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Formulary Management of Sodium-Glucose Cotransporter-2 Inhibitors and Glucagon-Like Peptide-1 Receptor Agonists

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Environmental Scan

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Abbreviations

ACEi	angiotensin-converting enzyme inhibitor
ARB	angiotensin II receptor blocker
CAF	Canadian Armed Forces
CDEC	Canadian Drug Expert Committee
CKD	chronic kidney disease
CSC	Correctional Service of Canada
CVD	cardiovascular disease
DPP-4	dipeptidyl peptidase-4
eGFR	estimated glomerular filtration rate
FMEC	Formulary Management Expert Committee
GFR	glomerular filtration rate
GLP-1	glucagon-like peptide-1
HF	heart failure
LOI	Letter of Intent
NIHB	Non-Insured Health Benefits
NOC	Notice of Compliance
NYHA	New York Heart Association
pCPA	pan-Canadian Pharmaceutical Alliance
SGLT2	sodium-glucose cotransporter-2
T2DM	type 2 diabetes mellitus
VAC	Veterans Affairs Canada

Key Messages

- Health Canada has approved 4 sodium-glucose cotransporter-2 (SGLT2) inhibitors (ertugliflozin, dapagliflozin, canagliflozin, and empagliflozin) and 5 glucagon-like peptide-1 (GLP-1) receptor agonists (semaglutide, liraglutide, dulaglutide, lixisenatide, and exenatide), with 5 fixed-dose combination products (SGLT2 inhibitors: dapagliflozin-metformin, canagliflozin-metformin, and empagliflozin-metformin; GLP-1 receptor agonists: liraglutide–insulin degludec and lixisenatide–insulin glargine).
- Data protection has ended for all SGLT2 inhibitors in Canada as well as their fixed-dose combinations. Eleven dapagliflozin generics are currently available, and there are several canagliflozin and empagliflozin generics under review at Health Canada. Patent protection has not expired for GLP-1 receptor agonists.
- There is heterogeneity in public drug program reimbursement criteria for each SGLT2 inhibitor and GLP-1 receptor agonist ranging from restricted to unrestricted benefit.
- This Environmental Scan highlights that as SGLT2 inhibitors and GLP-1 receptor agonists have matured, additional indications (heart failure, chronic kidney disease, weight management) have been added to their initial Health Canada–approved indication (type 2 diabetes mellitus). SGLT2 inhibitors are beginning to lose their exclusivity status and are experiencing generic competition.

Summary

Objective

This Environmental Scan was conducted to document the current landscape in Canada of sodium-glucose cotransporter-2 (SGLT2) inhibitors for the treatment of type 2 diabetes mellitus (T2DM), heart failure (HF), and chronic kidney disease (CKD) as well as glucagon-like peptide-1 (GLP-1) receptor agonists for T2DM and weight management. The scan focuses on the regulatory status, exclusivity status, and reimbursement status of these drugs across Canadian public formularies.

Regulatory Status

- Health Canada has approved 4 SGLT2 inhibitors (ertugliflozin, dapagliflozin, canagliflozin, and empagliflozin) and 5 GLP-1 receptor agonists (semaglutide, liraglutide, dulaglutide, lixisenatide, and exenatide), with 5 fixed-dose combinations products (SGLT2 inhibitors: dapagliflozin-metformin, canagliflozin-metformin, and empagliflozin-metformin; GLP-1 receptor agonists: liraglutide–insulin degludec and lixisenatide–insulin glargine).
- There are currently 3 Health Canada–approved SGLT2 inhibitors: dapagliflozin (Forxiga), canagliflozin (Invokana), and empagliflozin (Jardiance). Ertugliflozin (Steglatro) was cancelled post-market.
    - Each of these drugs have fixed-dose combinations available: dapagliflozin-metformin (Xigduo), canagliflozin-metformin (Invokamet, Invokamet XR), and empagliflozin-metformin (Synjardy).

- All available SGLT2 inhibitors have a Health Canada indication for the treatment of T2DM.
- Dapagliflozin and empagliflozin have a Health Canada indication for the treatment of HF.
- Dapagliflozin has a Health Canada indication for the treatment of CKD.
- There are currently 12 Health Canada–approved GLP-1 receptor agonist–branded products: semaglutide (Ozempic, Rybelsus, Wegovy), liraglutide (Victoza, Saxenda), liraglutide–insulin degludec (Xultophy), dulaglutide (Trulicity), lixisenatide (Adlyxine), lixisenatide–insulin glargine (Soliqua), and exenatide (Byetta, Bydureon, Bydureon BCise).
- All available GLP-1 receptor agonists have a Health Canada indication for the treatment of T2DM.
- Semaglutide and liraglutide have a Health Canada indication for weight management.

Exclusivity Status

- Data protection has ended for all SGLT2 inhibitors in 2023.
- Dapagliflozin generics are currently available, and there are several empagliflozin and canagliflozin generics under review at Health Canada. Patent protection has not expired for all SGLT2 inhibitors and their fixed-dose combinations; the last patent for canagliflozin is in 2031 and empagliflozin in 2034.
- Data protection has ended for liraglutide as well as its fixed-dose combination with insulin degludec (May 2018). Data protection has not expired for the other GLP-1 receptor agonists (semaglutide, dulaglutide, lixisenatide, and lixisenatide–insulin glargine).
- Patent protection has not expired for all GLP-1 receptor agonists and their fixed-dose combinations, with the earliest patent expiry date of November 2024 for liraglutide as well as its fixed-dose combination with insulin degludec.
- There is currently 1 generic version of liraglutide under review at Health Canada.

CADTH Review Status

- Except for ertugliflozin, all available SGLT2 inhibitors and their fixed-dose combinations (except Invokamet XR) have received a recommendation of reimburse with conditions from the Canadian Drug Expert Committee (CDEC) for the T2DM indication. CDEC recommended that ertugliflozin should not be reimbursed as an adjunct to diet and exercise in adult patients with T2DM.
- Dapagliflozin and empagliflozin have received a recommendation of reimburse with conditions from CDEC for the HF indication.
- Semaglutide (Ozempic, Rybelsus), liraglutide–insulin degludec, lixisenatide, and lixisenatide–insulin glargine have received a recommendation of reimburse with conditions from CDEC for the T2DM indication.
- No GLP-1 receptor agonists have received a reimburse recommendation from CDEC for the weight management indication.

Reimbursement Status

- **SGLT2 inhibitors:** Dapagliflozin is an unrestricted benefit in all jurisdictions, excluding Saskatchewan. Canagliflozin is an unrestricted benefit in 4 jurisdictions (Ontario, Veterans Affairs Canada [VAC], Correctional Service of Canada [CSC], and Canadian Armed Forces [CAF]), a restricted benefit in 9 jurisdictions (Alberta, Saskatchewan, Manitoba, New Brunswick, Nova Scotia, Newfoundland and Labrador, Prince Edward Island, Yukon, and Non-Insured Health Benefits [NIHB]), and is not a benefit in British Columbia. Empagliflozin is an unrestricted benefit in 5 jurisdictions (Ontario, NIHB, VAC, CSC, and CAF) and a restricted benefit in 9 jurisdictions (Alberta, British Columbia, Saskatchewan, Manitoba, New Brunswick, Nova Scotia, Newfoundland and Labrador, Prince Edward Island, and Yukon).
- **GLP-1 receptor agonists:** Semaglutide is an unrestricted benefit in 3 jurisdictions (Ontario, NIHB, and VAC) and a restricted benefit in 11 jurisdictions (Alberta, British Columbia, Saskatchewan, Manitoba, New Brunswick, Nova Scotia, Newfoundland and Labrador, Prince Edward Island, Yukon, CSC, and CAF). Lixisenatide is an unrestricted benefit in 3 jurisdictions (Ontario, NIHB, and VAC), a restricted benefit in 7 jurisdictions (Alberta, Saskatchewan, Manitoba, New Brunswick, Nova Scotia, Newfoundland and Labrador, and Prince Edward Island), and is not a benefit in 4 jurisdictions (British Columbia, Yukon, CSC, and CAF). Liraglutide is not a benefit across all jurisdictions included in this Environmental Scan; it received a negative reimbursement recommendation from CADTH, and negotiations with the pan-Canadian Pharmaceutical Alliance (pCPA) concluded without an agreement.

New Indications and Expanding Patient Populations

- This Environmental Scan highlights that as SGLT2 inhibitors and GLP-1 receptor agonists have matured, additional indications (HF, CKD, weight management) have been added to their initial Health Canada–approved indication (T2DM).
- With the entry of dapagliflozin generics in Canada, some public drug programs have made dapagliflozin an unrestricted benefit with reimbursement not limited by clinical criteria. Semaglutide is the primary GLP-1 receptor agonist reimbursed by public drug programs.

Disease and Treatments

SGLT2 inhibitors have been an integral part of the management of T2DM. There are 3 SGLT2 inhibitors publicly reimbursed in Canada: dapagliflozin (Forxiga), canagliflozin (Invokana), and empagliflozin (Jardiance), with several fixed-dose combination drug products also available.[1-5] SGLT2 inhibitors are an oral drug that reduce blood glucose concentrations by inhibiting the reabsorption of glucose in the kidney and facilitating the excretion of glucose in the urine.[6] In addition to the glycemic benefits for T2DM, some SGLT2 inhibitors have been shown to have beneficial cardiovascular and renal effects in patients with overt atherosclerotic cardiovascular disease (CVD), HF, and CKD.[7]

GLP-1 receptor agonists are a newer class of drugs used in the treatment of T2DM. There are 12 brand products of GLP-1 receptor agonists approved by Health Canada: semaglutide (Ozempic, Rybelsus, Wegovy), liraglutide (Victoza, Saxenda), liraglutide–insulin degludec (Xultophy), dulaglutide (Trulicity), lixisenatide (Adlyxine), lixisenatide–insulin glargine (Soliqua), and exenatide (Byetta, Bydureon, Bydureon BCise). GLP-1 receptor agonists are primarily administered via injection or orally, and they increase the production of insulin while also inhibiting glucagon, a hormone responsible for increasing glucose production.[8] In addition to the glycemic benefits of GLP-1 receptor agonists, some GLP-1 receptor agonists have shown benefits on weight management and potentially cardiovascular outcomes.

T2DM is a chronic condition characterized by high blood glucose levels resulting from insufficient insulin secretion or insulin resistance. It is estimated that more than 3 million people in Canada are living with diabetes, and approximately 90% of these people have T2DM.[9] Untreated hyperglycemia can contribute to the development of retinopathy, neuropathy, nephropathy, and CVD. Initial treatment for T2DM focuses on controlling glycemic levels with metformin and lifestyle modifications.[10] Metformin may or may not be used with insulin in the case of symptomatic hyperglycemia or metabolic decompensation. Lifestyle changes include diet, weight reduction, and exercise. If glycemic goals are not achieved with initial treatment, or in cases with contraindications, Diabetes Canada Clinical Practice Guidelines suggest second-line treatment options, including insulin secretagogues, insulins, dipeptidyl peptidase-4 (DPP-4) inhibitors, thiazolidinediones, SGLT2 inhibitors, and GLP-1 receptor agonists.

A body mass index (BMI) of 25 kg/m^2 to 30 kg/m^2 is considered overweight, and a BMI of more than 30 kg/m^2 is considered obese.[11] The Canadian Task Force on Preventive Health Care has reported that 67% of men and 54% of women are living with overweight or obesity in Canada.[12] Weight management is multifaceted and includes physical activity and behaviour modification. If BMI is 30 kg/m^2 or greater or is 27 kg/m^2 with at least 1 comorbidity, drug therapy can include semaglutide, orlistat, liraglutide, and the combination of naltrexone and bupropion.[13]

HF is a condition characterized by structural or functional impairment of ventricular filling or ejection of blood, resulting in the heart's inability to maintain the metabolic demands of tissues and organs.[14] Common symptoms of HF include dyspnea, fatigue, and edema. It is estimated that 750,000 people in Canada are living with HF.[15] The goal of treatment is to reduce symptoms and slow the decline of heart function by reducing, stopping, or reversing the progression of the underlying cause. Pharmacological treatment of HF with reduced ejection fraction includes angiotensin-converting enzyme inhibitors (ACEis), angiotensin II receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists, sacubitril-valsartan, ivabradine, and SGLT2 inhibitors.[16,17]

CKD is defined as abnormalities of kidney structure or function, which have been present for more than 3 months with implications for health.[18] CKD is characterized based on cause, glomerular filtration rate (GFR), and albuminuria category. CKD is characterized by gradual reduction in kidney function and is estimated to affect approximately 10% of adults living in Canada.[19] Decreased kidney function results in excess build up of fluid, electrolytes, and waste in the body. This leads to reduced quality of life and may result in kidney failure and death.[20,21] Treatment aims to reduce the risk of progression of CKD to kidney failure.[22] Pharmacological

therapy for CKD may include ACEis, ARBs, and statins.[23,24] More recently, SGLT2 inhibitors have also demonstrated benefits on renal outcomes in CKD.[25]

In 2018 and 2019, SGLT2 inhibitors were among the top 10 drug classes with the largest contribution to growth in public drug program spending in Canada.[26] In 2019, SGLT2 inhibitors contributed to an increase of $61.5 million in total public program spending, 13.2% of the total program spending growth, and 40% of the annual growth rate. In addition, empagliflozin and semaglutide were in the top 10 list of drugs in 2021.[27] Given that Health Canada indications for SGLT2 inhibitors and GLP-1 receptor agonists have expanded in recent years, both are expected to continue to contribute significantly to drug spending in Canada in the future. This Environmental Scan is to better understand the current reimbursement landscape of SGLT2 inhibitors in Canada for the treatment of T2DM, weight management, HF, and CKD.

Objectives

The objectives of this Environmental Scan were to provide a summary of the following for SGLT2 inhibitors in the treatment of T2DM, HF, and CKD, as well as for GLP-1 receptor agonists for T2DM and weight management:

1. **Regulatory status**: Notice of Compliance (NOC) date, first marketed date, and indications for T2DM, HF, CKD, and weight management
2. **Exclusivity status**: Data protection and patent expiry dates, including potential generic entrants
3. **CADTH review status**: Studies assessed and CDEC reasons for recommendations
4. **Reimbursement status**: Listing status and coverage criteria across federal, provincial, and territorial public drug plans

Methods

The components of the information presented in this scan are presented in Table 1.

Literature Search

A grey literature search was conducted on key resources, including the websites of Health Canada's drug product database, patent register, and data protection register; CADTH website (CADTH Common Drug Review [CDR] records); Canadian public drug plan formulary databases; and clinicaltrials.gov database. No bibliographic literature searches were performed. The public drug plan and Health Canada databases were searched between in November 2023.

Some information presented in this report was not available in the public domain and was obtained through personal communication with members of the CADTH Formulary Working Group Health Technology Assessment (FWG-HTA) committee.[28] In these cases, permission was obtained to publish this information in this report, and all details obtained through personal communication were referenced accordingly (Alka

Bhalla, Pharmacist, Correctional Services Canada, Ottawa, ON: personal communication, Nov 16, 2023). Information from 4 federal public drug plans was included: NIHB, CSC, VAC, and CAF. Publicly reimbursed medications for residents of Nunavut and the Northwest Territories follow the coverage category and reimbursement criteria of the NIHB program.[29,30]

Table 1: Components for Literature Screening and Information Gathering

Component	Description
Population	Patients with type 2 diabetes mellitus, heart failure, and chronic kidney disease; patients requiring weight management
Intervention	**SGLT2 inhibitors:** • dapagliflozin (Forxiga) • dapagliflozin-metformin (Xigduo) • dapagliflozin-saxagliptin (Qtern) • canagliflozin (Invokana) • canagliflozin-metformin (Invokamet, Invokamet XR) • empagliflozin (Jardiance) • empagliflozin-metformin (Synjardy) • empagliflozin-linagliptin (Glyxambi) **GLP-1 receptor agonists:** • semaglutide (Ozempic, Rybelsus, Wegovy) • liraglutide (Victoza, Saxenda) • liraglutide–insulin degludec (Xultophy) • dulaglutide (Trulicity) • lixisenatide (Adlyxine) • lixisenatide–insulin glargine (Soliqua) • exenatide (Byetta, Bydureon, Bydureon BCise)
Settings	**Canadian publicly funded drug plans** **Provincial and territorial plans:** • Alberta Drug Benefit List • British Columbia Pharmacare Formulary • Manitoba Pharmacare Drug Formulary • New Brunswick Drug Plans Formulary • Newfoundland and Labrador Prescription Drug Program Formulary • Nova Scotia Pharmacare Formulary • Ontario Drug Benefit Formulary • Prince Edward Island Pharmacare Formulary • Saskatchewan Drug Plan Formulary • Yukon Drug Program Formulary **Federal plans:** • Canadian Armed Forces Drug Benefit List • Correctional Service Canada National Formulary • Non-Insured Health Benefits Drug Benefit List (also applicable to Nunavut and the Northwest

Component	Description
	Territories) • Veterans Affairs Canada Drug Formulary
Types of Information	• Regulatory information including NOC dates, first marketed date, and indications • Data protection and patent expiry dates • CADTH Reimbursement Review status and reason for CDEC recommendations • pCPA negotiation status • Formulary listing status and coverage criteria across Canadian federal, provincial, and territorial drug plans ◦ Coverage categories: Special Authorization, Exceptional Access Program, Exceptional Drug Status, Limited Use, Limited Coverage Drug, Prior Authorization ◦ Coverage criteria: clinical criteria

CDEC = Canadian Drug Expert Committee; GLP-1 = glucagon-like peptide-1; NOC = Notice of Compliance; pCPA = pan-Canadian Pharmaceutical Alliance; SGLT2 = sodium-glucose cotransporter-2.

Exclusions

This Environmental Scan focused on the 3 current SGLT2 inhibitors publicly reimbursed in Canada: canagliflozin (Invokana), dapagliflozin (Forxiga), and empagliflozin (Jardiance), along with available fixed-dose combinations of these drugs. Other SGLT2 inhibitors were excluded from the report. Private payers and Quebec's public drug program, the Régie de l'assurance maladie du Québec, were excluded. Although the clinical and economic basis for a CADTH reimbursement recommendation for SGLT2 inhibitors and GLP-1 receptor agonists are included in the report, this Environmental Scan did not assess the comparative clinical effectiveness or the relative cost-effectiveness of the drugs used in the treatment of patients with T2DM, HF, CKD, or weight loss. Thus, any conclusions or recommendations about the value of these medications or their place in therapy were outside of the scope of the Environmental Scan.

Findings

Objective 1: Regulatory Status

SGLT2 Inhibitors

Health Canada has approved 6 SGLT2 inhibitors and fixed-dose combination products for the treatment of T2DM, including dapagliflozin, dapagliflozin-metformin, canagliflozin, canagliflozin-metformin, empagliflozin, and empagliflozin-metformin. Detailed regulatory information for SGLT2 inhibitors, including NOC dates, first marketed date, and their approved indications are presented in Appendix 1. Figure 1 shows the Health Canada approval timeline for SGLT2 inhibitors by marketed date as well as the NOC dates of their indication for T2DM, HF, and CKD.

