March 29, 2017

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

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

Please find feedback on the draft recommendations for the CADTH initiative, New Drugs for Type 2 Diabetes: Second Line Therapy: A Therapeutic Review Update. Diabetes Canada, with our experts, reiterates our serious concerns about the limitations and interpretation of the evidence, the conclusions and recommendations of this report.

In our previous correspondence, we strongly advised against policy recommendations based on the draft clinical and economic reports. However, these concerns, while acknowledged in the "Of Note" section did not cause your reviewers or the CDEC to reconsider the analysis or interpretation of the evidence. This steadfast and unrelenting approach, with little regard to the feedback from methodologists and clinical experts across the country and the impact on patient care is, indeed, very discouraging.

The role CADTH can play to guide effective and cost-effective treatment is founded on valid scientific review and expert recommendations from those knowledgeable about the evidence and the patient population. Yet, these recommendations do not provide appropriate direction to clinicians who need guidance on how to manage individual patients or policy makers who develop healthy public policy. As a result, some people living with diabetes may be deprived evidenced based therapies that can prevent mortality.

The comments below reflect the opinions of the staff of Diabetes Canada and our professional network across the country. Again, we would welcome the opportunity to discuss these views with you, in an effort to provide better advice to clinicians and policy makers.

Sincerely,

Jan Hux, MD, SM, FRCPC
Chief Science Officer
Diabetes Canada

CC: Brian O'Rourke, President and CEO, CADTH

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

Fundamental concerns

The introduction to the recommendation states "With evidence that the efficacy of treatments is similar across drug classes, the Committee identified the values of safety and efficient use of health care resources as particularly important in making its recommendation". The evidence does not show similar efficacy for all patients living with diabetes, rather the analysis chosen by your reviewers did not allow for detection of difference. Glycemic control measured by HbA1c is a surrogate outcome used in clinical trials that has been a standard metric for decades. In the absence of outcome data, HbA1c is useful to guide decision making. However, now that outcome data are available for some drugs and particularly because those favourable outcomes do not track closely with HbA1c, those data must be considered to be of highest relevance to guide public policy decisions. Your reviewers and committee have previously questioned the validity of HbA1c as a surrogate outcome, and yet now that health outcome data are available, the reviewers selectively diminish the value of these outcome data through their choice of analyses. Cleary, survival is a more important outcome than HbA1c and yet these data are not duly considered.

You are correct to note that there is an absence of cardiovascular outcome data for some of the classes of diabetes medications. However, this does not negate the mortality benefit that has been demonstrated with two of the currently available agents, one of which has a Health Canada indication for this purpose. To await these cardiovascular outcome data for all classes would deprive patients of the proven benefits for several drugs and would be unethical. To be clear, we represent clinicians who practice evidence-based medicine and we are an organization that produces world recognized evidence-based clinical practice guidelines. As such, we believe that patients should be treated based on the data that are currently available and that these data cannot and should not be extrapolated beyond the patient populations studied – specifically I am referring to patients with diabetes and cardiovascular disease. Yet the current analysis and report ignore these data, and make only passing reference to CDEC's previous recommendation regarding empagliflozin.

The use of the UKPDS model is not appropriate for the current evidence related to positive cardiovascular outcomes observed in randomized trials and inconsistent with newer approaches to clinical trial design. As you may know, the Food and Drug Administration (FDA) through its guidance document in 2008[1] has mandated that all the cardiovascular outcome trials (CVOTs) with antihyperglycemic agents be carried out with a design of glycemic equipoise (both the drug and placebo arm should continue to be treated during the trial to standard of care and HbA1c targets according to local guidelines in every country). Since then, all CVOTs have had an increased utilization of glucose lowering agents in the placebo and comparator arms of the trials and resulted in minimal HbA1c difference between the two arms (ranging from 0.2%-0.3%). This is relevant because the HbA1c effects are minimized and glucose lowering alone cannot explain the benefits in EMPA-REG, LEADER or SUSTAIN-6 trials. Accordingly, the clear cardiovascular benefits of these agents cannot be accommodated in the UKPDS model. The reviewers and the CDEC acknowledge the limitation, but choose to discount the implications. We suggest the use of alternative pharmacoeconomic modeling approaches, which can account for the survival benefit seen in these CVOTs .[2]

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Specific Concerns

Reason 2: "CDEC has previously provided recommendations regarding the use of empagliflozin for patients at high risk of cardiovascular events, where evidence was sufficient to support this recommendation." This evidence is not reflected in the current recommendation which is describing second line therapy. The recommendation statement states that a sulfonylurea should be added "for most adults with type 2 diabetes". This does not appropriately guide clinical or policy decision making. To be consistent with the evidence, an additional statement or sub-recommendation that highlights the mortality benefit with empagliflozin and liraglutide in the specific subgroup of patients with cardiovascular disease, consistent with the clinical trial evidence should be added. The recommendation as currently written may be interpreted as a stand-alone, and this important clinical and policy message may not be considered. Further, it should be explicitly consistent with previous CADTH advice.

To improve transparency to Reason 3, it should be explicitly stated that some data were not included in the cost-effectiveness analyses. We suggest: "The cardiovascular outcomes recently described in clinical trials were not accounted for in the current analysis, therefore the true cost effectiveness of the SGLT-2 inhibitor and GLP-1 agonist may not be fully captured. Furthermore, the impacts of each agent on hypoglycemia and weight gain were not incorporated into the economic evaluation."

Previously we stated that the base-case economic analysis should include the treatment implications on weight gain and hypoglycemia. These outcomes are extremely relevant to patients and should be included to support patient centred policies. Given this recommendation was not accepted, this document should describe the quantitative results of the sensitivity analysis with the inclusion of weight gain and hypoglycemia. While sulfonylureas were the cost-effective treatment in that sensitivity analysis, the gap narrowed, and it should be available to the reader to make an assessment of all of the relevant information.

Also, please note that in Reason #3 the authors describe the base-case findings for a "typical Canadian patient with diabetes". It may be helpful to describe who the typical Canadian patient is, from your perspective. From the experience of most clinicians, people with diabetes have various comorbid conditions, clinical risk factors, ethnic and family risk factors, and social circumstances that impact their management of diabetes and their complications. Please consider rewording this text for the better readability of all Canadians.

References:

1. U.S. Food and Drug Administration. Guidance for Industry Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes 2008 Center for Drug Evaluation and Research (CDER) Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf.
2. Ishack KJ, Kreif N, Benedict A et al; Overview of Parametric Survival Analysis for Health Economic Applications; PharmacoEconomics 2013 , 31, 663-675