Canada's Drug and Health Technology Agency

Proposed Project Scope

SGLT2 inhibitors in Type 2 Diabetes Mellitus Streamlined Drug Class Review

Date: September 2023

For Stakeholder Feedback

Introduction and Rationale

Diabetes Canada defines diabetes mellitus as *a heterogeneous metabolic disorder characterized by the presence of hyperglycemia due to impairment of insulin secretion, defective insulin action or both*.[1] Specifically for type 2 diabetes, predominant insulin resistance with relative insulin deficiency can occur as well as predominant secretory defect with insulin resistance.[1]

Pharmacological therapy in type 2 diabetes is an important mainstay treatment strategy. While first-line pharmacological therapy remains to be metformin with or without insulin based on the latest Clinical Practice Guidelines[1], subsequent add-on options are individualized based on evolving evidence and patient-specific factors.

According to the 2023 CADTH Health Technology Review Living with Type 2 Diabetes, people living with type 2 diabetes want treatment options that are less invasive and can reduce the burden of medication administration. In addition, there is a desire to increase access to and affordability of type 2 diabetes treatments in Canada. People living with type 2 diabetes also want medications that cause few or no adverse effects, especially hypoglycemia, weight gain and gastrointestinal and urogenital side effects.

Since the last CADTH Therapeutic Review on Type 2 Diabetes in 2018, new evidence on the use of sodium-glucose cotransporter-2 (SGLT2) inhibitors has emerged. For example, several network meta-analyses[2,3] have been published to inform the comparative benefits and harms of drug treatment in type 2 diabetes including SGLT2 inhibitors. Specifically, more evidence is now available to inform on clinically important outcomes such as all-cause mortality[3] and cardiovascular outcomes[3] and patient-important outcomes (e.g., safety)[3]. With the imminent loss of exclusivity and introduction of SGLT2 inhibitor generics, this important class of drugs may offer value-add and cost-savings opportunities in formulary management in Canada. Table 1 lists some of the non-insulin antihyperglycemics that are currently available in Canada.

Given the changing landscape of therapies available in type 2 diabetes and patients' desire to access more affordable and less invasive treatment options, a class review of SGLT2 inhibitors is warranted to inform decision makers on formulary management. This Streamlined Drug Class Review will review the comparative efficacy and harms of SGLT2 inhibitors among adult patients with type 2 diabetes following the first-line use or intolerance to metformin. This review will be used to inform the place in therapy of SGLT2 inhibitors and the optimal use of these drugs to improve health outcomes, while maximizing the efficient allocation of resources in this disease area.

Table I: Products Available in Canada

Generic Name (Brand Name)	Manufacturer
SGLT2 inhibitors	-
Canagliflozin (Invokana), Canagliflozin-metformin (Invokamet).	Janssen Inc.
Empagliflozin (Jardiance), Empagliflozin-metformin (Synjardy),	Boehringer Ingelheim (Canada) Ltd.
Dapagliflozin (Forxiga), Dapagliflozin-metformin (XigDuo).	AstraZeneca Canada Inc.
GLP1 agonists	-
Semaglutide (Ozempic), Semaglutide (Rybelsus), Insulin degludec-liraglutide (Xultophy), Liraglutide (Victoza).	Novo Nordisk Canada
Lixisenatide (Adlyxine), Lixisenatide-insulin glargine (Soliqua).	Sanofi-Aventis Canada Inc.

Exenatide (Byetta), Dulaglutide (Trulicity).	Eli Lilly Canada Inc.
DPP4 inhibitors	-
Alogliptin (Nesina) Alogliptin-metformin (Kazano)	Takeda Canada Inc.
Linagliptin (Trajenta), Linagliptin-metformin (Jentadueto).	Boehringer Ingelheim (Canada) Ltd.
Saxagliptin (Onglyza), Saxagliptin-metformin (Komboglyze)	AstraZeneca Canada and generics
Sitagliptin (Januvia), Sitagliptin-metformin (Janumet) Sitagliptin-metformin XR (Janumet XR)	Merck Canada Inc. and generics
Sulfonylurea	-
Gliclazide, Gliclazide modified-release, glimepiride, glyburide	Generics

SGLT2 = sodium-glucose cotransporter-2; GLP1 = glucagon like peptide; DPP4 = dipeptidyl peptidase-4

Objectives

The objective of this Streamlined Drug Class Review is to assess the comparative efficacy and harms of SGLT2 inhibitors with other non-insulin antihyperglycemics for the treatment of adult patients with type 2 diabetes after first line use or intolerance to metformin to support decision makers in formulary management.

Policy Question

Does current evidence support the improved efficacy and safety of SGLT2 inhibitors compared to other non-insulin antihyperglycemics (i.e., glucagon-like peptide-1 (GLP1) agonists, sulfonylureas, dipeptidyl peptidase-4 (DPP4) inhibitors) for the treatment of adult patients with type 2 diabetes after first line use or intolerance to metformin?

Research Questions

The project will address the following research questions:

1. What is the clinical efficacy of SGLT2 inhibitors compared to other non-insulin antihyperglycemics (i.e., GLP1 agonists, DPP4 inhibitors, sulfonylureas) in adult patients with type 2 diabetes mellitus?
2. What are the harms associated with SGLT2 inhibitors compared to other non-insulin antihyperglycemics (i.e., GLP1 agonists, DPP4 inhibitors, sulfonylureas) in adult patients with type 2 diabetes?
3. How do costs compare across SGLT2 inhibitors and other non-insulin antihyperglycemics (i.e., GLP1 agonists, DPP4 inhibitors, sulfonylureas) for the treatment of adult patients with type 2 diabetes after first line treatment with or intolerance to metformin?