All SGLT2 inhibitors (dapagliflozin, canagliflozin, empagliflozin) are indicated as monotherapy for T2DM, but only when metformin is ineffective or contraindicated. SGLT2 inhibitors may be used to improve glycemic control as an add-on therapy in adult patients when combined with metformin, a sulfonylurea, insulin,

sitagliptin (dapagliflozin), pioglitazone (canagliflozin and empagliflozin), and linagliptin (empagliflozin). Drugs that combine SGLT2 inhibitors and metformin are indicated for T2DM in patients who are already treated with some combination of SGLT2 inhibitor, metformin, a sulfonylurea, insulin, sitagliptin (dapagliflozin), and pioglitazone (canagliflozin and empagliflozin). Dapagliflozin is also indicated as an adjunct to diet, exercise, and standard care therapy in patients with T2DM and cardiovascular risk factors or established CVD. Canagliflozin is also indicated as an adjunct to diet, exercise, and standard-of-care therapy in patients with T2DM and established CVD or diabetic nephropathy. Empagliflozin is also indicated as an adjunct to diet, exercise, and standard-of-care therapy in patients with T2DM and established CVD.

Health Canada has approved 2 SGLT2 inhibitors (dapagliflozin and empagliflozin) for the treatment of HF. Dapagliflozin is indicated for the treatment of HF with reduced ejection fraction to reduce the risk of cardiovascular death, hospitalization for HF, and urgent HF visit. Empagliflozin is indicated as an adjunct to standard-of-care therapy for the treatment of chronic HF.

The only SGLT2 inhibitor with a Health Canada indication for the treatment of CKD is dapagliflozin. Dapagliflozin is indicated to reduce the risk of estimated GFR (eGFR) decline, end-stage kidney disease, and cardiovascular and renal death.

Dapagliflozin is the only SGLT2 inhibitor that has a Health Canada indication for T2DM, HF, and CKD.

Fixed-dose combination drugs that comprise SGLT2 inhibitors and DPP-4 inhibitors are not currently on the Canadian market and will not be discussed further in this Environmental Scan.

Health Canada has noted that the safety and efficacy of SGLT2 inhibitors have not been established in the pediatric population, and therefore are not indicated for patients younger than 18 years. Higher rates of adverse reactions have also been found for the older patients and therefore SGLT2 inhibitors should be used with caution for patients aged 65 years or older.

GLP-1 Receptor Agonists

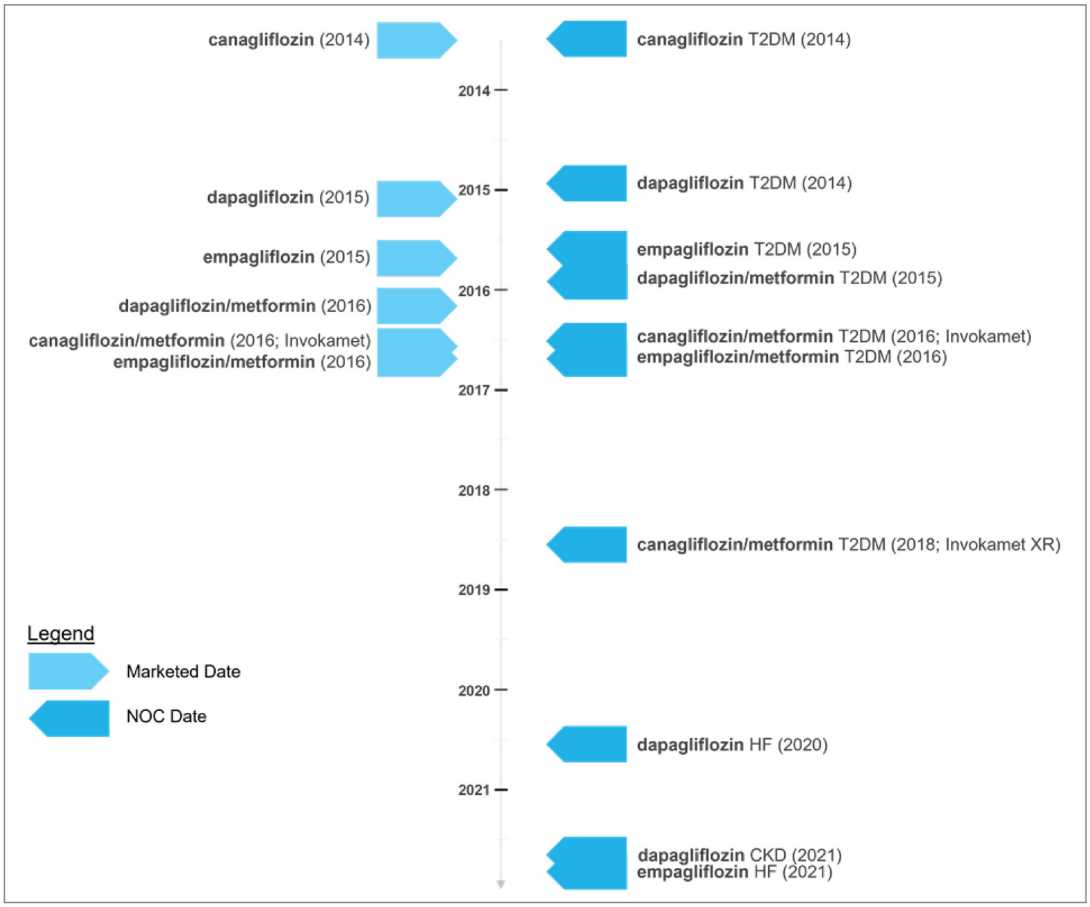
Health Canada has approved 6 GLP-1 receptor agonists and fixed-dose combination products for the treatment of T2DM and weight management, including semaglutide, liraglutide, liraglutide–insulin degludec, dulaglutide, lixisenatide, and lixisenatide–insulin glargine. Detailed regulatory information for GLP-1 receptor agonists, including NOC dates, first marketed date, and their approved indications are presented in Appendix 2. Figure 2 shows the Health Canada approval timeline for GLP-1 receptor agonists by marketed date and NOC date.

The GLP-1 receptor agonist exenatide (Byetta, Bydureon, Bydureon BCise) is not currently on the Canadian market and will not be discussed further in this Environmental Scan.

Except for liraglutide, GLP-1 receptor agonists are not indicated for patients younger than 18 years, and Health Canada has noted that safety and efficacy have not been established in the pediatric population. Liraglutide (Victoza) is indicated for patients with T2DM who are 10 years or older as an adjunct to metformin with or without basal insulin when glycemic levels are not within target rang on maximal dose of metformin combined with diet and exercise. Another liraglutide (Saxenda) has been approved for use in

pediatric patients 12 years and older. Health Canada has noted that GLP-1 receptor agonists should be used with caution in patients aged 65 years or older, because greater sensitivity cannot be ruled out.

Figure 1: Health Canada Approval Timeline for SGLT2 Inhibitors by Marketed Date and NOC Dates for T2DM, HF, and CKD Indications

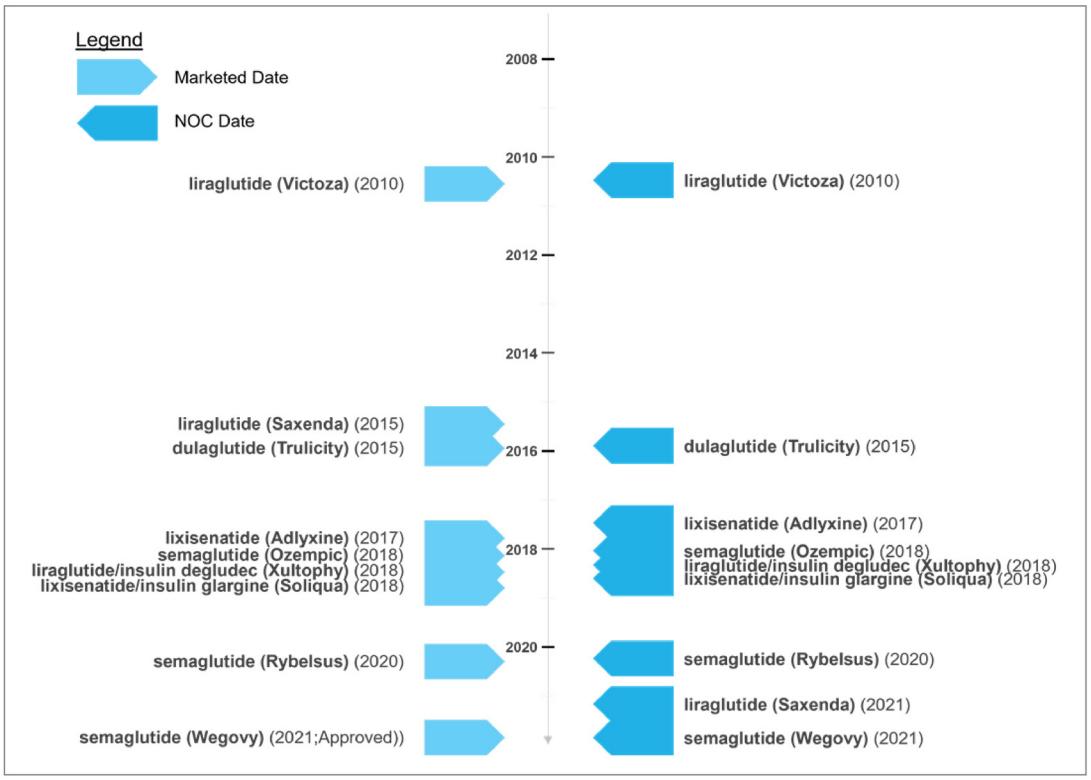


CKD = chronic kidney disease; HF = heart failure; NOC = Notice of Compliance; SGLT2 = sodium-glucose cotransporter-2; T2DM = type 2 diabetes mellitus.

Objective 2: Exclusivity Status

Exclusivity status is a function of patent and data protection. Patent protection is a 20-year period offered to innovative drugs from the date of filing that can be applied in various manners (e.g., chemical, change in use). Data protection regulations in Canada are governed by regulations under the Food and Drug Regulations published in 2006.[31,32] These regulations provide data protection for an 8-year term with a possibility of adding 6 more months for submissions that include pediatric studies. During this time, only the owner or generator of preclinical and clinical trial data can use these data to obtain marketing authorization for drugs, effectively preventing a second-entry manufacturer from filing a submission for a copy of that innovative drug. Data protection begins from the time of issuance of NOC by Health Canada and when the drug is added to the Health Canada's Register of Innovative Drugs.[31,32]

Figure 2: Health Canada Approval Timeline for GLP-1 Receptor Agonists by Marketed Date and NOC Dates



GLP-1 = glucagon-like peptide-1; NOC = Notice of Compliance.

SGLT2 Inhibitors

Exclusivity status for SGLTS inhibitors, including data protection expiry date and patent end date, is presented in Table 2. As of this Environmental Scan, data protection has ended for dapagliflozin and canagliflozin as well as their fixed-dose combination drugs with metformin. Data protection for empagliflozin and its fixed-dose combination drug with metformin has not expired. Patent end dates for all SGLT2 inhibitors have not expired. There are currently 2 generic dapagliflozin drugs under review at Health Canada. Similarly, 3 generic versions of canagliflozin, 8 generic versions of empagliflozin, and 1 generic version of empagliflozin-metformin were identified to be under review at Health Canada. Of the approved generic products, 15 dapagliflozin generic drugs have been already issued approval, 11 of which are currently marketed in Canada.

GLP-1 Receptor Agonists

Exclusivity status for GLP-1 receptor agonists, including data protection expiry date and patent end date, can be found in Table 3. As of this Environmental Scan, data protection has ended for liraglutide as well as its fixed-dose combination with insulin degludec. Data protection has not expired for semaglutide, dulaglutide, lixisenatide, and lixisenatide–insulin glargine. Patent end dates for all GLP-1 receptor agonists have not expired. There is currently 1 generic version of liraglutide under review at Health Canada.

Table 2: Status of Data Protection and Patent Expiry for SGLT2 Inhibitors

Generic name	Brand name	Data protection expiry date	Pediatric extension	Data protection ended (yes/no)	Patent end date (for longest filed)	Patent expired (yes/no)
Dapagliflozin	Forxiga	December 12, 2022	NA	Yes	March 21, 2028	No
Dapagliflozin-metformin	Xigduo	December 12, 2022	NA	Yes	November 12, 2030	No
Canagliflozin	Invokana	May 23, 2022	NA	Yes	May 11, 2031	No
Canagliflozin-metformin	Invokamet	May 23, 2022	NA	Yes	July 7, 2030	No
	Invokamet XR	May 23, 2022	NA	Yes	May 11, 2031	No
Empagliflozin	Jardiance	July 23, 2023	NA	Yes	April 16, 2034	No
Empagliflozin-metformin	Synjardy	July 23, 2023	NA	Yes	April 3, 2034	No

SGLT2 = sodium-glucose cotransporter-2.

Table 3: Status of Data Protection and Patent Expiry for GLP-1 Receptor Agonists

Generic name	Brand name	Data protection expiry date	Pediatric extension	Data protection ended (yes/no)	Patent end date (for longest filed)	Patent expired (yes/no)
Semaglutide	Ozempic	January 4, 2026	NA	No	March 20, 2026	No
	Rybelsus	January 4, 2026	NA	No	March 20, 2026	No
	Wegovy	January 4, 2026	NA	No	March 20, 2026	No
Liraglutide	Victoza	May 21, 2018	NA	Yes	November 18, 2024	No
	Saxenda	May 21, 2018	NA	Yes	November 18, 2024	No
Liraglutide–insulin degludec	Xultophy	May 21, 2018	NA	Yes	November 18, 2024	No
Dulaglutide	Trulicity	November 10, 2023	NA	No	September 25, 2039	No
Lixisenatide	Adlyxine	May 25, 2025	NA	No	October 26, 2032	No
Lixisenatide–insulin glargine	Soliqua	May 25, 2025	NA	No	October 26, 2032	No

GLP-1 = glucagon-like peptide-1.

Objective 3: CADTH Review Status

SGLT2 Inhibitors

CADTH review status and CDEC or Formulary Management Expert Committee (FMEC) recommendations for SGLT2 inhibitors are presented in Table 4, and a summary of the CDEC or FMEC recommendations for patients with T2DM, HF, and CKD are presented in Appendix 3.

CDEC recommendations for SGLT2 inhibitors as treatment for T2DM is to list with clinical and/or conditions. Dapagliflozin is recommended to be added on to treatment for patients with T2DM who have inadequate glycemic control on metformin or a sulfonylurea, and for whom insulin is not an option. It is also recommended to be added on to treatment for patients with T2DM who have inadequate glycemic control on insulin with metformin or insulin without metformin when metformin is contraindicated or not tolerated. Canagliflozin and empagliflozin are recommended to be added on to metformin and a sulfonylurea for patients with T2DM and inadequate glycemic control on metformin and a sulfonylurea, and for whom insulin is not an option. The cost condition associated with the recommendations for dapagliflozin, canagliflozin, and empagliflozin is that the drug plan cost of treatment should not exceed the drug plan cost of treatment with the least costly option within the SGLT2 inhibitor and DPP-4 inhibitor classes.

SGLT2 inhibitor and metformin fixed-dose combination drugs for patients with T2DM are recommended to be reimbursed with clinical criteria and/or conditions for patients with T2DM (except for Invokamet XR). Dapagliflozin-metformin is recommended to be reimbursed for patients with T2DM who are already stabilized on therapy with dapagliflozin and metformin separately. These patients should also have inadequate glycemic control on metformin (or metformin and insulin), a contraindication or intolerance to a sulfonylurea, and insulin is not an option for them. Canagliflozin-metformin is recommended to be reimbursed for patients with T2DM who have inadequate glycemic control on metformin and a sulfonylurea, and for whom insulin is not an option, and who are already stabilized on treatment with canagliflozin and metformin separately. Empagliflozin-metformin is recommended to be reimbursed for patients with T2DM who are eligible to receive empagliflozin and metformin separately based on participating drug plan reimbursement criteria. For all 3 SGLT2 inhibitor and metformin fixed-dose combination drugs, the drug plan costs for the fixed-dose combination should not exceed the combined cost of the SGLT2 inhibitor and metformin administered separately.

CDEC also recommends that dapagliflozin and empagliflozin be reimbursed for HF with clinical criteria and/or conditions as an adjunct for standard-of-care therapy in adults with New York Heart Association (NYHA) class II and III heart failure. Standard-of-care therapies include beta-blockers, ACEis or ARBs, or a mineralocorticoid receptor antagonist. Empagliflozin should only be reimbursed if the price is less costly than dapagliflozin for the treatment of chronic HF.

Recently, FMEC recommended that dapagliflozin be reimbursed for CKD in patients who meet the diagnostic criteria for CKD (eGFR 25 mL/minute/1.73 m^2 to 75 mL/minute/1.73 m^2) with a urine albumin-to-creatinine ratio of 200 mg/g to 5,000 mg/g and treated with an ACEi or ARB at the maximum-tolerated dose.

Table 4: CADTH Review Status and CDEC or FMEC Recommendation for SGLT2 Inhibitors

Generic name	Brand name	CADTH review for T2DM	CDEC or FMEC recommendation for T2DM (date of publication)	CADTH review for HF	CDEC or FMEC recommendation for HF (date of publication)	CADTH review for CKD	CDEC or FMEC recommendation for CKD (date of publication)
Dapagliflozin	Forxiga	Yes	List with clinical criteria and/or conditions	Yes	Reimburse with clinical criteria and/or conditions	Yes	Reimburse with clinical criteria and/or conditions
Dapagliflozin-metformin	Xigduo	Yes	Reimburse with clinical criteria and/or conditions	No	NA	NA	NA
Canagliflozin	Invokana	Yes	List with criteria/condition	No	NA	NA	NA
Canagliflozin-metformin	Invokamet	Yes	Reimburse with clinical criteria and/or conditions	No	NA	NA	NA
	Invokamet XR	No	NA	No	NA	NA	NA
Empagliflozin	Jardiance	Yes	List with clinical criteria and/or conditions	No	Reimburse with clinical criteria and/or conditions	NA	NA
Empagliflozin-metformin	Synjardy	Yes	Reimburse with clinical criteria and/or conditions	No	NA	NA	NA

CDEC = Canadian Drug Expert Committee; CKD = chronic kidney disease; FMEC = Formulary Management Expert Committee; HF = heart failure; NA = not applicable; SGLT2 = sodium-glucose cotransporter-2; T2DM = type 2 diabetes mellitus.

GLP-1 Receptor Agonists

CADTH review status and CDEC recommendations for GLP-1 receptor agonists are presented in Table 5, and summary of CDEC recommendations are presented in Appendix 4.

CDEC recommended not to list liraglutide (Victoza) as treatment for T2DM. For all other GLP-1 receptor agonists, CDEC recommendations for the treatment of T2DM is to reimburse with clinical criteria and/or conditions. Semaglutide (Ozempic) is recommended to be reimbursed for treatment with metformin when diet and exercise combined with metformin do not adequately control glycemic levels. It should not be reimbursed as add-on therapy to metformin and another antihyperglycemic drug. The cost for semaglutide should not exceed the least costly reimbursed drug that can be used when metformin alone cannot adequately control glycemic levels. Oral semaglutide (Rybelsus) is recommended to be reimbursed as an adjunct to diet and exercise in addition to metformin when glycemic control is not achieved with metformin alone or in addition to other antihyperglycemic agents. The drug plan cost of Rybelsus should not exceed the least costly treatment with GLP-1 receptor agonists, DPP-4 inhibitors, or SGLT2 inhibitors. CDEC recommended that dulaglutide be reimbursed for treatment in combination with metformin, or with metformin and sulfonylurea, as long as the drug plan cost does not exceed the least costly pharmacotherapy reimbursed in combination with metformin or metformin and a sulfonylurea. Lixisenatide is recommended

as an adjunct to diet and exercise in addition to basal insulin with or without metformin if the drug plan cost for lixisenatide does not exceed the least costly pharmacotherapy reimbursed for basal insulin with or without metformin.

