February 3, 2017

Canadian Agency for Drugs and
Technologies in Health (CADTH)
865 Carling Avenue, Suite 600
Ottawa, Ontario K1S 5S8

Subject: **Canadian Diabetes Association Feedback on New Drugs for Type 2 Diabetes: Second-Line Therapy: A Therapeutic Review Update**

Please find enclosed feedback on the draft science report for the CADTH initiative, New Drugs for Type 2 Diabetes: Second Line Therapy: A Therapeutic Review Update. The Canadian Diabetes Association (CDA) and its expert reviewers have serious concerns about the limitations of available evidence, the resultant interpretation and accordingly, the conclusions of the draft report. The CDA cautions against policy development based on its findings. These limitations cannot be dismissed; doing so would be at the peril of people living with diabetes and all Canadians as there may be missed opportunities for reductions in mortality and hospital costs from cardiovascular complications for those at highest risk.

In the introduction to the reports, CADTH states "The information in this report is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services." We know that CADTH takes this statement very seriously and thus anticipate the issues herein will be addressed in a revised document that more accurately reflects the true cost-effectiveness of agents used to treat type 2 diabetes.

In the spirit of providing meaningful information to Canadian policy makers, the CDA is available to meet with you, in order to pursue an alternate economic model which includes the clinical data from recent relevant high quality studies, with adjudicated, hard clinical outcomes rather than a network meta-analysis alone and a model that cannot be adapted to include new efficacy data. The efficacy data that I am referring to are very relevant: improved survival, cardiovascular events and end-stage renal disease (EMPA-REG), which occurred to a greater extent than could be explained solely by changes in glycemia. Clearly these data must be included to guide policy making related to treatment of type 2 diabetes in 2017.

The CDA leads the fight against diabetes by helping those affected by diabetes live healthy lives, preventing the onset and consequences of diabetes, and funding research to discover a cure. We speak for people with diabetes in the call for equitable and timely access to the drugs and supports needed to optimally manage their disease.

People with diabetes have a large stake in how medications are reviewed by CADTH and approved for reimbursement by public drug plans in Canada. We believe that drug review processes must incorporate the best available evidence, the interpretation should be clinically relevant, and that the conclusions should be transparent, consistent and fair. It is with these values in mind that we offer comments on the draft reports. These comments reflect the opinions of members of CDA's vast professional network across the country.

Thank you for the opportunity to provide comments on this important initiative.

Sincerely,

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Canadian Diabetes Association Feedback on New Drugs for Type 2 Diabetes: Second-Line Therapy: A Therapeutic Review Update

Major Concerns

1. The research questions for the project are relevant and appropriate. The comparative efficacy and safety of the listed agents after metformin are of interest to the diabetes community. The first research question was to determine the relative efficacy of glucose lowering agents in improving glycemic control and reducing cardiovascular effects in people who are sub-optimally controlled on metformin. Glycemic control measured by HbA1C is a surrogate outcome and is differentially associated with micro and macrovascular outcomes. These outcomes are of greater clinical importance. In the absence of outcome data, HbA1C is useful to guide decision making. However, when outcome data are available, as they are now, those data must be considered to be more important and relevant to guide clinical and policy decisions.

   Currently, the interpretation of the network meta-analysis (NMA) does not adequately reflect the importance of improved survival vis-à-vis the decrease in HbA1C as an outcome. The EMPA-REG and LEADER trials demonstrated improved survival; and in the NMA the SGLT-2 inhibitors were also shown to have a significant survival benefit. The NMA describing changes to HbA1C for second line therapy compared with SU shows no difference between the agents for this outcome.

   The authors place more value on the HbA1C outcome, presumably because of the number and consistency of findings. However, pursuing consistency of evidence at the cost of ignoring outcomes that are clinically important has produced misleading conclusions. In this case, survival is clearly the most important outcome. The current analysis and interpretation restricts the applicability of the entire report.

The CDA recommends that CADTH place greater importance on evidence related to cardiovascular outcomes and mortality than HbA1C when available, to draw conclusions from the evidence.

2. The authors state that "*Another limitation of the UKPDS model is its inability to account for potential cardiovascular benefits of SGLT-2 inhibitors and GLP-1 analogues beyond those due to improved glycemic control.*" This statement, buried within the limitations section of the report, is very concerning. CADTH's NMA itself found SGLT-2 inhibitors to significantly improve survival. Given the importance of survival, the exclusion of these evidence-based outcomes essentially makes the cost effective analysis, while interesting, meaningless to inform the development of public policy.

The CDA recommends that CADTH utilize an economic model that can incorporate <u>all</u> of the relevant evidence about the impact of therapies under review to appropriately inform the development of policies that impact millions of Canadians living with diabetes.

3. The second research question in the draft clinical report appears to be for academic purposes only. The results of this research cannot be used in the pharmacoeconomic analysis approach undertaken by CADTH. The presence of this research question can mislead the reader to believe that CADTH is willing to meaningfully consider the cardiovascular and survival benefits described by recent trials.

The CDA recommends that CADTH be transparent about not being able to employ the results from the clinical report research question 2 in any pharmacoeconomic analysis, and state that the clinical conclusions related to this question are for information only and not applicable to policy recommendations.