Feedback

CADTH has engaged the following organizations to inform them of the review and initiate a dialogue. These organizations include:

- Diabetes Canada
- BC Diabetes
- National Indigenous Diabetes Association
- Diabetes Action Canada
- Indigenous Diabetes Health Circle
- Healthcare Excellence Canada

In addition to the aforementioned outreach with specific organizations, a general call for feedback from all eligible stakeholders will be sought at key stages during this project, including at the time of posting of this project scope (i.e., refer to Status of the Document) and at the following milestones (as communicated through the CADTH Weekly Summary):

- Draft Summary Report
- Draft Recommendation Report
- Proposed revisions to existing recommendations from CADTH's single drug review programs (if applicable)

Methods

An information specialist performed the literature search for clinical studies, using a peer-reviewed search strategy according to CADTH's PRESS Peer Review of Electronic Search Strategies checklist.[4]

Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. All Ovid searches were run simultaneously as a multi-file search. Duplicates were removed using Ovid deduplication for multi-file searches, followed by manual deduplication in EndNote. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the PICOS framework and research questions. The main search concepts were Type 2 Diabetes and Sodium-Glucose Transporter 2 Inhibitors, including specific drug names as well as general terms for these drugs.

CADTH-developed search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or indirect treatment comparisons. Conference abstracts were excluded from the search results. The initial search was completed on August 31, 2023 and limited to English-language documents published since January 1, 2016. Regular alerts will update the search until project completion.

One reviewer screened the titles and abstracts of the screened citations for relevance to the clinical research question. Studies were excluded if they were in languages other than English and did not meet the selection criteria outlined in Table II. Potentially relevant studies were retrieved, and their full text was examined. This included reviewing the composing primary studies of systematic reviews and meta-analyses to determine primary study overlap.

Table II: Systematic Review Selection Criteria

Criteria	Description
Population	Adult patients (18 years and older) with type 2 diabetes
Interventions	**SGLT2 inhibitors** (Canagliflozin, dapagliflozin, empagliflozin)
Comparators	**Antihyperglycemics** **GLP1 agonists** • Short acting: exenatide, lixisenatide • Longer-acting: dulaglutide, exenatide extended-release, liraglutide, semaglutide **Sulfonylureas**: gliclazide, gliclazide MR, glimepiride, glyburide **DPP4 inhibitors**: alogliptin, linagliptin, saxagliptin, sitagliptin
Outcomes	**Efficacy:** • All cause mortality • Cardiovascular death • Non-fatal myocardial infarction • Non-fatal stroke • Admission to hospital for heart failure • End stage kidney disease • Health related quality of life score • Bodyweight change **Safety:** • Adverse events (e.g., genital infection, amputation, ketoacidosis, severe gastrointestinal events) • Serious adverse events (e.g., severe hypoglycemia, pancreatitis)
Study design	Published SRs of RCTs with meta-analysis
Search dates	2016 up to 2023

SGLT2 = sodium-glucose cotransporter-2; GLP1 = glucagon like peptide; DPP4 = dipeptidyl peptidase-4; RCT = randomized controlled trial; SR = Systematic Review

Data Source(s)

The literature search identified 1110 results and 177 network meta-analyses (NMAs). To avoid overlap of primary studies which could introduce bias if outcome data from the same studies are included multiple times, the most recent and comprehensive systematic review with meta-analysis that included all intervention and comparator drugs of interest was included. Criteria for the selection of the systematic review were based on a balance of comprehensiveness, relevance, recency and methodological quality[5].

One systematic review and network meta-analysis was selected to inform the evidence base of this streamlined drug class review. The quality of the identified NMA(s) was assessed using the AMSTAR2 (a MeaSurement Tool to Assess systematic Reviews) tool[6].

Shi Q. et al. Benefits and harms of drug treatment for type 2 diabetes: systematic review and network meta-analysis of randomized controlled trials. BMJ 2023;381:e074068 ***https://doi.org/10.1136/bmj-2022-074068***

Stakeholder Input

CADTH will summarize input received from all groups within the Summary Report and Recommendations Report.

Economic Analysis

A cost comparison table will be developed using list prices from a public drug plan incorporating the dosing regimens as described within the respective Product Monographs.

Utilization Analysis

A utilization analysis will be conducted using public claims data from the National Prescription Drug Utilization Information System to determine the current drug utilization patterns and expenditures for the drugs included in this review.

Process

The project will be conducted in accordance with the *Procedures for* CADTH Streamlined Drug Class Reviews*.* This will include the development of recommendations or advice from the CADTH Formulary Management Expert Committee (FMEC) and may include updates to previous reimbursement review recommendations that have been issued by CADTH in this therapeutic area.

Status of the Document

This proposed project scope is posted for 10 business days as of the date of this posting for stakeholder feedback. The feedback will be considered as the project plan is finalized.

References

1. Committee. DCCPGE. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Can J Diabetes.* 2018;42:S1-S325.
2. Palmer SC, Tendal B, Mustafa RA, et al. Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. *BMJ.* 2021;372:m4573.
3. Shi Q, Nong K, Vandvik PO, et al. Benefits and harms of drug treatment for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. *BMJ.* 2023;381:e074068.
4. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *J Clin Epidemiol.* 2016;75:40-46.
5. Pollock M, Fernandes RM, Newton AS, Scott SD, Hartling L. A decision tool to help researchers make decisions about including systematic reviews in overviews of reviews of healthcare interventions. *Syst Rev.* 2019;8(1):29.
6. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008.