Table 5: CADTH Review Status and CDEC Recommendation for GLP-1 Receptor Agonists

Generic name	Brand name	CADTH review for T2DM	CDEC recommendation for T2DM (date of publication)	CADTH review for weight management	CDEC recommendation for weight management (date of publication)
Semaglutide	Ozempic	Yes	Reimburse with clinical criteria and/or conditions	NA	NA
	Rybelsus	Yes	Reimburse with clinical criteria and/or conditions	NA	NA
	Wegovy	NA	NA	Yes	Do not reimburse
Liraglutide	Victoza	Yes	Do not list	NA	NA
	Saxenda	NA	NA	Yes	Do not reimburse
Liraglutide–insulin degludec	Xultophy	Yes	Reimburse with clinical criteria and/or conditions	NA	NA
Dulaglutide	Trulicity	Yes	Reimburse with clinical criteria and/or conditions	NA	NA
Lixisenatide	Adlyxine	Yes	Reimburse with clinical criteria and/or conditions	NA	NA
Lixisenatide–insulin glargine	Soliqua	Yes	Reimburse with clinical criteria and/or conditions	NA	NA

CDEC = Canadian Drug Expert Committee; GLP-1 = glucagon-like peptide-1; NA = not applicable; T2DM = type 2 diabetes mellitus.

Liraglutide–insulin degludec is recommended to be reimbursed for T2DM treatment as an adjunct to lifestyle changes in addition to metformin with or without sulfonylurea when these, combined with basal insulin, do not provide adequate control of glycemic levels. However, liraglutide–insulin degludec should be discontinued if glycemic control is not achieved at maximum dose (1.8 mg of liraglutide and 50 units of insulin degludec) after 26 weeks of treatment. Cost for this drug should also not exceed the least costly GLP-1 receptor agonist and least costly basal insulin administered separately or in combination. CDEC recommends that lixisenatide–insulin glargine be reimbursed for T2DM treatment as an adjunct to diet and exercise if the drug plan cost does not exceed the combined costs of lixisenatide and insulin glargine provided separately.

For weight management, CDEC recommendations for semaglutide (Wegovy) and liraglutide (Saxenda) are to do not reimburse.

Objective 4: Reimbursement Status

Negotiated Agreements

The pCPA was formed in 2010 for public drug plans to work together when entering negotiations with manufacturers for pharmaceuticals from which, if successful, a letter of intent (LOI) was created. The LOI

lists the terms and conditions for funding a drug and is used to create a product listing agreement between each participating member jurisdiction and the manufacturer.[30]

SGLT2 Inhibitors

Information on the pCPA negotiation status of SGLT2 inhibitors for T2DM, HF, and CKD can be found in Table 6. All SGLT2 inhibitors and metformin fixed-dose combination drugs have concluded with a LOI for T2DM. Dapagliflozin is the only SGLT2 inhibitor to conclude with an LOI for HF, while empagliflozin is under active negotiation. No LOIs have been negotiated for the CKD indication.

Table 6: Overview of the pCPA Negotiation Status of SGLT2 Inhibitors

Generic name	Brand name	Status of T2DM indication	Status of HF indication	Status of CKD indication
Dapagliflozin	Forxiga	Concluded with an LOI October 3, 2016	Concluded with an LOI November 18, 2021	NA
Dapagliflozin-metformin	Xigduo	Concluded with an LOI June 13, 2017	NA	NA
Canagliflozin	Invokana	Concluded with an LOI July 2, 2015	NA	NA
Canagliflozin-metformin	Invokamet	Concluded without agreement October 20, 2017	NA	NA
	Invokamet XR	NA	NA	NA
Empagliflozin	Jardiance	Concluded with an LOI September 11, 2018	Under consideration for negotiation	NA
Empagliflozin-metformin	Synjardy	Concluded with an LOI September 11, 2018	NA	NA

CKD = chronic kidney disease; HF = heart failure; LOI = letter of intent; NA = not applicable; pCPA = pan-Canadian Pharmaceutical Alliance; SGLT2 = sodium-glucose cotransporter-2; T2DM = type 2 diabetes mellitus.

GLP-1 Receptor Agonists

Table 7 shows the information on the pCPA negotiation status of GLP-1 receptor agonists for T2DM and weight management. Semaglutide (only Ozempic), lixisenatide, and lixisenatide–insulin glargine have concluded with a LOI for T2DM.

Table 7: Overview of the pCPA Negotiation Status of GLP-1 Receptor Agonists

Generic name	Brand name	Status of T2DM indication	Status of weight management indication
Semaglutide	Ozempic	Concluded with an LOI July 26, 2019 pCPA engagement letter also issued October 30, 2023	NA
	Rybelsus	Concluded without agreement December 20, 2022 pCPA engagement letter also issued November 7, 2023	NA

Generic name	Brand name	Status of T2DM indication	Status of weight management indication
	Wegovy	NA	Negotiations were not pursued October 25, 2022
Liraglutide	Victoza	Concluded without agreement March 29, 2019	NA
	Saxenda	NA	Negotiations were not pursued November 22, 2021
Liraglutide–insulin degludec	Xultophy	Concluded without agreement April 26, 2021	NA
Dulaglutide	Trulicity	Concluded without agreement September 27, 2019	NA
Lixisenatide	Adlyxine	Concluded with an LOI November 21, 2019	NA
Lixisenatide–insulin glargine	Soliqua	Concluded with an LOI November 21, 2019	NA

GLP-1 = glucagon-like peptide-1; LOI = letter of intent; NA = not applicable; pCPA = pan-Canadian Pharmaceutical Alliance; T2DM = type 2 diabetes mellitus.

Formulary Listing Status

The current process for formulary listings begins with an LOI, which leads to product listing agreements with individual drug plans. However, not all drugs achieve the LOI stage; when they do, not all LOIs lead to successful product listing agreements with jurisdictions. Some jurisdictions can choose to not participate in a negotiation, or formulary listings may take longer if the drug is not a priority.[33]

Type of Listing Status

Public drug plans list prescription medicines according to specific coverage categories that can be broadly classified as a restricted or unrestricted benefit. *Unrestricted benefit* refers to drugs with usage that is not limited by clinical criteria requiring authorization before drug plan coverage. Depending on the public drug plan, this type of formulary benefit status (coverage category) is referred to as benefit, open benefit, standard benefit, general benefit, or regular benefit. *Restricted benefit* refers to drugs with usage limited by specific clinical criteria or to a defined patient subgroup. Depending on the public drug plan, this type of formulary benefit status is categorized under Special Authorization, Exceptional Access Program, Exceptional Drug Status or Exception Status Drug, Limited Use, Limited Coverage Drug, or Prior Authorization.[34] The restricted benefit categories can be further classified by the following reimbursement processes:

> **Restricted Benefit – Active:** Special Authorization or Limited Coverage Drug (British Columbia), Special Authorization (Alberta, New Brunswick, Newfoundland and Labrador, Prince Edward Island, VAC, CAF), Exceptional Drug Status or Exception Status drug (Saskatchewan, Manitoba, Nova Scotia, Yukon), Exceptional Access Program (Ontario), or limited use (NIHB). Application for public reimbursement with the required clinical details must be made by the authorized prescriber using established processes (e.g., use of specific authorization forms). Each request is subject to a medication review by staff responsible for claims adjudication for the public drug plan.[35-48]
>
> **Restricted Benefit – Passive:** Limited Use (Ontario) and Benefit with Criteria Medications (CSC). In comparison with Restricted Benefit – Active, the use of specific authorization forms and a medication review is not a requirement. Rather, a Limited Use code (Ontario) or a Reason for Use code (CSC)

must be specified in the prescription.[48,49]

SGLT2 Inhibitors

The formulary listing status for SGLT2 inhibitors in each jurisdiction of interest are presented in Table 8.

Dapagliflozin (Forxiga)

Dapagliflozin is an unrestricted benefit in the following jurisdictions of Alberta, British Columbia, Manitoba, Ontario, New Brunswick, Nova Scotia, Newfoundland and Labrador, Prince Edward Island, VAC, CSC, and CAF. For patients with T2DM for whom insulin is not an option, Ontario's therapeutic notes allows dapagliflozin to be added on to metformin when there is inadequate glycemic control on metformin and there is a contraindication or intolerance to sulfonylurea, or vice versa. For patients with NYHA class II and III HF, Ontario's therapeutic notes allows dapagliflozin to be used as an adjunct to standard-of-care therapy, which includes beta-blockers, ACEis or ARBs, and an MRA.

Type 2 Diabetes

Restricted benefit: In Saskatchewan, special access may be given to patients with T2DM whose glycemic levels are within the target range, or who are intolerant to, metformin and a sulfonylurea.

Heart Failure

Restricted benefit: As an add-on therapy, Saskatchewan requires a reduced left ventricular ejection fraction less than or equal to 40% and NYHA class II or III HF symptoms. Standard therapy includes a stable dose of an ACEi or ARB, a beta-blocker, or an MRA.

Dapagliflozin-Metformin (Xigduo)

Dapagliflozin-metformin is an unrestricted benefit in British Columbia, Ontario, NIHB, VAC, and CSC. Ontario's therapeutic notes require patients with T2DM to be stabilized on therapy with individual components, to replace the individual components for patients who have inadequate glycemic control on metformin, a contraindication or intolerance to sulfonylurea, and for whom insulin is not an option.

Type 2 Diabetes

Restricted benefit: Three drug plans (New Brunswick, Yukon, CAF) require patients to be stabilized on therapy with individual components. Nova Scotia requires the same criteria in addition to insulin not being an option for the patient. In Prince Edward Island, special access may be granted for the treatment of patients with T2DM when already stabilized on therapy with dapagliflozin, metformin, as well as a sulfonylurea, and for whom insulin is not an option. Special access may also be granted to patients with T2DM in Alberta with inadequate glycemic control on a sufficient trial of metformin who are intolerant to sulfonylurea, or vice versa, and for whom insulin is not an option. Saskatchewan requires patients with T2DM who do not have stable glucose levels, or who are intolerant to, metformin and a sulfonylurea. Similar criteria exist for Newfoundland and Labrador, provided patients are not using insulin. Manitoba requires the patient to be stabilized on therapy with the combination of metformin and dapagliflozin, linagliptin, saxagliptin, or sitagliptin as separate components.

Canagliflozin (Invokana)

Canagliflozin is an unrestricted benefit in Ontario, and with VAC, CAF, and CSC. Ontario's therapeutic notes require that patients with T2DM on maximally tolerated doses of metformin have inadequate glycemic control (hemoglobin A1c > 0.07) and either a contraindication or intolerance to sulfonylurea, or on maximal doses of sulfonylurea and for whom insulin is not an option.

Type 2 Diabetes

Restricted benefit: Three drug plans (Saskatchewan, New Brunswick, NIHB) require that the patient be inadequately controlled on, or intolerant to, metformin and a sulfonylurea. As an add-on therapy, Newfoundland and Labrador requires intolerance to and/or inadequate glycemic control on metformin and sulfonylurea in patients not using insulin. Similarly, as an add-on therapy, 5 jurisdictions (Alberta, Manitoba, Nova Scotia, Prince Edward Island, Yukon) require intolerance to and/or inadequate glycemic control on metformin and sulfonylurea for those whom insulin in not an option.

Canagliflozin-Metformin (Invokamet-Invokamet XR)

Canagliflozin-metformin (only Invokamet) is an unrestricted benefit for CSC Health Services.

Type 2 Diabetes

Restricted benefit: Canagliflozin-metformin is not a benefit in the jurisdictions included in this Environmental Scan, except for CSC Health Services and CAF. CAF requires stabilization on therapy with canagliflozin and metformin as separate components.

Empagliflozin (Jardiance)

Empagliflozin is an unrestricted benefit in Ontario, NIHB, VAC, CSC, and CAF. Ontario's therapeutic notes require that patients with T2DM on maximally tolerated doses of metformin have inadequate glycemic control (hemoglobin A1c > 0.07) and either a contraindication or intolerance to sulfonylurea, or on maximal doses of sulfonylurea and for whom insulin is not an option. In patients with T2DM and established CVD who have inadequate glycemic control (hemoglobin A1c > 0.07) after an adequate trial of metformin, Ontario also allows empagliflozin to be used as an adjunct to diet, exercise, and standard-of-care therapy to reduce cardiovascular death.

Type 2 Diabetes

Restricted benefit: British Columbia requires inadequate glycemic control on the maximum-tolerated dose of metformin. Saskatchewan requires that glycemic control in patients with T2DM are not adequately controlled on, or are intolerant to, metformin and a sulfonylurea. Yukon requires that glycemic control in patients with T2DM are not adequately on maximum-tolerated doses of dual therapy of metformin and a sulfonylurea, or metformin and insulin. As an add-on therapy, for patients not using insulin Newfoundland and Labrador requires inadequate glycemic control on metformin and a sulfonylurea. Similarly, as an add-on therapy, 3 drug plans (Alberta, Nova Scotia, Prince Edward Island) require inadequate glycemic control on metformin and a sulfonylurea for those for whom insulin is not an option. As an add-on to metformin and a sulfonylurea, New Brunswick requires inadequate glycemic control on metformin and a sulfonylurea.

Type 2 Diabetes and Established CVD

Restricted benefit: Eight drug plans (Alberta, Saskatchewan, Manitoba, New Brunswick, Nova Scotia, Prince Edward Island, Yukon, Newfoundland and Labrador) allow special authorization to patients with T2DM and established CVDs who have inadequate glycemic control on metformin for empagliflozin to reduce the incidence of cardiovascular death.

Empagliflozin-Metformin (Synjardy)

Empagliflozin-metformin is an unrestricted benefit in Ontario, NIHB, VAC, and CSC. Ontario's therapeutic notes require that patients with T2DM on maximally tolerated doses of metformin have inadequate glycemic control (hemoglobin A1c > 0.07) and either a contraindication or intolerance to sulfonylurea, or on maximal doses of sulfonylurea and for whom insulin is not an option. In patients with T2DM and established CVD who have inadequate glycemic control (hemoglobin A1c > 0.07) after an adequate trial of metformin, Ontario also allows empagliflozin-metformin to be used as an adjunct to diet, exercise, and standard-of-care therapy to reduce CV death.

Type 2 Diabetes

Restricted benefit: British Columbia provides special authorization in patients that have inadequate glycemic control on the maximum-tolerated dose of metformin. Saskatchewan requires that patients are not adequately controlled on, or are intolerant to, metformin and a sulfonylurea. Alberta requires patients have intolerance to and/or inadequate glycemic control on metformin and a sulfonylurea, and in whom insulin is not an option. Similarly, Newfoundland and Labrador require patients have intolerance to and/or inadequate glycemic control on metformin and a sulfonylurea and are not using insulin. Six drug plans (Manitoba, New Brunswick, Nova Scotia, Prince Edward Island, Yukon, CAF) allow special authorization in patients stabilized on therapy with empagliflozin and metformin as separate components.

Type 2 Diabetes and Established CVD

Restricted benefit: Alberta and Saskatchewan allow special authorization to patients with T2DM and established CVDs who have inadequate glycemic control on metformin to reduce the incidence of cardiovascular death.

GLP-1 Receptor Agonists

The formulary listing status for GLP-1 receptor agonists in each jurisdiction of interest are presented in Table 9.

Table 8: Overview of Listing Status for SGLT2 Inhibitors for T2DM

Generic name	Brand name	AB	BC	SK	MB	ON	NB	NS	NL	PEI	YK	NIHB	VAC	CSC[a]	CAF
Dapagliflozin	Forxiga	RB	UB	EDS	RB	UB	RB	RB	OB	GB	RB	UB	UB	OB	UB
Dapagliflozin plus metformin	Xigduo	RB	NAB	EDS	EDS	UB	SA	EDS	SA	SA	EDS	UB	UB	OB	SA
Canagliflozin	Invokana	SA	—	EDS	EDS	UB	SA	EDS	SA	SA	EDS	LU	UB	OB	UB
Canagliflozin-metformin	Invokamet	NAB[a]	NAB[a]	—	—	—	—	—	—	—	—	—	—	OB	SA[a]
	Invokamet XR	—	—	—	—	—	—	—	—	—	—	—	—	—	SA
Empagliflozin	Jardiance	SA	SA	EDS	EDS	UB	SA	EDS	SA	SA	EDS	UB	UB	OB	UB
Empagliflozin-metformin	Synjardy	SA	SA	EDS	EDS	UB	SA	EDS	SA	SA	EDS	UB	UB	OB	SA

AB = Alberta; BC = British Colombia; CAF = Canadian Armed Forces; CSC = Correctional Service of Canada; EDS = Exception Drug Status; GB = general benefit; LU = Limited Use; MB = Manitoba; NAB = not a benefit; NB = New Brunswick; NIHB = Non-Insured Health Benefits; NL = Newfoundland and Labrador; NS = Nova Scotia; OB = open benefit; ON = Ontario; PEI = Prince Edward Island; SA = Special Authorization; SGLT2 = sodium-glucose cotransporter-2; SK = Saskatchewan; T2DM = type 2 diabetes mellitus; RB = regular benefit; UB = unrestricted benefit; VAC = Veterans Affairs Canada; YK = Yukon

[a]Applies to the following canagliflozin-metformin combinations: canagliflozin 50 mg–metformin 500 mg, canagliflozin 50 mg–metformin 1,000 mg, canagliflozin 150 mg–metformin 500 mg, canagliflozin 150 mg–metformin 1,000 mg; otherwise not applicable (—).

Table 9: Overview of Listing Status for GLP-1 Receptor Agonists

Generic name	Brand name	AB	BC	SK	MB	ON	NB	NS	NL	PEI	YK	NIHB	VAC	CSC	CAF
Semaglutide	Ozempic	SA	SA	EDS	EDS	GB	SA	EDS	SA	SA	EDS	OB	OB	SA	SA
	Rybelsus	—	NAB	—	—	—	—	—	—	—	—	—	—	—	—
	Wegovy	—	NAB	—	—	—	—	—	—	—	—	—	—	—	—
Liraglutide	Victoza	NAB	NAB	—	—	—	—	—	—	—	—	—	—	—	—
	Saxenda	—	NAB	—	—	—	—	—	—	—	—	—	—	—	—
Liraglutide–insulin degludec	Xultophy	NAB	NAB	—	—	—	—	—	—	—	—	—	—	—	—
Dulaglutide	Trulicity	—	NAB	—	—	—	—	—	—	—	—	—	—	—	—
Lixisenatide	Adlyxine	SA	NAB	EDS	EDS	GB	SA	EDS	SA	—	—	OB	OB	—	—
Lixisenatide–insulin glargine	Soliqua	—	NAB	EDS	EDS	GB	—	—	SA	—	—	OB	OB	—	—

AB = Alberta; BC = British Colombia; CAF = Canadian Armed Forces; CSC = Correctional Service of Canada; EDS = Exception Drug Status; GB = general benefit; GLP-1 = glucagon-like peptide-1; LU = Limited Use; MB = Manitoba; NA = not applicable; NAB = not a benefit; NB = New Brunswick; NIHB = Non-Insured Health Benefits; NL = Newfoundland and Labrador; NS = Nova Scotia; OB = open benefit; ON = Ontario; PEI = Prince Edward Island; SA = Special Authorization; SK = Saskatchewan; T2DM = type 2 diabetes mellitus; VAC = Veterans Affairs Canada; YK = Yukon

Semaglutide (Ozempic)

Ozempic is an unrestricted benefit in Ontario, NIHB, and VAC. Ontario's therapeutic notes allow for the addition of Ozempic in combination with metformin and a sulfonylurea when diet and exercise with metformin and a sulfonylurea does not adequately control glycemic levels.

