Summary of SGLT2i Canadian Cardio-Renal Indications

		Dapagliflozin (FORXIGA®)	Empagliflozin (JARDIANCE®)	Canagliflozin (INVOKANA®)
T2D	with CV Risk Factors	reduce the risk of hHF	---	---
	with Established CV Disease	reduce the risk of hHF	reduce the incidence of CV death	reduce the risk of CV death, nonfatal MI & nonfatal stroke
	with Diabetic Nephropathy (albuminuria >33.9 mg/mmol)	*(see CKD)*	---	reduce the risk of ESKD, doubling of serum creatinine & CV death
Heart Failure with Reduced Ejection Fraction		reduce the risk of CV death, hHF or urgent HF visits	treatment of HFrEF	---
Chronic Kidney Disease		reduce the risk of sustained eGFR decline, ESKD, & CV & renal death	---	---
eGFR considerations		Initiation not recommended if eGFR <25 **Contraindicated** in patients on dialysis	Discontinue eGFR <30 in T2D Not recommended eGFR<20 in HF **Contraindicated** in T2D with eGFR <20, ESKD, & dialysis	Initiation not recommended if eGFR <30 mL/min/1.73m^2 **Contraindicated** in patients on dialysis

Forxiga product monograph, AstraZeneca (Canada) August 2021. Invokana product monograph, Janssen Inc. (Canada) May 2020,. Jardiance product monograph, Boehringer Ingelheim (Canada) Ltd, Oct 2021
CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; hHF = hospitalization for heart failure; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; SGLT2i = Sodium-glucose linked transporter inhibitor; T2D = type 2 diabetes mellitus; eGFR units = mL/min/1.73m^2

SGLT2i Product Monographs: Glucose Indications in Canada

FORXIGA®

Monotherapy: FORXIGA (dapagliflozin) is indicated for use 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: FORXIGA is indicated in adult patients with type 2 diabetes mellitus 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.

JARDIANCE®

Monotherapy: JARDIANCE (empagliflozin) is indicated for use 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: JARDIANCE is indicated in adult patients with type 2 diabetes mellitus to improve glycemic control, when metformin used alone does not provide adequate 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 the existing therapy, along with diet and exercise, does not provide adequate glycemic control.

INVOKANA®

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.

Forxiga product monograph, AstraZeneca (Canada) August 2021. Invokana product monograph, Janssen Inc. (Canada) May 2020,. Jardiance product monograph, Boehringer Ingelheim (Canada) Ltd, June 2021
SGLT2i – Sodium-glucose linked transporter inhibitor; CV = cardiovascular; CVD = cardiovascular death

SGLT2i Product Monographs: Renal Indications in Canada

FORXIGA®

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).

INVOKANA®

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 diabetes mellitus and diabetic nephropathy with albuminuria** (>33.9 mg/mmol).

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SGLT2i – Sodium-glucose linked transporter inhibitor; CV = cardiovascular; CVD = cardiovascular death

SGLT2i Product Monographs: Heart Failure Indications in Canada

FORXIGA®

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

JARDIANCE®

Heart Failure

JARDIANCE is indicated in adults, as an adjunct to standard of care therapy, for the **treatment of heart failure with reduced ejection fraction**.

Forxiga product monograph, AstraZeneca (Canada) August 2021. Invokana product monograph, Janssen Inc. (Canada) May 2020,. Jardiance product monograph, Boehringer Ingelheim (Canada) Ltd, Oct 2021
SGLT2i – Sodium-glucose linked transporter inhibitor; CV = cardiovascular; CVD = cardiovascular death

SGLT2i Product Monographs: Cardiovascular Indications in Canada

FORXIGA®

Type 2 Diabetes Mellitus

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**

JARDIANCE®

Type 2 Diabetes Mellitus

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 cardiovascular death in patients with **T2DM and established cardiovascular disease**

INVOKANA®

Type 2 Diabetes Mellitus

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).

