17th March 2014

National Institute for Health and Care Excellence
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Dear [redacted]

RE: ACD - Consultees & Commentators: (Diabetes (type 2) - canagliflozin) [554]

Further to your invitation to comment on the appraisal consultation document (ACD) for the above appraisal received on 25th February, please find below our comments.

ACD Section	Comments
Section 4.5 Network of evidence	In the insulin failure network there are differences in concomitant medication across the network; concomitant medication is expected to have a considerable impact on treatment effects. If the concomitant medications are not the same this may make the indirect comparison biased. No discussion provided around the differences in trial design (treat-to-target insulin vs. static insulin doses) or baseline characteristics (weight and HbA_{1c}). One study included insulin-naïve patients. The networks presented in the canagliflozin and dapagliflozin manufacturer submissions (MS) are different. The canagliflozin network is much larger and the individual studies appear heterogeneous.
Section 4.16, 4.17 Cost-effectiveness analysis	The majority of assumptions were reasonable; however, the assumption behind HbA_{1c} drift (one of the largest drivers of the model) is unclear. There is an underlying assumption that canagliflozin, dapagliflozin, DPP-4s and GLP-1ra all have equal HbA_{1c} drift but it appears to have been modelled independently for each product, therefore breaking this assumption and potentially introducing additional uncertainty to the results. The baseline characteristics for the canagliflozin on insulin background were of patients at high risk for cardiovascular disease (CVD); it is unknown to what extent this will impact the results however it may bias in favour of interventions which affect CVD risk factors including systolic blood pressure (SBP) and lipid (e.g. canagliflozin). More detailed information on assumptions around the modelling is described in the appendices of the MA. Unfortunately, Novo Nordisk did not have access to these documents since they are

	not distributed as part of the evaluation report. It would be beneficial for the consultees and commentators to have access to this information as part of the review process to contribute to the development their informed response.
Section 3.38 Uncertainty	An incomplete deterministic sensitivity analysis (DSA) was submitted and therefore uncertainty was not fully explored. Upper and lower bounds used in the DSA were poorly described and tornado diagrams excluded dominated or dominant results. The probabilistic sensitivity analysis (PSA) was poorly documented and the extent to which uncertainty was explored is unclear. Multiple cost-effectiveness acceptability curves (CEAC) and the cost-effectiveness acceptability frontiers (CEAF) were absent from the MS (the model was restricted to pair-wise analysis only) which is not in line with the NICE reference case.
Section 4.21 External validation	The results in the dapagliflozin and canagliflozin MS conflict when the respective SGLT-2s are compared with DPP-4s in combination with insulin. This increases the uncertainty of the results in the canagliflozin MS. MS Dapagliflozin: Dapagliflozin is cost-effective compared with sitagliptin. MS Canagliflozin: Dapagliflozin is dominated by canagliflozin. To be consistent with the dapagliflozin MS, canagliflozin should be cost-effective compared with sitagliptin, which it is not.
ACD Advice	The committee rejected the analysis against GLP-1 in combination with insulin (out of scope) and Canagliflozin 100 mg is recommended with insulin background despite being dominated by DPP-4s and GLP-1ra. From Novo Nordisk's point of view the combination of GLP-1ra with insulin is a relevant comparator in the add-on to insulin indication and it should be considered to inform the final recommendation on the grounds that is a commonly used option in clinical practice.