Type 2 Diabetes

Restricted benefit: As add-on therapy for patients with T2DM, British Columbia and CSC require intolerance, contraindication, or inadequate glycemic control on a trial of metformin. Alberta requires patients with T2DM to have a contraindication, intolerance to, and/or inadequate glycemic control on a sufficient trial of metformin and a sulfonylurea, and for whom insulin is not an option. Six drug plans (Saskatchewan, Manitoba, Nova Scotia, Prince Edward Island, Newfoundland and Labrador, Yukon) allow access as an add-on to metformin and a sulfonylurea when this dual therapy with diet and exercise do not achieve adequate glycemic control. New Brunswick allows access as an add-on to metformin or metformin and a sulfonylurea when patients with T2DM have inadequate control on metformin or metformin and a sulfonylurea. CAF requires patients with T2DM have inadequate glycemic control after a trial of metformin and DPP-4 inhibitor, and metformin plus an SGLT2 inhibitor.

Semaglutide (Rybelsus)

Type 2 Diabetes

Restricted benefit: Rybelsus is not a benefit in any of the jurisdictions included in this Environmental Scan.

Semaglutide (Wegovy)

Weight Management

Restricted benefit: Wegovy is not a benefit in any of the jurisdictions included in this Environmental Scan.

Liraglutide (Victoza)

Victoza is an unrestricted benefit in Nova Scotia.

Type 2 Diabetes

Restricted benefit: Victoza is not a benefit in any of the jurisdictions included in this Environmental Scan.

Liraglutide (Saxenda)

Weight Management

Restricted benefit: Saxenda is not a benefit in any of the jurisdictions included in this Environmental Scan.

Liraglutide–Insulin Degludec (Xultophy)

Type 2 Diabetes

Restricted benefit: Liraglutide–insulin degludec is not a benefit in any of the jurisdictions included in this Environmental Scan.

Dulaglutide (Trulicity)

Type 2 Diabetes

Restricted benefit: Dulaglutide is not a benefit in any of the jurisdictions included in this Environmental Scan.

Lixisenatide (Adlyxine)

Lixisenatide is an unrestricted benefit in Ontario, NIHB, and VAC. Ontario's therapeutic notes allow for the addition of lixisenatide to metformin and 1 of sulfonylurea, pioglitazone, or basal insulin when glycemic control is not achieved by diet and exercise with dual therapy.

Type 2 Diabetes Mellitus

Restricted benefit: Two drug plans (New Brunswick and Nova Scotia) allow lixisenatide to be added to basal insulin or basal insulin and metformin in patients with T2DM who have inadequate glycemic control on basal insulin or basal insulin and metformin. Alberta allows access as add-on therapy for treatment of T2DM in patients with contraindication to, intolerance to, and/or inadequate glycemic control on a trial of metformin, a sulfonylurea, and insulin. Saskatchewan and Manitoba allow lixisenatide to be combined with a basal insulin with or without metformin when patients with T2DM have inadequate glycemic control on, or intolerance to, metformin and a sulfonylurea. Newfoundland and Labrador allow the combination of lixisenatide with metformin and a sulfonylurea when diet and exercise plus metformin and a sulfonylurea do not achieve adequate glycemic levels.

Lixisenatide–Insulin Glargine (Soliqua)

Lixisenatide–insulin glargine is an unrestricted benefit in Ontario, NIHB, and VAC. Ontario's therapeutic notes allows for lixisenatide–insulin glargine to be added to diet and exercise when glycemic levels are not adequately controlled on basal insulin (less than 60 units daily) in combination with metformin.

Type 2 Diabetes Mellitus

Restricted benefit: Saskatchewan and Manitoba allow lixisenatide–insulin glargine to be added to a basal insulin (less than 60 units per day) for adequate glycemic control in patients with T2DM. Newfoundland and Labrador allows access to lixisenatide–insulin glargine as an adjunct to diet and exercise when glycemic levels are inadequately controlled on basal insulin (60 units per day) in combination with metformin.

Conclusion

As SGLT2 inhibitors and GLP-1 receptor agonists have matured, Health Canada indications have expanded. With the entry of dapagliflozin generics in Canada, some public drug programs have made dapagliflozin an unrestricted benefit with reimbursement not limited by clinical criteria. Semaglutide is the GLP-1 receptor agonist reimbursed by most public drug programs in Canada, with most jurisdictions requiring specific clinical criteria to be met for reimbursement. With the expiration of data protection for SGLT2 inhibitors, the emergence of additional generics outside of dapagliflozin are expected.

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Appendix 1: Regulatory Information for SGLT2 Inhibitors

Table 10: Overview of Regulatory Information for SGLT2 Inhibitors

Generic name	Brand name	Manufacturer	NOC dates	Marketed date	Indication(s)
dapagliflozin	Forxiga	AstraZeneca Canada Inc.	**T2DM** December 12, 2014 **HF** June 30, 2020 **CKD** August 10, 2021	January 16, 2015	**Type 2 Diabetes Mellitus** **Monotherapy:** FORXIGA (dapagliflozin propanediol monohydrate) is indicated for use as an adjunct to diet and exercise to improve glycemic control in adult patients with T2DM for whom metformin is inappropriate due to contraindications or intolerance. **Add-on combination:** FORXIGA is indicated in adult patients with T2DM to improve glycemic control in combination with • metformin • a sulfonylurea • metformin and a sulfonylurea • sitagliptin (alone or with metformin) • insulin (alone or with metformin) when metformin alone or the existing therapy listed above, along with diet and exercise, do not provide adequate glycemic control. **Add-On Combination in Patients with Cardiovascular Risk Factors or Established Cardiovascular Disease:** FORXIGA is indicated as an adjunct to diet, exercise, and standard-of-care therapy to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and CV risk factors or established CV disease. **Heart Failure:** FORXIGA is indicated in adults, as an adjunct to standard-of-care therapy, for the treatment of heart failure with reduced ejection fraction (HFrEF) to reduce the risk of cardiovascular (CV) death, hospitalization for heart failure and urgent heart failure visit. **Chronic Kidney Disease:** FORXIGA is indicated to reduce the risk of sustained eGFR decline, end-stage kidney disease, and cardiovascular and renal death in adults with chronic kidney disease (CKD).

Generic name	Brand name	Manufacturer	NOC dates	Marketed date	Indication(s)
					Pediatrics (< 18 years of age): Safety and efficacy of FORXIGA have not been established in patients under 18 years of age; therefore, Health Canada has not authorized an indication for pediatric use. **Geriatrics** (≥ 65 years of age): FORXIGA should be used with caution in this population as a higher proportion of patients ≥ 65 years of age treated with FORXIGA had adverse reactions related to volume depletion and renal impairment or failure, compared to patients treated with placebo.
dapagliflozin plus metformin	Xigduo	AstraZeneca Canada Inc.	**T2DM** December 10, 2015	February 8, 2016	**Type 2 Diabetes Mellitus:** XIGDUO (dapagliflozin/metformin hydrochloride) is indicated for use as an adjunct to diet and exercise in adults with type 2 diabetes mellitus who are already being treated with dapagliflozin and metformin as separate tablets and achieving glycemic control. **Add-on combination:** XIGDUO is indicated for use in combination with a sulfonylurea as an adjunct to diet and exercise in adults with type 2 diabetes mellitus who are already achieving glycemic control with dapagliflozin, metformin and a sulfonylurea. XIGDUO is indicated for use in combination with sitagliptin as an adjunct to diet and exercise in adults with type 2 diabetes mellitus who are already achieving glycemic control with dapagliflozin, metformin and sitagliptin. XIGDUO is indicated for use in combination with insulin as an adjunct to diet and exercise in adults with type 2 diabetes mellitus who are already achieving glycemic control with dapagliflozin, metformin and insulin. **Pediatrics (< 18 years of age):** XIGDUO should not be used in pediatric patients. Safety and efficacy of XIGDUO have not been established in patients under 18 years of age. **Geriatrics (≥ 65 years of age):** No dosage adjustment for dapagliflozin is recommended on the basis of age. XIGDUO should be used with caution in this population as a higher proportion of patients ≥ 65 years of age treated with dapagliflozin had adverse reactions related to volume depletion and renal

Generic name	Brand name	Manufacturer	NOC dates	Marketed date	Indication(s)
					impairment or failure, compared to patients treated with placebo. Metformin is eliminated by the kidney, and the risk of serious adverse reactions to the drug is greater in patients with impaired renal function. As aging is associated with renal function, XIGDUO should be used with caution as age increases.
dapagliflozin plus saxagliptin	Qtern	AstraZeneca Canada Inc.	**T2DM** November 22, 2016	cancelled pre-market	–
canagliflozin	Invokana	Janssen Inc.	**T2DM** May 23, 2014	May 28, 2014 (300 MG) June 3, 2014 (100 MG)	**Type 2 Diabetes Mellitus** **Monotherapy:** INVOKANA (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus for whom metformin is inappropriate due to contraindications or intolerance. **Add-on combination:** INVOKANA (canagliflozin) is indicated for use in adult patients with type 2 diabetes mellitus to improve glycemic control in combination with: • metformin • sulfonylurea (with or without metformin) • pioglitazone with metformin • metformin and sitagliptin • insulin (with or without metformin) when the therapy listed above, along with diet and exercise, does not provide adequate glycemic control. **Add-On Combination in Patients with Established Cardiovascular Disease:** INVOKANA is indicated as an adjunct to diet, exercise, and standard-of-care therapy to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD). **Patients with Diabetic Nephropathy:** INVOKANA is indicated as an adjunct to diet, exercise, and standard-of-care therapy to reduce the risk of end-stage kidney disease, doubling of serum creatinine, and cardiovascular (CV) death in adult patients with type 2

Generic name	Brand name	Manufacturer	NOC dates	Marketed date	Indication(s)
					diabetes mellitus and diabetic nephropathy with albuminuria (> 33.9 mg/mmol). **Pediatrics (< 18 years of age):** The safety and efficacy of INVOKANA in pediatric patients under 18 years of age have not been established. Therefore, INVOKANA should not be used in this population. **Geriatrics (≥ 65 years of age):** Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA, including hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration. Reactions were more common in patients over 75 years of age and with the 300 mg daily. Smaller reductions in hemoglobin A1C with INVOKANA relative to placebo were seen in patients 65 years and older, compared to younger.
canagliflozin plus metformin	Invokamet	Janssen Inc.	**T2DM** June 1, 2016	June 28, 2016	**Type 2 Diabetes Mellitus:** INVOKAMET is indicated to improve glycemic control as an adjunct to diet and exercise in adult patients with type 2 diabetes mellitus inadequately controlled on: • metformin • a sulfonylurea in combination with metformin • pioglitazone in combination with metformin • insulin in combination with metformin Or in patients already being treated and achieving glycemic control with: • metformin and canagliflozin as separate tablets • a sulfonylurea in combination with metformin and canagliflozin as separate tablets • pioglitazone in combination with metformin and canagliflozin as separate tablets • insulin in combination with metformin and canagliflozin as separate tablets **Pediatrics:** The safety and efficacy of INVOKAMET in pediatric patients under 18 years of age have not been established. Therefore, INVOKAMET should not be used in this population.

Generic name	Brand name	Manufacturer	NOC dates	Marketed date	Indication(s)
					Geriatrics: Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with canagliflozin, including hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration. Reactions were more common in patients over 75 years of age and with the 300 mg daily dose. Smaller reductions in hemoglobin A1C with canagliflozin relative to placebo were seen in patients 65 years and older, compared to younger patients. Treatment with INVOKAMET can reduce renal function. Metformin is eliminated by the kidney, and the risk of serious adverse reactions to the drug is greater in patients with impaired renal function. INVOKAMET should be used with caution as age increases. The dosage of INVOKAMET should be adjusted based on renal function. Regular assessment of renal function is necessary.
	Invokamet XR	Janssen Inc.	**T2DM** June 19, 2018	Cancelled Premarket	**Type 2 Diabetes Mellitus:** INVOKAMET XR is indicated to improve glycemic control as an adjunct to diet and exercise in adult patients with type 2 diabetes mellitus inadequately controlled on: • metformin • a sulfonylurea in combination with metformin • pioglitazone in combination with metformin • insulin in combination with metformin Or in patients already being treated and achieving glycemic control with: • metformin and canagliflozin as separate tablets • a sulfonylurea in combination with metformin and canagliflozin as separate tablets • pioglitazone in combination with metformin and canagliflozin as separate tablets • insulin in combination with metformin and canagliflozin as separate tablets **Pediatrics:** The safety and efficacy of INVOKAMET XR in pediatric patients under 18 years of age have not been established. Therefore, INVOKAMET XR should not be used in this population.

Generic name	Brand name	Manufacturer	NOC dates	Marketed date	Indication(s)
					Geriatrics (≥ 65 years of age): INVOKAMET XR should be used with caution in geriatric patients. Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with canagliflozin, including hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration. Reactions were more common in patients over 75 years of age and with the canagliflozin 300 mg daily dose. Smaller reductions in hemoglobin A1C with canagliflozin relative to placebo were seen in patients 65 years and older, compared to younger patients. Treatment with INVOKAMET XR can reduce renal function. Metformin is eliminated by the kidney, and the risk of serious adverse reactions to the drug is greater in patients with impaired renal function. The dosage of INVOKAMET XR should be adjusted based on renal function. Regular assessment of renal function is necessary.
empagliflozin	Jardiance	Boehringer Ingelheim Canada Ltd.	**T2DM** July 23, 2015 **HF** October 29, 2021	August 11, 2015	**Type 2 diabetes mellitus** **Monotherapy:** JARDIANCE (empagliflozin) is indicated for use as an adjunct to diet and exercise to improve glycemic control in adult patients with T2DM for whom metformin is inappropriate due to contraindications or intolerance. **Add-on combination:** JARDIANCE is indicated in adult patients with T2DM to improve glycemic control in combination with • metformin • metformin and a sulfonylurea • pioglitazone (alone or with metformin) • linagliptin and metformin • basal or prandial insulin (alone or with metformin) when metformin alone or the existing therapy listed above, along with diet and exercise, do not provide adequate glycemic control. **Add-on combination in patients with established cardiovascular disease:** JARDIANCE is indicated as an adjunct to diet, exercise, and standard care therapy to reduce the incidence of

Generic name	Brand name	Manufacturer	NOC dates	Marketed date	Indication(s)
					cardiovascular death in patients with T2DM and established cardiovascular disease. **Important Limitations of Use:** Use of JARDIANCE with insulin mix (regular or analogue mix) has not been studied. Therefore, JARDIANCE should not be used with insulin mix. **Heart Failure:** JARDIANCE is indicated in adults as an adjunct to standard of care therapy for the treatment of chronic heart failure. **Pediatrics (< 18 years of age):** Safety and efficacy of JARDIANCE have not been established in patients under 18 years of age; therefore, Health Canada has not authorized an indication for pediatric use. **Geriatrics (> 65 years of age):** JARDIANCE should be used with caution in geriatric patients with type 2 diabetes mellitus. A greater increase in risk of adverse reactions in geriatric patients with type 2 diabetes mellitus treated for glycemic control, was seen with JARDIANCE in the elderly, compared to younger patients. In the EMPEROR-Reduced study, a total of 2,312 (62%) treated patients with HFrEF were 65 years of age and older. In the EMPEROR-Preserved study, a total of 4,786 (80%) treated patients with HFpEF were 65 years of age and older. Safety and efficacy in both studies were similar for patients 65 years and younger and those older than 65.
empagliflozin plus metformin	Synjardy	Boehringer Ingelheim Canada Ltd.	**T2DM** July 29, 2016	August 3, 2016	**Type 2 diabetes mellitus:** SYNJARDY (empagliflozin and metformin hydrochloride) is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus inadequately controlled on: • metformin; • sulfonylurea in combination with metformin; • pioglitazone in combination with metformin; • insulin in combination with metformin; Or in patients already being treated and achieving glycemic control with:

Generic name	Brand name	Manufacturer	NOC dates	Marketed date	Indication(s)
					• metformin and empagliflozin as separate tablets; • sulfonylurea in combination with metformin and empagliflozin as separate tablets; • pioglitazone in combination with metformin and empagliflozin as separate tablets; • insulin in combination with metformin and empagliflozin as separate tablets; **Important Limitations of Use:** In combination therapy, use of empagliflozin with insulin mix (regular or analogue mix) has not been studied. Therefore, SYNJARDY should not be used with insulin mix. **Pediatrics (< 18 years of age):** SYNJARDY should not be used in pediatric patients. Safety and effectiveness of SYNJARDY have not been studied in patients under 18 years of age. **Geriatrics (≥ 65 years of age):** A greater increase in risk of adverse reactions was seen with empagliflozin in the elderly, compared to younger patients, therefore, SYNJARDY should be used with caution in this population. Empagliflozin is expected to have diminished efficacy in elderly patients as older patients are more likely to have impaired renal function. Metformin is eliminated by the kidney and the risk of serious adverse reactions to the drug is greater in patients with impaired renal function. SYNJARDY should only be used in patients with normal renal function. Because aging is associated with reduced renal function, SYNJARDY should be used with caution in geriatric patients. SYNJARDY treatment should not be initiated in patients older than 80 years of age, unless measurement of creatinine clearance demonstrates that renal function is not reduced.
empagliflozin plus linagliptin	Glyxambi	Boehringer Ingelheim Canada Ltd.	**T2DM** December 15, 2016	cancelled post-market	—

CKD = Chronic Kidney Disease; CV = Cardiovascular; CVD = Cardiovascular Disease; eGFR = estimated Glomerular Filtration Rate; hemoglobin A1C = Hemoglobin A1c; HF = Heart Failure; HFrEF = Heart Failure with Reduced Ejection Fraction; HFpEF = Heart Failure with Preserved Ejection Fraction; T2DM = Type 2 Diabetes Mellitus

Note that this table has not been copy-edited.