Additional Concerns

4. The NMA is technically accurate. A benefit of NMA is that it allows for comparisons across multiple studies and synthesis of the evidence across trials. However, the limitations of such methodology need to be more explicitly stated so that policy makers can better understand the weaknesses of the analysis. Please see Cipriani A, Higgins JP, Geddes JR, Salanti G. Conceptual and Technical Challenges in Network Meta-analysis. Ann Intern Med. 2013;159:130-137.

The CDA recommends that, in order to be more transparent, CADTH explicitly state the limitations of NMA and add these to the executive summary as many readers do not read the technical report.

5. The authors state that "*NMA could not be conducted for a number of outcomes due to low event rates observed in many studies. Data from several RCTs could not be included in any of the network or pairwise meta-analyses due to variation in the methods of reporting for key outcomes, zero events in one or both study arms (not robust with continuity corrections) or because the study compared two treatments within the same drug class.*"

The CDA recommends that CADTH transparently state the best available evidence available when data cannot be analyzed by NMA (e.g. large RCTs) rather than nothing at all. This will ensure the reader is not misled to believe that there is an absence of data.

6. The authors state that "*Due to the small number of studies in the network, we are unable to investigate inconsistency, heterogeneity, and the impact of the network geometry on the effect estimates produced*". This is an important limitation which is understated in the report given that the conclusions and recommendations are based on this analysis.

The CDA recommends that CADTH describe the implications of this limitation in the spirit of transparency. The results must always be considered in the context of the analysis and its limitations. In this case, the analysis limitations cast doubt on the validity of the entire exercise. CADTH should provide data from critical individual studies alongside findings of the network analysis.

7. It is not clear why non-sulfonylurea insulin secretagogues (i.e. meglitinides) and TZDs were not included in this analysis. These agents are discussed in the text of the report but not included in the analysis.

The CDA recommends an addition of these agents to the analysis or a statement explaining their exclusion from the analysis.

8. The authors state that because hard outcomes are not routinely reported in the majority of studies, outcomes were inferred from HbA1C data. This is problematic, as recent trials have reported health outcomes in a much more robust manner. While the analysis cannot weigh these new and very important data within the confines of the NMA, the experts interpreting the NMA in context should duly consider these results.

The CDA recommends that CADTH appropriately consider and report the recent large clinical trials showing significant improvement in cardiovascular mortality within the main report and the executive summary.

9. The utilities used within the pharmacoeconomic model do not represent the most appropriate evidence and outcomes that impact patients living with diabetes.
    a. As acknowledged by the authors, no disutility is attached to the weight gain associated with insulins and sulfonylureas nor is the potential gain in utility from weight loss associated with other agents included in the base case scenario. This does not represent the experience of patients living with diabetes who unequivocally say that weight gain has a significant impact on health and well-being. Indeed, this is why CADTH included weight gain utilities in the sensitivity analysis. The results of this sensitivity analysis show a decrease of the gap between SU and SGLT-2 inhibitors and GLP-1 analogues when this was considered. Incorporating weight gain as a sensitivity analysis is insufficient given the magnitude of this concern and that conclusions are drawn from the base case.
    b. The utility decrements for some outcomes are significantly lower than those commonly used in the literature. For example, -0.0635 is used for congestive heart failure; however, based on a 2000 study by Gohler et al. (Value Health), the utility scores for heart failure ranged from 0.60 to 0.90 (i.e. decrements of -0.1 to -0.4). Similarly the utility decrement for myocardial infarction was 0.0409 in the current analysis, but there was a decrement in utility of -0.07 (based on Lewis et al., JACC Heart Failure). Given that these outcomes and costs are precisely those modified by the agents under review, the under-valuing of the utility scores associated with outcomes may bias the overall economic evaluation against the cost-effectiveness of these medications. The choice of the utility decrements used should be based on evidence and should also be more transparent.

The CDA recommends that CADTH employ utilities within the base case economic model that reflect the real patient experience and are supported by published literature.

10. The authors state that "*Such benefits are not accounted for in the current analysis, therefore the true cost effectiveness of the SGLT-2 inhibitor and GLP-1 analogue classes may be more attractive than suggested by the estimated ICURs.*" The executive summary does not address this critical point. Given that the majority of readers will not read the technical document, it is imperative that the executive summary include acknowledgement that the data showing survival and cardiovascular benefits have not been included in the analysis.

The CDA recommends increased transparency in explaining the limitations of the pharmacoeconomic analysis with explicit statements in the executive summary, in the results and in the discussion sections stating that data demonstrating survival benefits of some agents in the review have not been included in the economic analysis.

11. The UKPDS model predicts outcomes based on a predominately middle-aged, relative ethnically homogenous (81% white) population. The event rates in a younger or more diverse population may be somewhat different.

The CDA recommends the addition of this limitation to the report.

12. It appears that the model uses HbA1C derived from the NMA to estimate the probability of diabetes complications. It is not clear if the events that could be reduced by the use of SGLT-2 inhibitors or GLP-1 analogues were incorporated into the analysis. This blind emphasis on HbA1C will lead to under-valuing of the SGLT-2 inhibitors, given they work largely through non-glycemia mechanisms. This is not appropriate in light of currently available outcome data.

The CDA recommends clarification of the methodology used to estimate the probability of diabetes complications. If the analysis is based on reduction of outcomes inferred from HbA1C, there should be better transparency and acknowledgement of the limitations.