 273, appendices section 10.7.15, for dual therapy with a metformin background, the submission gives a mean difference versus placebo of -0.63 in HbA1c change at 52 weeks for Cana 100mg QD (table 133). However the economic model input data sheet gives a value of -0.77 versus placebo for 'Fixed First-Year Change in HbA1c (Unrelated to HbA1c at Treatment Start)' for the treatment profile 'NMA DUAL 52WKS (MET BACKGROUND) CANA100 VS. SITA'. (This treatment profile is specified as the intervention arm in the input data spreadsheet.) Other figures given in table 133 are also not the same as those presented for the HbA1c

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treatment effect in the economic model input data spreadsheet. Please explain why these figures are different?

B7. On page 277, appendices section 10.7.15, the mean results for the difference in BMI versus placebo presented in table 140 do not agree with figures used in the input data spreadsheet. For example the mean of-0.56 for Cana 100mg QD contrasts with the value of -0.595379183 used in the input data spreadsheet for the 'NMA DUAL 52WKS (MET BACKGROUND) CANA100 VS. SITA' profile. Other figures given in Table 140 are also not the same as those presented for the 'First-Year Change in BMI in Responders' in the economic model input data. Please explain why these figures are different?

Section C: Clarification on the economic technical guide

C1. Please clarify whether the equation given in the text on page 60 is correct as it does not appear to be correctly specified for a model with time-varying covariates **Xt**.

C2. Please confirm that the 1000 stochastic draws of parameter values provided by Philip Clarke on page 61 include correlation between parameters.

C3. Please explain what is shown in table 6 on page 61 as it is not referred to in the text.