Appendix 2: Regulatory Information for GLP-1 Receptor Agonists

Table 11: Overview of Regulatory Information for GLP-1 Receptor Agonists

Generic name	Brand name	Manufacturer	NOC date	Marketed date	Indication(s)
semaglutide	Ozempic	Novo Nordisk	January 4, 2018	February 22, 2018	OZEMPIC is indicated for the once-weekly treatment of adult patients with type 2 diabetes mellitus to improve glycemic control, in combination with: • diet and exercise in patients for whom metformin is inappropriate due to contraindication or intolerance. • metformin, when diet and exercise plus maximal tolerated dose of metformin do not achieve adequate glycemic control. • metformin and a sulfonylurea, when diet and exercise plus dual therapy with metformin and a sulfonylurea do not achieve adequate glycemic control. • metformin or a sulfonylurea and a SGLT2 inhibitor, when diet and exercise plus metformin or a sulfonylurea, in addition to an SGLT2 inhibitor, do not achieve adequate glycemic control. • basal insulin with metformin, when diet and exercise plus basal insulin with metformin do not achieve adequate glycemic control. OZEMPIC has not been studied in combination with prandial insulin (short acting). OZEMPIC is not a substitute for insulin. OZEMPIC should not be used in patients with type 1 diabetes mellitus (formerly known as insulin-dependent diabetes mellitus or IDDM) or for the treatment of diabetic ketoacidosis. **Pediatrics (< 18 years of age):** The safety and efficacy of OZEMPIC have not been studied in pediatric populations. OZEMPIC is not indicated for use in pediatric patients. **Geriatrics (> 65 years of age):** OZEMPIC was studied in a limited number of patients 75 years of age or older.
	Rybelsus	Novo Nordisk	March 30, 2020	April 19, 2020	RYBELSUS is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: • as monotherapy when metformin is considered inappropriate due to intolerance or contraindications;

Generic name	Brand name	Manufacturer	NOC date	Marketed date	Indication(s)
					• in combination with other medicinal products for the treatment of diabetes. **Pediatrics** (< 18 years of age): The safety and efficacy of Rybelsus have not been studied in pediatric populations. Rybelsus® is not indicated for use in pediatric patients. **Geriatrics** (≥ 65 years of age): Evidence from a pooled analysis of phase III clinical studies suggests that use in the geriatric population (n = 1,229) was associated with no significant differences in safety or efficacy, but greater sensitivity of some older individuals cannot be rule out. Therapeutic experience in patients ≥ 75 years of age is limited.
	Wegovy	Novo Nordisk	November 23, 2021	November 23, 2021 (Approved)	Wegovy (semaglutide injection) is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of: • 30 kg/m^2 or greater (obesity), or • 27 kg/m^2 or greater (overweight) in the presence of at least 1 weight-related comorbidity such as hypertension, type 2 diabetes mellitus, dyslipidemia, or obstructive sleep apnea. **Limitations of Use:** • Wegovy should not be used in combination with any other semaglutide-containing drug (e.g., Ozempic®, Rybelsus®) or any other GLP-1 receptor agonist. • The efficacy and safety of Wegovy in combination with other products intended for weight management, including prescription drugs, over-the-counter drugs, and herbal preparations, have not been established. • Wegovy is not indicated for the treatment of type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis **Pediatrics (< 18 years of age):** The efficacy and safety of Wegovy have not been studied in pediatric patients. Wegovy is not indicated for use in pediatric patients. **Geriatrics (> 65 years of age):** In the Wegovy clinical trials, 233 (8.8%) Wegovy-treated patients were between 65 and 75 years of age and a limited number (23 [0.9%]) of Wegovy-treated patients were 75 years of

Generic name	Brand name	Manufacturer	NOC date	Marketed date	Indication(s)
					age and over. No overall differences in safety or efficacy were detected between these patients and younger patients, but greater sensitivity of older individuals cannot be ruled out.
liraglutide	Victoza	Novo Nordisk	May 21, 2010	May 27, 2010	Victoza is indicated for once-daily administration for the treatment of adults, with type 2 diabetes to improve glycemic control in combination with: • diet and exercise in patients for whom metformin is inappropriate due to contraindication or intolerance. • metformin, when diet and exercise plus maximal tolerated dose of metformin do not achieve adequate glycemic control. • metformin and a sulfonylurea, when diet and exercise plus dual therapy with metformin and a sulfonylurea do not achieve adequate glycemic control. • metformin and a SGLT2 inhibitor, when diet and exercise plus dual therapy with metformin and a SGLT2 inhibitor do not achieve adequate glycemic control. • metformin and basal insulin, when diet and exercise plus dual therapy with Victoza and metformin do not achieve adequate glycemic control. **Add-on combination:** • Victoza is indicated as an adjunct to diet, exercise, and standard-of-care therapy to reduce the incidence of cardiovascular death in patients with type 2 diabetes mellitus and established cardiovascular disease. • There is limited clinical experience with the combination of Victoza® and prandial (short acting) insulin. • Victoza is not a substitute for insulin. Victoza® should not be used in type 1 diabetes. **Pediatrics (≥ 10 years of age):** In adolescents and children aged 10 years and above with type 2 diabetes, Victoza® is indicated as an adjunct to metformin with or without basal insulin, when diet and exercise plus maximal tolerated dose of metformin do not achieve adequate glycemic control.

Generic name	Brand name	Manufacturer	NOC date	Marketed date	Indication(s)
					Geriatrics (≥ 65 years of age): No overall difference in safety or efficacy was observed in clinical trial subjects' ≥ 65 years of age compared to younger patients, but greater sensitivity of older individuals cannot be ruled out.
	Saxenda	Novo Nordisk	February 25, 2021	May 27, 2015	SAXENDA (liraglutide injection) is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of: • 30 kg/m^2 or greater (obesity), or • 27 kg/m^2 or greater (overweight) in the presence of at least 1 weight-related comorbidity (e.g., hypertension, type 2 diabetes, or dyslipidemia) and who have failed a previous weight management intervention. **Limitation of Use:** Clinical efficacy and safety data from patients with BMI 27 to 29.9 kg/m^2 in the presence of at least 1 weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia) are limited (N = 149). Saxenda® is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in pediatric patients aged 12 to less than 18 years with: • an inadequate response to reduced-calorie diet and increased physical activity alone, and • a body weight above 60 kg (132 lbs), and • an initial body mass index (BMI) corresponding to ≥ 30 kg/m^2 for adults (obesity) by international cut-offs. **Limitations of Use:** The safety and effectiveness of Saxenda® in pediatric patients with type 2 diabetes have not been established. **Pediatrics (aged 12 to less than 18 years):** Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Saxenda in pediatric patients aged 12 to less than 18 Years has been established; therefore, Health Canada has authorized an indication for pediatric use in pediatric patients aged 12 to less than 18 years. The safety and efficacy of Saxenda in children and adolescents below

Generic name	Brand name	Manufacturer	NOC date	Marketed date	Indication(s)
					18 years of age with secondary causes of obesity has not been studied. **Geriatrics (≥ 65 years of age):** Patients ≥ 65 years may experience more gastrointestinal side effects when treated with Saxenda. Therapeutic experience in patients ≥ 75 years of age is very limited. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.
liraglutide + insulin degludec	Xultophy	Novo Nordisk	April 11, 2018	June 6, 2018	Xultophy is a combination of insulin degludec and liraglutide and is indicated for once-daily treatment, as an adjunct to diet and exercise and in combination with oral medicinal products for the treatment of diabetes, to improve glycemic control in adults with type 2 diabetes mellitus. Xultophy should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. Patients on basal insulin or GLP-1 receptor agonist should not continue these drugs when beginning treatment with Xultophy, since Xultophy contains both basal insulin and a GLP-1 receptor agonist. Xultophy has not been studied in combination with prandial insulin (short acting). **Pediatrics (< 18 years of age):** Xultophy is not indicated for use in children and adolescents below 18 years of age. No studies have been performed with Xultophy in patients below 18 years of age. **Geriatrics (> 65 years of age):** Xultophy can be used in elderly patients. No overall difference in safety or efficacy was observed in clinical trial subjects ≥ 65 years of age compared to younger patients, but greater sensitivity of older individuals cannot be ruled out. Xultophy was studied in a limited number of patients 75 years of age or older. Glucose monitoring is to be intensified and the dose adjusted on an individual basis.
dulaglutide	Trulicity	Eli Lilly and Company	November 10, 2015	November 24, 2015	TRULICITY (dulaglutide) is indicated for the once-weekly treatment of adult patients with type 2 diabetes mellitus to improve glycemic control, in combination with: • diet and exercise in patients for whom metformin is inappropriate due to contraindication or intolerance.

Generic name	Brand name	Manufacturer	NOC date	Marketed date	Indication(s)
					• metformin, when diet and exercise plus maximal tolerated dose of metformin do not achieve adequate glycemic control. • metformin and a sulfonylurea, when diet and exercise plus dual therapy with metformin and a sulfonylurea do not achieve adequate glycemic control. • SGLT2 inhibitor with metformin, when diet and exercise plus SGLT2 inhibitor with or without metformin do not achieve adequate glycemic control. • basal insulin with metformin, when diet and exercise plus basal insulin with or without metformin do not achieve adequate glycemic control. • prandial insulin with metformin, when diet and exercise plus basal or basal-bolus insulin therapy (up to 2 injections of basal or basal plus prandial insulin per day) with or without oral antihyperglycemic medications, do not achieve adequate glycemic control. TRULICITY is indicated as an adjunct to diet, exercise, and standard-of-care therapy to reduce the risk of nonfatal stroke in adults with type 2 diabetes mellitus who have multiple cardiovascular risk factors or established cardiovascular disease. TRULICITY is not a substitute for insulin. TRULICITY should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. **Pediatrics (< 18 years of age):** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use. **Geriatrics (≥ 65 years of age):** No overall differences in safety or efficacy were observed in clinical trial subjects ≥ 65 years of age compared to younger patients, but greater sensitivity of some older individuals cannot be ruled out.
lixisenatide	Adlyxine	Sanofi-Aventis Canada Inc.	May 25, 2017	September 12, 2017	ADLYXINE (lixisenatide injection) is indicated for use as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus in combination with: • metformin,

Generic name	Brand name	Manufacturer	NOC date	Marketed date	Indication(s)
					• a sulfonylurea (alone or with metformin), • pioglitazone (alone or with metformin), • a basal insulin (alone or with metformin) when the therapy listed above does not provide adequate glycemic control. **Limitations of Use:** • Adlyxine has not been studied with short acting insulin. • Adlyxine should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. **Pediatrics (< 18 years of age):** The safety and efficacy of ADLYXINE have not been established in patients younger than 18 years of age, therefore ADLYXINE is not indicated in pediatric patients. **Geriatrics (≥ 65 years of age):** ADLYXINE should be used with caution in patients 65 years and older, since a greater sensitivity of some older individuals cannot be ruled out.
lixisenatide + insulin glargine	Soliqua	Sanofi-Aventis Canada Inc.	July 6, 2018	September 12, 2018	SOLIQUA, a fixed ratio combination of insulin glargine and lixisenatide, once daily injection, is indicated in combination with metformin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on: • basal insulin (less than 60 units daily) alone or in combination with metformin • a glucagon-like peptide-1 receptor agonist (GLP-1RA) in combination with metformin Use alternative antidiabetic products if patients require basal insulin below 15 units or over 60 units. Therapy with basal insulin or a GLP-1 receptor agonist should be discontinued before initiation of SOLIQUA, since SOLIQUA contains both basal insulin and a GLP-1 receptor agonist (lixisenatide). **Limitations of Use:** • SOLIQUA has not been studied with short acting insulin. • SOLIQUA should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. • SOLIQUA is not recommended for use in combination with any other

Generic name	Brand name	Manufacturer	NOC date	Marketed date	Indication(s)
					product containing lixisenatide or another GLP-1 receptor agonist. • SOLIQUA has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis. • SOLIQUA is not recommended for use in patients with gastroparesis. **Pediatrics (< 18 years of age):** The safety and efficacy of SOLIQUA in pediatric patients have not been established. Therefore, Health Canada has not authorized an indication for pediatric use. **Geriatrics (≥ 65 years of age):** The therapeutic experience in patients ≥ 75 years of age is limited. SOLIQUA should be used with caution in patients 65 years and older, since a greater sensitivity of some older individuals cannot be ruled out. The dose should be adjusted on an individual basis, based on glucose monitoring.
exenatide	Byetta	AstraZeneca	NA	Cancelled post-market	**Add-on to metformin and/or sulfonylurea:** BYETTA (exenatide) injection is indicated in combination with metformin, and/or a sulfonylurea to improve glycemic control in patients with type 2 diabetes mellitus, when maximally tolerated doses of these oral therapies in addition to diet and exercise do not provide adequate glycemic control. **Add-on to insulin glargine:** BYETTA is indicated in combination with insulin glargine (with or without metformin) to improve glycemic control in patients with type 2 diabetes mellitus when insulin glargine (with or without metformin) in addition to diet and exercise, does not provide adequate glycemic control. Management of type 2 diabetes should also include nutritional counselling, weight reduction as needed, and exercise.
	Bydureon	AstraZeneca	October 30, 2015	Cancelled post-market	**Monotherapy:** BYDUREON is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus for whom metformin is inappropriate due to contraindications or intolerance. **Combination with metformin:** BYDUREON is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin when metformin used alone, with diet and exercise,

Generic name	Brand name	Manufacturer	NOC date	Marketed date	Indication(s)
					does not provide adequate glycemic control. **Combination with a sulfonylurea:** BYDUREON is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with a sulfonylurea when the sulfonylurea used alone, with diet and exercise, does not provide adequate glycemic control. **Combination with metformin and a sulfonylurea:** BYDUREON is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin and a sulfonylurea when dual therapy with these 2 agents, with diet and exercise, does not provide adequate glycemic control. **Combination with basal insulin (alone or with metformin):** BYDUREON is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with basal insulin (alone or with metformin) when therapy with these agents, with diet and exercise, does not provide adequate glycemic control.
	Bydureon BCise	AstraZeneca	NA	Cancelled pre-market	**Monotherapy:** BYDUREON BCise (exenatide prolonged-release injectable suspension) is indicated for use as an adjunct to diet and exercise to improve glycemic control in patients with T2DM for whom metformin is inappropriate due to contraindications or intolerance. **Add-on combination:** BYDUREON BCise (exenatide prolonged-release injectable suspension) is indicated in adult patients with T2DM to improve glycemic control, in combination with: • metformin • sulfonylurea (alone or with metformin) when the existing therapy (with or without metformin), along with diet and exercise, does not provide adequate glycemic control.

BMI = Body Mass Index; GLP-1 = Glucagon-Like Peptide 1; GLP-1RA = Glucagon-Like Peptide 1 Receptor Agonist; IDDM = Insulin-Dependent Diabetes Mellitus; NA = Not Applicable; SGLT2 = Sodium-Glucose Transporter 2; T2DM = Type 2 Diabetes Mellitus

Note that this table has not been copy-edited.

Appendix 3: CADTH Review of SGLT2 Inhibitors

Table 12: Summary of CDEC Recommendations for SGLT2 Inhibitors in Patients With T2DM

Drug recommendation	Clinical rationale		Economic rationale
	Study details	Clinical reasons for recommendation	
dapagliflozin (Forxiga) Recommended to be listed for use in patients with type 2 diabetes mellitus to improve glycemic control, if the clinical criteria and condition are met for any 1 of the following 4 scenarios: **Clinical criteria:** • **Added on to metformin for patients:** ◦ Who have inadequate glycemic control on metformin ◦ Who have a contraindication or intolerance to a sulfonylurea ◦ For whom insulin is not an option. • **Added on to a sulfonylurea for patients:** ◦ Who have inadequate glycemic control on a sulfonylurea ◦ Who have a contraindication or intolerance to metformin ◦ For whom insulin is not an option. • Added on to insulin in combination with metformin for patients with inadequate glycemic control on insulin with metformin. • Added on to insulin without metformin for patients with the following: ◦ Inadequate glycemic control on insulin	**Six Phase III double-blinded RCTs** Four of the studies were conducted in patients with inadequate glycemic control with metformin (Studies 4, 12, 14, and 18), 1 study enrolled patients with inadequate glycemic control with a sulfonylurea (Study 5), and 1 study enrolled patients with inadequate glycemic control with insulin (Study 6). **Study 4 (N = 801):** A 52-week noninferiority study comparing dapagliflozin (2.5 mg, 5 mg, or 10 mg) with glipizide (5 mg, 10 mg, or 25 mg), both added on to metformin. The study included an extension phase of up to 204 weeks. **Study 12 (N = 180):** A 24-week placebo-controlled study with patients randomized (1:1) to either dapagliflozin 10 mg or placebo added on to metformin. The study included an extension phase of up to 78 weeks. **Study 14 (N = 546):** A 24-week placebo-controlled study with patients randomized (1:1:1:1) to either dapagliflozin 2.5 mg, dapagliflozin 5 mg, dapagliflozin 10 mg, or placebo added on to metformin. The study included an extension phase of up to	**Dapagliflozin vs. glipizide:** Study 4 demonstrated that dapagliflozin was noninferior to glipizide for improving glycemic control, and superior to it for reducing body weight and blood pressure. **Dapagliflozin vs. placebo:** Dapagliflozin was superior to placebo for improving glycemic control when taken in combination with metformin (Studies 12 and 14), a sulfonylurea (Study 5), and insulin (Study 6).	Reanalyses of the manufacturer's pharmacoeconomic model conducted by CDR suggested that dapagliflozin is associated with the following incremental cost-utility ratios (ICURs): $25,939 to $342,374 per quality-adjusted life-year (QALY) compared with a sulfonylurea as add-on to metformin; $12,453 to $1,021,404 per QALY compared with a DPP-4 inhibitor as add-on to a sulfonylurea; and $2,486 to $53,123 per QALY compared with a DPP-4 inhibitor as add-on to insulin.

Drug recommendation	Clinical rationale		Economic rationale
	Study details	Clinical reasons for recommendation	
◦ Contraindication or intolerance to metformin. **Condition:** Drug plan cost of treatment with dapagliflozin should not exceed the drug plan cost of treatment with the least costly option from within the sodium-glucose cotransporter-2 (SGLT2) inhibitor and dipeptidyl peptidase-4 (DPP-4) inhibitor classes.	78 weeks. **Study 18 (N = 534):** A 24-week study with patients randomized (1:1:1) to either dapagliflozin 10 mg, saxagliptin 5 mg, or dapagliflozin (10 mg per day) plus saxagliptin (5 mg per day) added on to metformin. This study was designed to compare triple therapy vs. dual therapy; therefore, no analysis comparing dapagliflozin to saxagliptin was conducted. **Study 5 (N = 438):** Enrolled patients with inadequate glycemic control with a sulfonylurea. Patients were randomized (1:1:1) to either dapagliflozin 5 mg, dapagliflozin 10 mg, or placebo added on to their existing sulfonylurea therapy. The study included an extension phase of up to 48 weeks. **Study 6 (N = 598):** A 24-week placebo-controlled study with patients randomized (1:1:1) to either dapagliflozin 5 mg, dapagliflozin 10 mg, or placebo added on to insulin. The study included an extension phase of up to 80 weeks. **Primary Outcomes:** Change from baseline in A1C was the primary outcome in all studies, with the exception of Study 12, which evaluated change in total body weight as the primary end point.		