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SGLT2i – Sodium-glucose linked transporter inhibitor; CV = cardiovascular; CVD = cardiovascular death

SGLT2 inhibitors
Renal Indications in Canada

<table>
<tr><th></th><th>DAPAGLIFLOZIN (FORXIGA®)</th><th>CANAGLIFLOZIN (INVOKANA®)</th></tr>
<tr><td>Indications</td><td>Reduce the risk of sustained eGFR decline, ESKD, and cardiovascular and renal death in adults with chronic kidney disease.</td><td>Adjunct to diet, exercise, and standard of care therapy to reduce the risk of ESKD, doubling of serum creatinine, and cardiovascular death in adult patients with type 2 diabetes mellitus and diabetic nephropathy with albuminuria (>33.9 mg/mmol).</td></tr>
<tr><td>Primary outcome in clinical trials</td><td>DAPA-CKD
Composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes
<table><tr><th></th><th>Dapagliflozin</th><th>Placebo</th><th>HR (95% CI)</th><th>P value</th></tr><tr><td>Events/2152 participants</td><td>197</td><td>312</td><td>0.61 (0.51-0.72)</td><td><0.001</td></tr></table></td><td>CREDENCE
Composite of ESKD, a doubling of the serum creatinine level, or death from renal or cardiovascular causes
<table><tr><th></th><th>Canagliflozin</th><th>Placebo</th><th>HR (95% CI)</th><th>P value</th></tr><tr><td>Events/1000 patient-years</td><td>43.2</td><td>61.2</td><td>0.70 (0.59-0.82)</td><td><0.001</td></tr></table></td></tr>
<tr><td>Number needed to treat (NNT) to prevent one composite outcome</td><td>19 (95% CI, 15 to 27)</td><td>22 (95% CI, 15 to 38)</td></tr>
<tr><td>Ideal patients for treatment initiation</td><td>• Adults with chronic kidney disease (with or without type 2 diabetes mellitus)
• eGFR between 25 and 60 mL/min/1.73m^2 AND/OR UACR ≥3.39 mg/mmol
• eGFR >60 mL/min/1.73m^2 AND UACR ≥3.39 mg/mmol</td><td>• Adults with type 2 diabetes mellitus and albuminuric chronic kidney disease
• eGFR >30 mL/min/1.73m^2 AND UACR >33.9 mg/mmol</td></tr>
<tr><td>eGFR cut-off considerations for treatment initiation</td><td>Initiation not recommended if eGFR <25 mL/min/1.73m^2. <i>However, in DAPA-CKD trial treatment was continued if eGFR fell to levels below 25.</i></td><td>Initiation not recommended if eGFR <30 mL/min/1.73m^2. <i>However, treatment can be continued if albuminuria > 33.9 mg/mmol and eGFR falls to levels below 30.</i></td></tr>
<tr><td>Contraindication</td><td>Patients on dialysis
T1D</td><td>Patients on dialysis
T1D</td></tr>
<tr><td>Serious Warnings</td><td>Diabetic ketoacidosis</td><td>Diabetic ketoacidosis and lower limb amputations</td></tr>
<tr><td>Dose</td><td>10 mg once daily</td><td>100 mg once daily
(if eGFR ≥ 60, can be increased to 300 mg once daily for additional glycemic control)</td></tr>
<tr><td>Dosing considerations</td><td colspan="2">• Assess renal function prior to initiation of therapy and regularly thereafter.
• Assess volume status and, if necessary, correct volume depletion prior to initiation of therapy.
• When SGLT2 inhibitors are used as add-on therapy with insulin or an insulin secretagogue (e.g., sulfonylurea), a lower dose of insulin or the insulin secretagogue may be considered to reduce the risk of hypoglycemia.
• The glucose-lowering efficacy of SGLT2 inhibitors are dependent on renal function and declines with decreasing renal function.</td></tr>
</table>

Please consult the Product Monographs for warnings, precautions, adverse reactions, drug interactions, dosing, and conditions of clinical use.

Forxiga product monograph, AstraZeneca (Canada) August 2021. Invokana product monograph, Janssen Inc. (Canada) May 2020,.

eGFR – estimated glomerular filtration rate; ESKD – end stage kidney disease; SGLT2 – Sodium-glucose linked transporter; UACR – urine albumin-to-creatinine ratio

SGLT2i Product Monographs: Geriatrics (≥65 years of age)

FORXIGA®
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.
No dosage adjustment for FORXIGA is required based on age; however **renal function** and **risk of volume depletion** should be taken into account.

JARDIANCE®
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
No dose adjustment for JARDIANCE is required based on age; however **renal function** and **risk of volume depletion** should be taken into account. Initiation of JARDIANCE therapy is **not recommended in patients** with type 2 diabetes mellitus treated for glycemic control, **aged ≥85 years** as therapeutic experience is limited in this population

INVOKANA®
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**.
Renal function and risk of **volume depletion** should be taken into account.
Reactions were **more common in patients over 75 years of age and with the 300 mg daily**. Smaller reductions in HbA1C with INVOKANA® relative to placebo were seen in older patients

SGLT2i – Sodium-glucose linked transporter inhibitor; CV = cardiovascular; CVD = cardiovascular death
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