Drug recommendation	Clinical rationale		Economic rationale
	Study details	Clinical reasons for recommendation	
dapagliflozin/metformin (Xigduo) Recommended to be reimbursed for patients with type 2 diabetes mellitus if the following criterion and condition are met: • Patients who are already stabilized on therapy with metformin and dapagliflozin, to replace the individual components of dapagliflozin and metformin for those patients who: ◦ Have inadequate glycemic control on metformin, a contraindication or intolerance to a sulfonylurea, and for whom insulin is not an option, or ◦ Have inadequate glycemic control on metformin and insulin. **Condition:** The drug plan cost for the dapagliflozin/metformin fixed-dose combination (FDC) should not exceed the combined cost of dapagliflozin and metformin administered separately.	One double-blind (DB), placebo-controlled, multicentre, randomized, parallel assignment phase III trial Study D1691C00003 (N = 400) had a 16-week DB period that evaluated the efficacy and safety of dapagliflozin treatment regimens of 2.5 mg twice daily and 5 mg twice daily co-administered with metformin therapy, compared with placebo plus metformin in patients with type 2 diabetes treated with stable doses of metformin monotherapy ≥ 1,500 mg/day monotherapy for at least 10 weeks before enrolment who had A1C ≥ 6.7% and ≤ 10.5% at screening or A1C ≥ 6.5% and ≤ 10.0% 1 week before randomization. **Primary Outcomes:** Change from baseline in A1C was the primary outcome.	**Dapagliflozin/metformin combined vs. separate components:** In study D1691C00007, dapagliflozin/metformin FDC given twice daily has been shown to be bioequivalent to comparable doses of the individual drug components given twice daily in both fasting and fed conditions. This FDC product, Xigduo, reduces the overall pill burden and regimen complexity for patients who would have taken these medications individually. **Dapagliflozin/metformin vs. placebo and metformin:** In study D1691C00003, at 16 weeks, the dapagliflozin/metformin FDC was shown to achieve a statistically higher reduction of hemoglobin A1C compared with placebo and metformin. In addition, statistical significance was shown at 16 weeks for fasting plasma glucose, body weight, and the proportion of participants with a baseline hemoglobin A1C of ≥ 7% who achieved a hemoglobin A1C of < 7%.	Dapagliflozin/metformin FDC represents cost savings over the combination of the individual components.
canagliflozin (Invokana) Recommended to be listed for the treatment of type 2 diabetes, if the following clinical criterion and condition are met: • Added on to metformin and a sulfonylurea for patients with inadequate glycemic control on metformin and a sulfonylurea and for	**Two double-blind phase III RCTs** Investigating the efficacy and safety of canagliflozin in patients with type 2 diabetes and inadequate glycemic control with metformin and sulfonylurea combination therapy. DIA3015 (N = 756) randomized patients using metformin and a sulfonylurea to	**Canagliflozin vs. sitagliptin:** Randomized controlled trial (DIA3015) demonstrated that canagliflozin was superior to sitagliptin for improving glycemic control, reducing body weight, and lowering systolic blood pressure (SBP). **Canagliflozin vs. placebo:** Randomized controlled trial (DIA3002) demonstrated	At the submitted price of $2.62 per 100 mg or 300 mg tablet, the CADTH Common Drug Review (CDR) estimated that the incremental cost-utility ratio (ICUR) for canagliflozin compared with sitagliptin ranges from being dominant (lower net cost and greater net quality-adjusted life-years [QALYs]) to $35,150 per QALY.

Drug recommendation	Clinical rationale		Economic rationale
	Study details	Clinical reasons for recommendation	
whom insulin is not an option. **Condition:** Drug plan costs for canagliflozin should not exceed the drug plan cost of dipeptidyl peptidase-4 (DPP-4) inhibitors.	either canagliflozin 300 mg once daily or sitagliptin 100 mg once-daily add-on therapy over a period of 52 weeks. DIA3002 (N = 469) randomized patients to either canagliflozin 100 mg once daily, canagliflozin 300 mg once daily, or matching placebo added on to their existing metformin and sulfonylurea therapy over a period of 26 weeks in the primary study, and an additional 26 weeks in an extension study. Adults with type 2 diabetes were eligible for these studies if they had poor glycemic control (i.e., glycated hemoglobin [A1C] ≥ 7% and ≤ 10.5%) despite using the maximum-tolerated dose of metformin (≥ 1,500 mg/day) and a sulfonylurea (greater than or equal to half of the maximum recommended dose). **Primary Outcomes:** The primary efficacy end point in both studies was the difference in A1C levels from baseline to the end of the study period (52 weeks in DIA3015 and 26 weeks in DIA3002).	that canagliflozin was superior to placebo for improving glycemic control, reducing body weight, and lowering systolic blood pressure (SBP).	
canagliflozin/metformin (Invokamet) Recommended to be reimbursed for patients with type 2 diabetes mellitus if the following criterion and condition are met: • Patients who are already stabilized on therapy with metformin and	**Two pivotal phase III clinical trials for canagliflozin previously reviewed by CDR** For this review, the phase II study (DIA2003) provided additional data for canagliflozin/metformin FDC. **Primary Outcomes:** Change from	**Canagliflozin/metformin combined vs. separate components:** In 8 studies, canagliflozin/metformin FDC given twice daily has been shown to be bioequivalent to comparable doses of the individual drug components given twice daily in both fasting and fed	At the submitted price, the canagliflozin/metformin FDC is more costly than the combination of the individual components. The annual incremental cost for the FDC is between $75 and $110.

Drug recommendation	Clinical rationale		Economic rationale
	Study details	Clinical reasons for recommendation	
canagliflozin, to replace the individual components of canagliflozin and metformin, for those patients who: ◦ Have inadequate glycemic control on metformin and a sulfonylurea, and for whom insulin is not an option. **Condition:** Drug plan costs for the canagliflozin/metformin fixed-dose combination (FDC) should not exceed the combined cost of canagliflozin and metformin administered separately.	baseline in A1C was the primary outcome.	conditions. This FDC product reduces the overall pill burden and regimen complexity for patients who would have taken these medications individually. **Canagliflozin/metformin vs. placebo and metformin:** In study DIA2003, at 18 weeks, the canagliflozin/metformin FDC was shown to achieve a statistically higher reduction of glycated hemoglobin A1C compared with placebo and metformin. In addition, statistical significance was shown at 18 weeks for body weight, and the proportion of participants who achieved a hemoglobin A1C of < 7%.	
empagliflozin (Jardiance) Recommended to be listed for the treatment of type 2 diabetes, if the following clinical criterion and condition are met: • Added on to metformin and a sulfonylurea for patients with inadequate glycemic control on metformin and a sulfonylurea and for whom insulin is not an option. **Condition:** The drug plan cost of treatment with empagliflozin should not exceed the drug plan cost of treatment with the least costly option from within the sodium-glucose cotransporter-2 (SGLT2) inhibitor and dipeptidyl peptidase-4 (DPP-4) inhibitor classes.	**One 24-week double-blind RCT (study 23), as well as its 52-week double-blind extension phase (study 31)** Study 23 was an international, multicentre trial composed of 2 independent substudies of identical design. Patients with a stable dose regimen of metformin were entered in 1 substudy (metformin background), and patients with a stable dose regimen of metformin plus a sulfonylurea were entered in the second substudy (metformin plus sulfonylurea background [N = 668]). The CDR review and CDEC deliberations focused on the results of the metformin plus sulfonylurea substudy. Patients were randomized (1:1:1) to either empagliflozin 10 mg, empagliflozin	**Empagliflozin vs. placebo** One randomized controlled trial (RCT; N = 666) demonstrated that empagliflozin was superior to placebo for improving glycemic control, reducing body weight, and lowering systolic blood pressure (SBP) at 24 weeks. A network meta-analysis (NMA) suggested that empagliflozin has efficacy similar to other SGLT2 inhibitors and DPP-4 inhibitors.	At the submitted price ($2.62 per 10 mg or 25 mg tablet), the cost of treatment with empagliflozin ($2.62 per day) is the same as canagliflozin ($2.62 per day), lower than sitagliptin ($2.98 per day), and higher than linagliptin ($2.25 to $2.55 per day).

Drug recommendation	Clinical rationale		Economic rationale
	Study details	Clinical reasons for recommendation	
	25 mg, or placebo added on to their existing therapy. The planned treatment period was 24 weeks after an open-label placebo run-in period of 2 weeks. **Primary Outcomes:** The primary outcome of study 23 was the change from baseline to 24 weeks in A1C. No primary outcome was identified for the extension phase.		
empagliflozin/metformin (Synjardy) Recommended to be reimbursed for patients with type 2 diabetes mellitus if the following clinical criterion and condition are met: • Patients who are eligible to receive metformin and empagliflozin based on participating drug plan reimbursement criteria, to replace the individual components of empagliflozin and metformin. **Condition:** Drug plan costs for the empagliflozin/metformin FDC should not exceed the combined cost of empagliflozin and metformin administered separately.	**Three manufacturer-submitted pivotal studies. They were double-blind, placebo-controlled, multicentre RCTs** All 3 studies had a 24-week treatment period that evaluated the efficacy and safety of empagliflozin 10 mg or 25 mg once daily in patients with type 2 diabetes who had inadequate glycemic control (A1C ≥ 7.0% and ≤ 10%) on a background therapy of metformin alone (Study 1245.23met), metformin + sulfonylurea (Study 1245.23met+su), or metformin and pioglitazone (Study 1245.19). No phase III RCTs of empagliflozin/metformin FDC were identified from the literature search. Additional evidence was summarized in the appendices of the CDR Clinical Review report, including evidence from 2 nonpivotal, double-blind, phase III RCTs: Study 1245.28 (N = 1,549; 104 weeks) compared empagliflozin 25 mg once daily against glimepiride (1 mg to 4 mg daily) for patients with inadequate	**Empagliflozin and metformin vs. placebo:** Three randomized controlled trials (RCTs) (Study 1245.23met [N = 638], Study 1245.23met+su [N = 669], and Study 1245.19 [N = 499]) demonstrated that empagliflozin and metformin administered separately twice daily is statistically significantly superior to placebo in reducing glycated hemoglobin (A1C) after 24 weeks of treatment among patients on background therapy of metformin alone, metformin and sulfonylurea, and metformin and pioglitazone. **Empagliflozin/metformin combined vs. separate components:** Empagliflozin/metformin FDC has been shown to be bioequivalent to similar doses of the individual drug components given twice daily. This FDC product likely reduces the overall pill burden and regimen complexity for patients who would have taken these medications individually.	At the submitted price ($1.35 per tablet, or $2.70 per day, for all 6 strengths), the empagliflozin/metformin FDC is $2 to $35 less expensive than the combination of the individual components, or $35 to $70 less expensive if pharmacy fees and markup are included.

Drug recommendation	Clinical rationale		Economic rationale
	Study details	Clinical reasons for recommendation	
	glycemic control with metformin monotherapy, and Study 1245.49 (N = 566; 52 weeks) compared the addition of empagliflozin (10 mg or 25 mg once daily) against placebo for patients with inadequate glycemic control on their existing multiple daily insulin with or without metformin. As well, CDR reviewed evidence from 4 phase I, single-dose, open-label crossover RCTs (Studies 1276.5, 1276.6, 1276.7, and 1276.8) that evaluated the bioequivalence of empagliflozin and metformin administered as an FDC tablet compared with administration of the individual components. Lastly, key findings of the 1245.31 extension study and a phase IIb, double-blind RCT (Study 1275.10) conducted to evaluate the efficacy and safety of empagliflozin twice daily vs. once daily were reviewed. **Primary Outcomes:** The primary outcome in the 3 pivotal RCTs was the change from baseline in A1C at week 24.		

CDEC = Canadian Drug Expert Committee; DB = Double-Blinded; DPP-4 = Dipeptidyl Peptidase-4; FDC = Fixed-Dose Combination; ICUR = Incremental Cost-Utility Ratio; NA = Not Applicable; QALY = Quality-Adjusted Life-Year; RCT = Randomized Controlled Trial; SBP = Systolic Blood Pressure; SGLT2 = Sodium-Glucose Cotransporter-2.

Note that this table has not been copy-edited.

Table 13: Summary of CDEC Recommendations for SGLT2 Inhibitors in Patients With HF

Drug recommendation	Clinical rationale		Economic rationale
	Study details	Clinical reasons for recommendation	
dapagliflozin (Forxiga) Recommended to be reimbursed as an adjunct to standard of care therapy, for the treatment of HFrEF only if the following condition is met. **Initiation criteria: Reimburse as an adjunct to standard of care therapy only in adults with NYHA class II and III heart failure. Standard-of-care therapies include beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, plus a mineralocorticoid receptor antagonist.**	**Two double-blind randomized placebo-controlled trials of patients with HFrEF** The DAPA-HF study (N = 4,744) evaluated the efficacy of dapagliflozin 10 mg daily vs. placebo as add-on to standard-of-care therapy in adults with HFrEF (LVEF ≤ 40%; NYHA function class II to IV). The median follow-up duration of this event driven trial was 18.2 months, with > 99% of patients completing the study. The 12-week DEFINE-HF study (N = 263) evaluated the effect of dapagliflozin in patients with HFrEF (LVEF ≤ 40%). Patients were randomized to dapagliflozin 10 mg daily or placebo as add-on to standard-of-care HF therapy. **Primary Outcomes:** The primary outcome in the DAPA-HF study was the time to first occurrence of CV death, hospitalization for HF, or an urgent HF visit. In the DEFINE-HF study, the co-primary outcomes included biomarker and health status measures that were not outcomes of interest according to the CADTH review protocol.	**Dapagliflozin vs. placebo:** In the pivotal trial (DAPA-HF), 16.3% of patients in the dapagliflozin group and 21.2% of patients in the placebo group reported a composite primary outcome event of CV death, HF hospitalization or urgent HF visit. The time to occurrence of the composite of primary events was greater for the dapagliflozin-treated patients (hazard ratio (HR) 0.74, 95% confidence interval (CI), 0.65 to 0.85, P < 0.0001) relative to placebo. Similar treatment effects were noted for the analysis of time to first occurrence of CV death or HF hospitalization (HR 0.75 95% CI, 0.65 to 0.85, P < 0.0001). For each component of the primary outcome, the time to first event was greater for dapagliflozin-treated patients. The total number of CV deaths or HF hospitalizations was lower in the dapagliflozin vs. placebo groups (average 16.3 events per 100 person years [PYs] vs. 21.6 events per 100 PYs, respectively) with a rate ratio of 0.75 (95% CI, 0.65 to 0.88, P = 0.0002).	At the sponsor-submitted price, in patients with HF in NYHA class II, dapagliflozin is associated with an incremental cost-effectiveness ratio (ICER) of $8,760 per quality-adjusted life-year (QALY) compared to standard of care. For patients in class III or IV, dapagliflozin was dominated by standard of care; that is dapagliflozin was more costly and was associated with fewer QALYs; however, this was associated with a high degree of uncertainty about the clinical efficacy of dapagliflozin in patients with NHYA class III and IV HF.
empagliflozin (Jardiance) Recommended to be reimbursed for the treatment of chronic heart failure as an adjunct to standard-of-care therapy if certain conditions are met: • Patients 18 years and older whose heart	**Two phase III, double-blind, placebo-controlled randomized controlled trials** EMPEROR-Reduced and EMPEROR-Preserved were pivotal trials and included in the systematic review. Both pivotal trials were multinational, multicentred, and	**Empagliflozin vs. placebo:** Evidence from 2 clinical trials demonstrated that Jardiance reduced the risk of cardiovascular death or hospitalizations for heart failure in patients with chronic heart failure.	Based on CADTH's assessment of the health economic evidence, Jardiance does not represent good value to the health care system at the public list price. The committee determined that there is not enough

Drug recommendation	Clinical rationale		Economic rationale
	Study details	Clinical reasons for recommendation	
is unable to pump enough blood to keep up with the body's needs (heart failure) because the heart is either too weak (heart failure with reduced ejection fraction [HFrEF]) or too stiff (heart failure with preserved ejection fraction [HFpEF]). The patient should either have a slight limitation in physical activity (NYHA functional classification class II) or a marked limitation in physical activity (NYHA class III). **Condition:** Jardiance should only be reimbursed if the price is less costly than dapagliflozin for the treatment of chronic heart failure. Jardiance should be prescribed as an added therapy to standard therapy for chronic heart failure.	included Canadian sites. The EMPEROR-Reduced trial (N = 3,730) was designed to assess the superiority of empagliflozin at 10 mg compared with matched placebo as an adjunct to SOC treatment in patients with HF with reduced left ventricular ejection fraction (LVEF ≤ 40%). In the EMPEROR-Reduced trial, the mean age of the patients was 66.8 years (standard deviation [SD] = 11.0 years), 76.1% were male, 23.9% were female, and the mean LVEF was 27.5% (SD = 6.0), and most patients (75.1%) were classified as NYHA functional class II. The EMPEROR-Preserved trial (N = 5,988) was designed to assess the superiority of empagliflozin at 10 mg compared with matched placebo as an adjunct to SOC treatment in patients with HF with preserved left ventricular ejection fraction (LVEF > 40%). In the EMPEROR-Preserved trial, the mean age of the patients was 71.9 years (SD = 9.4 years), 55.3% were male, 44.7% were female, and the mean LVEF was 54.3% (SD = 8.8), and most patients (81.5%) were classified as NYHA functional class II. **Primary Outcomes:** In both EMPEROR trials, the primary efficacy end point was the time to first event of adjudicated CV death or HHF.		evidence to justify a greater cost for Jardiance compared with dapagliflozin for the treatment of HFrEF. Based on public list prices, reimbursement of Jardiance for the treatment of chronic heart failure is expected to cost the public drug plans approximately $170,069,261.

CI = confidence interval; CV = cardiovascular; HFrEF = heart failure with reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; LVEF = left ventricular ejection fraction; NHYA = New York Heart Association; NYHA = New York Heart Association; PYs = person-years; QALY = quality-adjusted life-year; RCT = randomized controlled trial; SOC = standard of care.

Note that this table has not been copy-edited.

Table 14: Summary of CDEC and FMEC Recommendations for SGLT2 Inhibitors in Patients With CKD

Drug recommendation	Clinical rationale		Economic rationale
	Study details	Clinical reasons for recommendation	
dapagliflozin (Forxiga) Dapagliflozin should be reimbursed in patients who meet the diagnostic criteria for CKD (eGFR 25 mL/minute/1.73 m^2 to 75 mL/minute/1.73 m^2) with a UACR of 200 mg/g to 5,000 mg/g and treated with an ACE inhibitor or ARB at the maximum-tolerated dose. **Patients whose CKD is caused by polycystic kidney disease or autoimmune conditions managed with immunosuppressants should not receive dapagliflozin because there are no data on efficacy or safety in these patients. Patients who are already taking an SGLT2 inhibitor for glycemic control or because of risk of heart failure do not necessarily require switching to dapagliflozin to reduce the risk of progression of renal disease. If clinically indicated, patients with CKD and diabetes may take dapagliflozin in combination with finerenone for preservation of renal status. Contraindication or intolerance to an ACE inhibitor or ARB does not preclude a patient from receiving dapagliflozin for CKD; however, this remains an evidence gap.**	Evidence from 4 RCTs suggests that dapagliflozin as an add-on to SOC is an effective and safe treatment for adults with CKD (with or without T2DM). Evidence from DAPA-CKD suggested that among patients with CKD (with or without T2DM), dapagliflozin as an add-on to SOC therapy increases the time to CV and renal events relative to placebo. Dapagliflozin also resulted in fewer hospitalizations, reduced all-cause mortality, and reduced CV mortality or hospitalization for HF relative to placebo in DAPA-CKD. At longest follow-up in DAPA-CKD, dapagliflozin resulted in greater reduction in UACR relative to placebo; these results were supported by short-term results in DELIGHT but not DERIVE. Across all RCTs, the number of patients experiencing at least 1 AE or SAE was similar across groups. In all RCTs except for Kohan et al. (2014), most notable harms (i.e., amputations, genital infections, UTIs, DKA, palpitations, fractures, major hypoglycemia) were infrequent. No evidence was identified for HRQoL, symptom severity, or functional status, so the effect of dapagliflozin on these outcomes among patients with CKD is not known. The results of 5 NMAs suggested that canagliflozin 100	Initiation criteria reflect the enrolment criteria for the DAPA-CKD trial (eGFR of 25 mL/minute/1.73 m^2 to 75 mL/minute/1.73 m^2 and a UACR of 200 mg/g to 5,000 mg/g) and is reflective of clinical practice in Canada and standard of care, as per clinical practice guidelines. In DAPA-CKD, all participants were required to be receiving a stable dose of an ACE inhibitor or ARB for at least 4 weeks. Of the 2,152 participants in the dapagliflozin arm, 673 of (31.3%) and 1,444 (67.1%) were on an ACE inhibitor and ARB, respectively. Benefits from dapagliflozin for patients with CKD with lower proteinuria (i.e., UACR < 200 mg/g) is unclear and remains an evidence gap.	The review framework was part of the CADTH nonsponsored reimbursement review program in which an application filed by a sponsor is absent, as such, CADTH did not have access to an economic model for dapagliflozin in this clinical condition. As a result, the economic review consisted of only a cost comparison for dapagliflozin as an add-on to ARBs or ACEs compared to appropriate comparators for the treatment of patients with CKD. The assessment lacked a cost-effectiveness analysis, preventing a conclusive determination of dapagliflozin's cost-effectiveness when combined with ACE inhibitors and/or ARBs in adults with CKD. The cost comparison revealed an annual increase of $996 for dapagliflozin plus ACE inhibitors and/or ARBs vs. ACE inhibitors and/or ARBs alone due to dapagliflozin being an add-on therapy. However, within the T2DM subgroup, dapagliflozin might yield cost savings compared to finerenone or canagliflozin as add-on therapies to ACE inhibitors and/or ARBs (annual savings of $223 against finerenone and $59 against canagliflozin).

Drug recommendation	Clinical rationale		Economic rationale
	Study details	Clinical reasons for recommendation	
	mg was favoured over dapagliflozin for change from baseline eGFR and UACR. The results of 2 NMAs suggested that dapagliflozin was favoured over finerenone for the renal composite outcome. However, due to methodological limitations, these results should be considered to be uncertain. The effect estimates were too imprecise to draw a conclusion for other outcomes (e.g., cardiorenal composite outcomes, mortality, MACE, AEs), and no NMAs compared AEs between dapagliflozin and finerenone. The findings of the NMAs are primarily applicable to patients with both CKD and T2DM.		

ACE = Angiotensin-Converting Enzyme; AE = Adverse Event; ARB = Angiotensin Receptor Blocker; CKD = Chronic Kidney Disease; CV = Cardiovascular; DAPA-CKD = Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; DKA = Diabetic Ketoacidosis; eGFR = Estimated Glomerular Filtration Rate; HF = Heart Failure; HRQoL = Health-Related Quality of Life; MACE = Major Adverse Cardiovascular Event; NMA = Network Meta-Analysis; RCT = Randomized Controlled Trial; SAE = Serious Adverse Event; SGLT2 = Sodium-Glucose Cotransporter-2; SOC = Standard of Care; T2DM = Type 2 Diabetes Mellitus; UACR = Urine Albumin-to-Creatinine Ratio; UTI = Urinary Tract Infection.

Note that this table has not been copy-edited.

Appendix 4: CADTH Review of GLP-1 Receptor Agonists

Table 15: Summary of CDEC Recommendations for GLP-1 Receptor Agonists

Drug recommendation	Clinical rationale		Economic rationale
	Study details	Clinical reasons for recommendation	
semaglutide (Ozempic) Recommended that semaglutide be reimbursed for the treatment of type 2 diabetes mellitus to improve glycemic control, if the following conditions are met: • **Initiation Criteria:** ◦ Adult patients diagnosed with type 2 diabetes mellitus with inadequate glycemic control. • **Administration Criteria:** ◦ In combination with metformin alone, when diet and exercise plus maximal tolerated dose of **metformin do not** achieve adequate glycemic control. ◦ Semaglutide should not be reimbursed for use as add-on therapy to metformin and another antihyperglycemic drug. • **Pricing conditions:** ◦ **Drug plan costs for semaglutide should not exceed the drug plan costs of the least costly currently reimbursed drug used when metformin alone is insufficient to achieve glycemic control in the treatment of patients with type 2 diabetes mellitus.**	**Eight RCTs (SUSTAIN-1 to −7 and the Seino study) of patients with T2DM (N = 308 to 3,297)** These trials evaluated the efficacy and safety of semaglutide 0.5 mg or 1 mg once weekly, alone or in combination with an OAD such as MET or MET plus a SU, or basal insulin, compared with placebo or active comparators in adults with T2DM with inadequate glycemic control with background therapy. All 3 placebo-controlled trials (SUSTAIN-1, 5 and 6) and one active-controlled trial (SUSTAIN-2) included a randomized, double-blind treatment period, and all other active-controlled trials had an open-label design (SUSTAIN-3, −4, −7, and the Seino study). The primary objective of the included trials was to compare the effect of semaglutide once weekly with its respective comparators on change in hemoglobin A1C from baseline, except for SUSTAIN-6 and the Seino study. "Time from randomization to first occurrence of MACE" was the primary outcome in SUSTAIN-6. The occurrence of treatment emergent adverse event (AE) was the primary outcome	**Semaglutide vs. dulaglutide:** One phase III, open-label, randomized controlled trial (RCT) (SUSTAIN-7) demonstrated that semaglutide 0.5 mg and 1 mg administered subcutaneously once weekly was statistically superior compared with dulaglutide for improving glycemic control (change from baseline in glycated hemoglobin [A1C]) and body weight reduction at 40 weeks in patients with T2DM and inadequate glycemic control on treatment with MET. The findings of post hoc subgroup data from 3 other phase III RCTs (SUSTAIN 2, 3, and 4) were consistent with the findings of SUSTAIN-7 and indicated that semaglutide (0.5 mg and/or 1 mg added on to MET) is likely noninferior to sitagliptin, exenatide, and insulin glargine with respect to reduction in A1C and body weight. **Exploratory post hoc analyses:** In SUSTAIN-2, 3, and 4, exploratory post hoc subgroup analyses based on prior antidiabetic therapy were performed to explore the treatment effect of semaglutide as add-on therapy to 1 or more antihyperglycemic drugs (i.e., as a third-line drug). However, because	The cost-effectiveness of semaglutide could not be assessed because the manufacturer-provided cost-utility analysis was associated with significant limitations and lack of transparency. At the manufacturer-submitted price of $195.06 per prefilled pen, semaglutide is more expensive than all other treatment options, with the exception of liraglutide 1.8 mg per day. Based on the clinical evidence provided, a conclusion could be reached that semaglutide has similar effects to some other currently reimbursed second-line antihyperglycemic drugs and there is insufficient information available to justify a price greater than currently reimbursed second-line treatments.

Drug recommendation	Clinical rationale		Economic rationale
	Study details	Clinical reasons for recommendation	
	in the Seino study. The occurrence of diabetes-related comorbidities (macrovascular and microvascular) was also measured in the only CV outcomes trial (SUSTAIN-6). Change in body weight, body mass index, blood pressure, and blood lipid profile were evaluated in all trials. Health-related quality of life (HRQoL) was evaluated in all trials but SUSTAIN-1 and the Seino study. Noninferiority of treatment with semaglutide vs. active comparators on glycemic control was assessed in 4 SUSTAIN trials (SUSTAIN-2, −3, −4, and −7). Noninferiority of treatment with semaglutide compared with placebo on increase in CV events was assessed in patients who had prior or concomitant CV conditions in SUSTAIN-6. In SUSTAIN2, −3, −4, −6, and −7, superiority of semaglutide compared with placebo or active treatment for either change in hemoglobin A1C or change in body weight was tested if the noninferiority test criterion for the primary end point was met. Treatment duration of the included trials ranged from 30 weeks to 104 weeks. **Primary Outcomes:** Change in A1C from baseline was the primary efficacy outcome in all included trials, except for SUSTAIN-6 and the Seino study. Time from randomization to first occurrence of MACE was the primary outcome in	of the limitations existing with this approach, such as potential imbalance in baseline characteristics between subgroups, multiplicity and potential inflated type I error, and potential interactions between treatment and background therapy, there was a high degree of uncertainty in the conclusions that could be drawn on the results.	

Drug recommendation	Clinical rationale		Economic rationale
	Study details	Clinical reasons for recommendation	
	SUSTAIN-6, and the occurrence of AEs was the primary outcome in the Seino study.		

semaglutide (Rybelsus)
Recommended that oral semaglutide should be reimbursed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM), only if certain conditions are met.
• **Initiation criteria:**
  ◦ As an add-on therapy for adults with type 2 diabetes in either of the following:
  ▪ In addition to metformin in patients who do not achieve adequate glycemic control with metformin alone
  ▪ In addition to other antihyperglycemic agents
• **Prescribing criteria:**
  ◦ Oral semaglutide should not be used in combination with any other GLP-1 RA or with DPP-4 inhibitors.
• **Pricing condition:**
  ◦ **The drug plan cost of treatment with oral semaglutide should not exceed the drug plan cost of treatment with the least costly GLP-1 RA, DPP-4 inhibitor, or SGLT2 inhibitor currently reimbursed for the treatment of T2DM.**
	9 randomized, parallel-group, multicentre trials (PIONEER 1 to 6 and PIONEER 8 to 10)
	All included trials were double-blind except PIONEER 2 and 10, which were open-label and PIONEER 9, which was a combination of double-blind for semaglutide tablets and placebo, and open-label liraglutide.
	The trials evaluated the efficacy and safety of semaglutide tablets (3 mg, 7 mg, and 14 mg once daily) in adults with T2DM over 26 to 78 weeks of therapy. Although semaglutide 3 mg was evaluated as a maintenance dose in the trials and summarized as such, it is intended for use as a starting dose (for up to 30 days) as indicated in the product monograph. The trials were designed to assess semaglutide in comparison to a SGLT2 inhibitor (empagliflozin, PIONEER 2), a DPP-4 inhibitor (sitagliptin, PIONEER 3), and subcutaneous GLP-1 RAs (liraglutide, PIONEER 4 and 9, and dulaglutide, PIONEER 10), as well as placebo (PIONEER 1, 4 to 6, 8, and 9). Of note, PIONEER 4 and 9 were both active- and placebo-controlled trials. Semaglutide was evaluated as monotherapy (PIONEER 1, 6 and 9), as an add-on to
		Semaglutide vs. placebo: The efficacy and safety of oral semaglutide was reviewed in 6 randomized clinical trials in patients with T2DM as an add-on to metformin (PIONEER 2 and 5), as an add-on to 1 or 2 oral antihyperglycemic agents (OADs) (PIONEER 3, 4, 5, and 10), or as an add-on to insulin with or without metformin (PIONEER 5 and 8). In the active comparator trials (PIONEER 2, 3, and 4), oral semaglutide was evaluated as a second- or third-line therapy. In the placebo-controlled trials (PIONEER 5 and 8), all 3 doses of oral semaglutide (3 mg, 7 mg, and 14 mg) were superior to placebo in reducing A1C levels after 26 weeks of treatment.
		Semaglutide vs. empagliflozin, liraglutide, sitagliptin: Based on the outcome of A1C reduction after 26 weeks of treatment, oral semaglutide (14 mg) was superior when compared to empagliflozin (PIONEER 2; between-group difference: −0.4% (95% CI, −0.6 to −0.3, P < 0.0001) and was noninferior when compared to liraglutide (PIONEER 4; between-group difference: −0.1% (95% CI, −0.3 to 0.0, P < 0.0001). Both oral semaglutide 7 mg and 14 mg were superior to sitagliptin (PIONEER 3; between-group
			CADTH identified limitations with the submitted economic evaluation relating to the patient population being assessed, the lack of comparative cardiovascular outcomes data, quality of life data, and lack of transparency with the model resulting in uncertainty in the cost-effectiveness of oral semaglutide. At a submitted price of $6.97 per tablet (regardless of the dose) the daily cost of oral semaglutide ($6.97) is more costly than all SGLT2 based products ($2.45 to $3.24), DPP4 based products ($2.20 to $3.47), and some GLP-1 RAs, depending on dose ($3.55 to $9.34).

Drug recommendation	Clinical rationale		Economic rationale
	Study details	Clinical reasons for recommendation	
	metformin (PIONEER 2), as an add-on to 1 to 2 OADs (PIONEER 3, 4, 10) or insulin with or without metformin (PIONEER 8). A total of 9,039 adult patients with T2DM were randomized in PIONEER 1 to 6 and 8 to 10. Across the PIONEER trials, 8% or less of patients discontinued from the studies, with the most common reasons being withdrawal by patient and lost to follow-up. **Primary Outcomes:** The change from baseline in A1C (%) at week 26 was the primary outcome in PIONEER 1 to 5, 8, and 9. In PIONEER 6, the primary outcome was time from randomization to first occurrence of a MACE, and in PIONEER 10 the primary outcome was the number of treatment emergent adverse events during exposure to treatment.	difference: −0.3% (95% CI, −0.4 to −0.1, P < 0.0001) and −0.5% (95% CI, −0.6 to −0.4, P < 0.0001), respectively. This clinical evidence suggests that oral semaglutide, the first oral glucagon-like peptide-1 receptor agonist (GLP-1 RA) approved by Health Canada, meets the needs of patients with T2DM as a treatment that improves glycemic control. Oral semaglutide provides patients with an alternative formulation to subcutaneous options used to treat hyperglycemia in T2DM, including subcutaneous semaglutide.	
semaglutide (Wegovy) **Recommended that semaglutide not be reimbursed as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI of 30 kg/m^2 or greater (obesity) or 27 kg/m^2 or greater (overweight) in the presence of at least 1 weight-related comorbidity such as hypertension, type 2 diabetes mellitus, dyslipidemia, or obstructive sleep apnea.**	**4 placebo-controlled, double-blind (DB) randomized controlled trials (RCTs)** Treatment with semaglutide injection 2.4 mg resulted in body weight reduction for individuals with an initial BMI of 30 kg/m^2 or greater (obesity) or 27 kg/m^2 or greater (overweight) in the presence of at least 1 weight-related comorbidity but did not demonstrate improvement in or reducing the risk of weight-related comorbidities. The STEP 1 (N = 1,961), STEP 2 (N =	**Semaglutide vs. placebo:** Semaglutide demonstrated effectiveness in weight loss for up to 2 years with an acceptable side effect profile, but it is unclear whether this translates into a reduction in weight-related comorbidities or improvement in HRQoL.	Treatment with Wegovy is expected to cost approximately $4,726 per patient per year. In the CADTH base case, the ICER for semaglutide was $204,928 per QALY compared with standard of care (incremental costs: $9,385; incremental QALYs: 0.046) in the reimbursement request population. A price reduction of 71% would be required for semaglutide to be considered cost-effective at a $50,000 per QALY threshold.

Drug recommendation	Clinical rationale		Economic rationale
	Study details	Clinical reasons for recommendation	
	1,210), STEP 3 (N = 611), and STEP 4 (N = 803) trials demonstrated that 68 weeks of treatment with semaglutide 2.4 mg once weekly, with a background regimen of reduced-calorie diet and increased physical activity, was associated with statistically significant improvements in percent change from baseline in body weight over placebo, with mean between-group differences ranging from −6.21% to −14.75%. In addition, the STEP 1, STEP 2, and STEP 3 trials demonstrated statistically significant improvements in the percentage of patients with at least 5%, 10%, and 15% reduction in body weight. Comorbidities such as major adverse cardiovascular events, osteoarthritis, and obstructive sleep apnea were not outcomes in the STEP trials. Although there were statistically significant improvements in the 36-Item Short Form Survey (SF-36) Physical Functioning score and the Impact of Weight on Quality of Life Lite for Clinical Trials scale (IWQOL-Lite CT) Physical Function score with semaglutide treatment vs. placebo, the MID for the SF-36 Physical Functioning score was not met, and the MID for the IWQOL-Lite CT Physical Function score is unknown. Patients identified a need for treatments that are effective for weight loss and reducing weight-related		

Drug recommendation	Clinical rationale		Economic rationale
	Study details	Clinical reasons for recommendation	
	comorbidities, improve HRQoL, are easy to administer, and have reduced side effects. **Primary Outcome:** Percent change from baseline in body weight.		
liraglutide (Victoza) **Recommended that liraglutide not be listed at the submitted price.**	**Six RCTs of patients with type 2 diabetes mellitus** Trials investigated the use of liraglutide in dual therapy (LEAD-1, LEAD-2, Study 1860, and Study 1796), triple therapy (LEAD-5), and either dual or triple therapy (LEAD-6). **Dual Therapy Trials:** LEAD-1 (N = 1,041) was a 26-week double-blind RCT that randomized patients with inadequate glycemic control (based on a run-in period of up to 4 weeks with glimepiride titrated to 4 mg daily) to 1 of the following 5 treatment groups: liraglutide (1.8 mg, 1.2 mg, or 0.6 mg daily), rosiglitazone 4 mg daily, or placebo. All patients continued glimepiride as established during the run-in period. LEAD-2 (N = 1,091) was a 26-week double-blind RCT that randomized patients with inadequate glycemic control (based on a run-in period of up to 6 weeks with metformin 1,500 mg to 2,000 mg daily) to 1 of the following 5 treatment groups: liraglutide (1.8 mg, 1.2 mg, or 0.6 mg daily), glimepiride 4 mg daily, or placebo. All patients	**Liraglutide (+ metformin, or metformin and a sulfonylurea) vs. antihyperglycemic agents from other drug classes:** Based on a systematic review including 6 randomized controlled trials (RCTs), liraglutide demonstrated similar or greater reductions in hemoglobin A1c in combination with metformin, or with metformin and a sulfonylurea, compared with antihyperglycemic agents from other drug classes. Liraglutide was also associated with statistically significant weight loss compared with other drug classes. The clinical significance of these results with respect to diabetes-related morbidity and mortality is unknown for this new class of drug therapy.	The daily cost of liraglutide ($4.89 to $7.34) is greater than sulfonylureas (< $1.00), thiazolidinediones (< $3.00), dipeptidyl peptidase-4 (DPP-4) inhibitors (< $3.00), insulin NPH (< $2.00), and insulin analogues (< $3.00).

Drug recommendation	Clinical rationale		Economic rationale
	Study details	Clinical reasons for recommendation	
	continued metformin as established during the run-in period. Study 1860 (N = 665) was a 26-week open-label RCT that randomized patients with inadequate glycemic control (based on prestudy metformin of ≥ 1,500 mg daily for at least 3 months) to 1 of the following 3 treatment groups: liraglutide (1.8 mg or 1.2 mg daily), or sitagliptin 100 mg daily. All patients continued metformin at stable prestudy doses. Study 1796 (N = 929) was a 16-week double-blind RCT that randomized patients with inadequate glycemic control (based on a run-in period of up to 6 weeks with metformin 1,500 to 2,000 mg daily) to 1 of the following 4 treatment groups: liraglutide (1.8 mg, 1.2 mg, or 0.6 mg daily) or glimepiride 4 mg daily. All patients continued metformin as established during the run-in period. **Triple Therapy Trial:** LEAD-5 (N = 581) was a 26-week double-blind (liraglutide and placebo) and open-label (insulin glargine) RCT that randomized patients with inadequate glycemic control (based on a run-in period of up to 6 weeks with metformin 2,000 mg daily plus glimepiride 4 mg daily) to 1 of the following 3 treatment groups: liraglutide 1.8 mg daily, placebo, or insulin glargine titrated as per algorithm. All patients		

Drug recommendation	Clinical rationale		Economic rationale
	Study details	Clinical reasons for recommendation	
	continued metformin and glimepiride as established during the run-in period. **Dual or Triple Therapy Trial:** LEAD-6 (N = 464) was a 26-week open-label RCT that randomized patients with inadequate glycemic control (based on stable prestudy doses of maximally tolerated metformin and/or a sulfonylurea for at least 3 months) to either liraglutide 1.8 mg daily or exenatide 10 mcg twice daily. All patients continued prestudy doses of metformin and/or sulfonylureas. Mean baseline hemoglobin A1c was similar between all trials and ranged from 8.2% to 8.6%. There were a large and disproportionate number of withdrawals (for any reason) in the placebo groups of LEAD-1, LEAD-2, and LEAD-5, primarily due to ineffective therapy. In studies 1796 and 1860, study withdrawal occurred more frequently in liraglutide treatment groups compared with glimepiride and sitagliptin, respectively. **Primary Outcomes:** Change in hemoglobin A1c from baseline to end of study. All trials were designed to test the noninferiority of liraglutide with the comparators based on the primary outcome. Noninferiority was concluded if the upper limit of the 95% confidence interval (CI) for the treatment difference between liraglutide and the active		

Drug recommendation	Clinical rationale		Economic rationale
	Study details	Clinical reasons for recommendation	
	comparator was below 0.4%. None of the included trials evaluated clinical end points in general, or those related to known macrovascular or microvascular complications of type 2 diabetes mellitus.		
liraglutide (Saxenda) **Recommended that Saxenda should not be reimbursed by public drug plans for chronic weight management in adult patients.**	**4 phase III, randomized controlled trials** Evaluating the efficacy of liraglutide 3 mg to reduce and maintain weight in adult patients who are overweight or living with obesity. The Study 1839, and Study 1923 were conducted in patients without diabetes (N = 3,731 and 422, respectively), whereas Study 1922 and Study 3970 were conducted in patients with T2DM (N = 846) and OSA (N = 359), respectively. All studies were parallel-group, multicentre, double-blind, placebo-controlled trials conducted in multiple sites and multiple countries (at least 2), including Canada. In all studies, patients were randomly assigned to receive once-daily subcutaneous injections of liraglutide at a dose of 3 mg or matching placebo with background counselling on lifestyle modification involving reduced-calorie intake and increased physical activity for all participating patients. The study duration was 32 weeks for Study 3970 and 56 weeks for Study 1839, Study 1922, and Study 1923. In	**Liraglutide vs. placebo:** Evidence from 3 studies demonstrated that Saxenda was associated with statistically significant reductions in body weight compared with placebo after 56 weeks of treatment. No conclusions could be drawn about long-term benefits, particularly for clinically meaningful improvements in comorbidities identified as priorities by patients, such as diabetes, sleep apnea, osteoarthritis, and cardiovascular complications.	Treatment with Saxenda is expected to cost approximately $4,389 per patient in the first year of treatment and $4,564 per patient per year thereafter.

Drug recommendation	Clinical rationale		Economic rationale
	Study details	Clinical reasons for recommendation	
	addition to its 56-week main phase, Study 1839 had a 104-week extension phase involving patients diagnosed with prediabetes at screening. Thus, in Study 1839, the total treatment duration in patients with prediabetes at screening was 160 weeks. Overall, the treatment groups in all included studies were well-balanced with respect to baseline demographics and other characteristics. The overall rates of treatment discontinuation in Study 1839 (main phase), Study 1922, and Study 1923 ranged from 23.4% to 28.1% with liraglutide 3 mg and 20.7% to 34.0% with placebo. In Study 3970, treatment discontinuation rates for the liraglutide and placebo groups were 25.6% and 20.7%, respectively. The corresponding rates for the Study 1839 extension were 47.4% and 55.0% for liraglutide and placebo, respectively. Overall, adverse events (AEs) were the leading cause for discontinuing treatment with liraglutide 3 mg, although withdrawal of consent occurred at a higher rate than AEs in 1 study. For the placebo group, the main reasons for treatment discontinuation included the withdrawal of consent, ineffective therapy, and AEs. **Primary Outcomes:** Change in severity of OSA from baseline was reported as a standalone primary end point in		

Drug recommendation	Clinical rationale		Economic rationale
	Study details	Clinical reasons for recommendation	
	Study 3790. The remaining outcomes were reported as co-primary end points in the other studies' (Study 1839 main phase, Study 1922, and Study 1923) first 3 outcomes. The percentage change in fasting body weight and the proportion of patients losing at least 5% of baseline fasting body weight (5% responders) were common co-primary outcomes in all 3 studies. The third co-primary end point was the proportion of patients losing more than 10% of baseline fasting body (10% responders) in 2 of the studies (Study 1839 main phase and Study 1922), and the percentage of patients maintaining run-in fasting weight loss in Study 1923. Time to new onset of T2DM was a co-primary end point in Study 1839, reported only in the extension phase conducted in patients with prediabetes at screening. Baseline body weight was used to assess weight-based outcomes such as the percentage change in fasting body weight, the proportion of patients losing at least 5% of their body weight, and the proportion of patients losing 10% or more of their baseline body weight after a prespecified treatment duration.		

Drug recommendation	Clinical rationale		Economic rationale
	Study details	Clinical reasons for recommendation	
liraglutide/insulin degludec (Xultophy) Recommended that insulin degludec and liraglutide (IDegLira) should be reimbursed as an adjunct to lifestyle modification, for the once-daily treatment of adults with T2DM to improve glycemic control in combination with metformin (MET), with or without sulfonylurea (SU), when these, combined with basal insulin (at doses of 20 to 50 units per day) do not provide adequate glycemic control, only if the following conditions are met: **Discontinuation criteria:** IDegLira should be discontinued if the patient does not achieve a desirable level of glycemic control despite receiving a maximum dose of IDegLira (50 units of insulin degludec [IDeg] and 1.8 mg of liraglutide) after 26 weeks of treatment. **Pricing condition:** Drug plan costs for IDegLira should not exceed the cost of the least costly glucagon-like peptide-1 receptor agonist plus the least costly basal insulin administered separately or in combination.	**Four phase III RCTs** The DUAL II trial (N = 413) was a randomized, double-blind, superiority trial in patients with T2DM inadequately controlled with basal insulin (between 20 and 40 units per day) and MET with or without SU or glinides comparing the efficacy and safety of IDegLira once daily with insulin degludec (IDeg) once daily, both added on to MET. The DUAL V trial (N = 557) was a randomized, open-label, noninferiority (NI) trial that compared the efficacy and safety of IDegLira once daily with insulin glargine (IGlar) once daily, both in combination with MET in patients with T2DM inadequately controlled on IGlar at a daily dose between 20 and 50 units (both inclusive) in combination with MET. The DUAL VII trial (N = 506) was a randomized, open-label, NI trial that compared the efficacy and safety of IDegLira once daily with basal-bolus therapy (once-daily IGlar plus prandial insulin aspart [IAsp]), both arms in combination with MET in patients with T2DM inadequately controlled on IGlar at a daily dose between 20 units and 50 units (both inclusive) in combination with MET. The DUAL III trial (N = 438) was a randomized, open-label, superiority trial that compared IDegLira vs. unchanged	**Liraglutide/insulin degludec vs. insulin glargine/prandial insulin aspart:** In DUAL VII, an open-label randomized controlled trials (RCT) in patients with inadequate glycemic control on insulin glargine (IGlar) at a daily dose between 20 units and 50 units (inclusive) in combination with MET, IDegLira was noninferior to IGlar plus prandial insulin aspart (IAsp), both groups in combination with MET, for the change from baseline in glycated hemoglobin (A1C) after **Liraglutide/insulin degludec + metformin vs. liraglutide or exenatide and metformin ± pioglitazone ± sulfonylurea:** In 1 phase III open-label RCT (DUAL III), conducted in insulin-naive patients with inadequate glycemic control on a combination of the maximum recommended (or tolerated) dose of a GLP-1 RA (Victoza [liraglutide] or Byetta [exenatide]) and MET ± pioglitazone ± SU, IDegLira in combination with MET resulted in statistically significantly reduced A1C levels after 26 weeks of treatment compared with the baseline regimen; LS Mean difference (95% CI) was −0.94 (−1.11 to −0.78).	The extent to which IDegLira represents a cost-effective treatment option in the patient population for whom reimbursement is recommended is uncertain, given several limitations of the clinical and economic evidence with respect to relevant comparators and clinical outcomes.

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	GLP-1 RA therapy in controlling glycaemia in insulin-naive patients with T2DM inadequately controlled on a maximum-tolerated dose or maximum dose according to local label of GLP-1 RA (Victoza [liraglutide] or Byetta [exenatide injection]) and MET ± pioglitazone ± SU. These trials examined short-term (26 weeks) surrogate outcomes including A1C, body weight, and blood pressure. **Primary Outcomes:** Change from baseline in A1C after 26 weeks of treatment.		
dulaglutide (Trulicity) **Recommendation 1:** • Recommended that dulaglutide be reimbursed for the treatment of adults with type 2 diabetes mellitus in combination with metformin to improve glycemic control, if the following condition is met: ◦ Condition: Drug plan cost not to exceed that of the least costly pharmacotherapy reimbursed in combination with metformin. **Recommendation 2:** • CDEC recommends that dulaglutide be reimbursed for the treatment of adults with type 2 diabetes mellitus in combination with metformin and a sulfonylurea to improve glycemic control if the following condition is met:	**Second-line treatment:** Two phase III multicentre, active-controlled, noninferiority trials. AWARD-5 was an adaptive, inferentially seamless phase II/3 study that randomized 1,098 participants to 1 of 4 primary treatment arms — dulaglutide 0.75 mg, dulaglutide 1.5 mg, sitagliptin 100 mg, and placebo/sitagliptin for 24 months. AWARD-6 was an open-label study that randomized 599 participants to receive dulaglutide 1.5 mg or liraglutide 1.8 mg for 26 weeks. **Third-line treatment:** One phase III multicentre, active-controlled, noninferiority trial. AWARD-2 was an open-label trial, although double-blind with respect to the dulaglutide assignments, which	**Dulaglutide vs. sitagliptin vs. liraglutide:** Two phase III multicentre, active-controlled, noninferiority trials in patients on ≥ 1,500 mg/day of metformin found that dulaglutide 0.75 mg and 1.5 mg administered subcutaneously (SC) once weekly was likely clinically superior to sitagliptin 100 mg orally daily at reducing glycated hemoglobin (A1C) up to 104 weeks compared with baseline, and that dulaglutide 1.5 mg SC weekly was statistically noninferior to liraglutide 1.8 mg SC daily at 26 weeks. **Dulaglutide vs. insulin glargine:** In 1 phase III multicentre, active-controlled, noninferiority trial in patients on ≥ 1,500 mg/day of metformin and ≥ 4 mg/day of glimepiride, dulaglutide 0.75 mg SC weekly was found to be noninferior to	**Recommendation 1:** Dulaglutide was not cost-effective at the submitted price when compared with relevant second-line therapeutic options for type 2 diabetes mellitus used in combination with metformin. Furthermore, there are limited direct clinical comparative data with other less costly medications typically used as a second-line therapy. The CADTH Common Drug Review (CDR) base-case incremental cost-utility ratios (ICURs) were $278,000 and $1,500,000 compared with a sulfonylurea and a dipeptidyl peptidase-4 (DPP-4) inhibitor. **Recommendation 2:** Dulaglutide was not cost-effective at the submitted price when compared with relevant comparators as a third-line drug. The CDR base-case ICURs were $192,000 to $243,000 per quality-adjusted life-year (QALY) compared with insulin NPH,

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◦ **Condition:** Drug plan cost not to exceed the least costly pharmacotherapy reimbursed in combination with metformin and a sulfonylurea.	randomized 810 participants to dulaglutide 0.75 mg, dulaglutide 1.5 mg, or insulin glargine for 78 weeks. **Primary Outcomes:** Glycemic control (A1C, fasting plasma glucose [FPG])	insulin glargine, and dulaglutide 1.5 mg SC weekly was found to be statistically superior to insulin glargine for reducing A1C up to 78 weeks compared with baseline when used in combination with metformin and a sulfonylurea.	and $123,000 to $182,000 per QALY compared with insulin glargine.
lixisenatide (Adlyxine) Recommended that lixisenatide be reimbursed for use as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus if the following criterion and condition are met: **Criterion:** Lixisenatide should be used only in combination with a basal insulin (with or without metformin). **Condition:** Drug plan costs for lixisenatide should not exceed the drug plan costs of the least costly pharmacotherapy reimbursed for the treatment of type 2 diabetes mellitus in combination with a basal insulin (with or without metformin).	**Five RCTs met the inclusion criteria of the systematic review conducted by CDR.** Four double-blind, 24-week, placebo-controlled, phase III RCTs were included (GETGOAL – L [N = 496], GETGOAL – L Asia [N = 311], GETGOAL – DUO 1 [N = 446] and GETGOAL – L – C [N = 448]). All trials enrolled adult patients with type 2 diabetes mellitus with inadequate glycemic control on basal insulin therapy (alone or in combination with metformin) with the exception of GETGOAL – L Asia, which included patients with type 2 diabetes mellitus with inadequate glycemic control on basal insulin therapy (alone or in combination with sulfonylurea). The intervention in all placebo-controlled trials consisted of lixisenatide (initial dose 10 mcg titrated up to 20 mcg maintenance dose) in addition to permitted background therapy compared with placebo in addition to permitted background therapy). All placebo-controlled trials comprised a two-week screening phase, a one- to 12-week placebo run-in phase (to	**Lixisenatide vs. placebo:** In 4 double-blind, placebo-controlled phase III randomized controlled trials (RCTs), lixisenatide in combination with basal insulin (alone or with metformin) was superior to placebo in decreasing glycated hemoglobin (A1C) levels over 24 weeks in adult patients with type 2 diabetes mellitus. **Lixisenatide vs. insulin glulisine:** In 1 open-label, active-controlled RCT, lixisenatide in combination with basal insulin (with or without metformin) was noninferior to insulin glulisine once daily and insulin glulisine 3 times a day in decreasing A1C over 26 weeks.	CDEC noted that there is a high degree of uncertainty associated with the cost-effectiveness results of lixisenatide based on the limitations identified in the economic analysis, particularly regarding the dose and price of prandial insulin, as well as utility decrements for hypoglycemic events. There is also substantial uncertainty in the actual dose of prandial insulin over time and with extrapolating the short-term effects prandial insulin and lixisenatide observed in clinical trials to a lifetime time horizon.

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	ensure optimal basal insulin titration), and a 24-week double-blind treatment phase followed by 3 days of follow-up. One open-label, 26-week, active-controlled, phase III, noninferiority RCT was also included (GETGOAL – DUO 2 [N = 894]). The GETGOAL – DUO 2 study also enrolled adult patients with type 2 diabetes mellitus with inadequate glycemic control on basal insulin (insulin glargine) therapy (alone or in combination with metformin). The intervention consisted of lixisenatide (initial dose 10 mcg titrated up to 20 mcg maintenance dose) in addition to permitted background therapy compared with insulin glulisine once daily and insulin glulisine 3 times a day in addition to permitted background therapy. Subcutaneous insulin glulisine was administered within 15 minutes before breakfast or dinner in the group taking insulin glulisine once daily, and within 15 minutes before each meal in the group taking insulin glulisine 3 times a day. The initial insulin glulisine dose was 3 to 5 units per injection and subsequently titrated to obtain a self-monitored plasma glucose value between greater than 5.6 mmol/L and less than and equal to 7.8 mmol/L while avoiding hypoglycemia at every visit. GETGOAL – DUO 2 comprised a two-week screening phase, a 12-week		

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	run-in phase used to switch and optimize basal insulin (insulin glargine), and a 26-week open-label treatment phase followed by 3 days of follow-up. **Primary Outcomes:** In the placebo-controlled trials, the primary efficacy outcomes were the absolute change from baseline in A1C at week 24. In the GETGOAL – DUO 2 study, the primary efficacy outcome was the absolute change from baseline in A1C at week 26.		
lixisenatide/insulin glargine (Soliqua) Recommended that insulin glargine and lixisenatide (iGlarLixi) be reimbursed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, if the following condition is met: **Condition:** Drug plan costs for iGlarLixi should not exceed the combined drug plan costs of lixisenatide and insulin glargine provided separately in jurisdictions that reimburse both drugs for the treatment of type 2 diabetes mellitus.	**One phase III RCT:** (Lixilan-L, N = 736) of patients with T2DM with inadequate glycemic control, despite the use of basal insulin with or without metformin. Lixilan-L was an open-label, active-controlled, treat-to-target, parallel-group superiority trial. Patients were randomly assigned to either iGlarLixi or insulin glargine, with or without the use of metformin, for at least 30 weeks, after a six-week run-in period. **Primary Outcomes:** Change in hemoglobin A1C from baseline to week 30.	**Lixisenatide/insulin glargine vs. insulin glargine:** One open-label, multicentre, parallel-group randomized controlled trial (RCT) (Lixilan-L) in adults with T2DM (N = 736) who were inadequately controlled on basal insulin compared the use of iGlarLixi to insulin glargine for up to 30 weeks. The RCT demonstrated a statistically significant improvement in glycated hemoglobin (hemoglobin A1C) in favour of iGlarLixi compared with insulin glargine from baseline to week 30 (−0.52%; 95% CI, −0.633 to −0.397; P < 0.0001). Although there were limitations associated with this study, CDEC noted that the individual components of iGlarLixi have been reviewed previously through the CADTH Common Drug Review (CDR) — specifically, lixisenatide (Adlyxine, 0.05 mg/mL or 0.1 mg/mL prefilled pen) and insulin glargine	The cost of iGlarLixi will depend on the dose; at lower doses, iGlarLixi will be less costly than the publicly available prices of the individual components; at higher doses, iGlarLixi will be more costly than the individual components.

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		(Basaglar, solution for injection 100 U/mL) — and that the clinical evidence reviewed at that time was sufficient for CDEC to recommend that these products be reimbursed. **Lixisenatide/insulin glargine vs. basal insulin regimens vs glucagon-like peptide-1 receptor agonists + basal insulin:** A manufacturer-provided indirect comparison of iGlarLixi vs. currently available regimens for T2DM suggested that iGlarLixi has a favourable hypoglycemic profile against basal insulin regimens alone and against glucagon-like peptide-1 (GLP-1) receptor agonists in combination with basal insulin, although comparisons between iGlarLixi and insulin degludec in combination with liraglutide, liraglutide alone, dulaglutide, or any dipeptidyl peptidase-4 (DPP-4) inhibitor, were not available.	

A1C = glycated hemoglobin; AE = adverse event; CI = confidence interval; CDEC = Canadian Drug Expert Committee; CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; ICUR = incremental cost-utility ratio; IDegLira = insulin degludec and liraglutide; IGlar = insulin glargine; iGlarLixi = insulin glargine and lixisenatide; MACE = major adverse cardiovascular events; MET = metformin; OAD = oral antihyperglycemic drug; RA = receptor agonist; RCT = randomized controlled trial; SU = sulfonylurea; T2DM = type 2 diabetes mellitus.

Note that this table has not been copy-edited.

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