Clinical use:

Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume, including hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration. Reactions were more common in patients over 75 years of age and with 300 mg daily. Smaller reductions in A1C with INVOKANA® relative to placebo were seen in patients 65 years and older, compared to younger patients.

Contraindications:

Patients on dialysis.

Most serious warnings and precautions:

Diabetic Ketoacidosis (DKA): Clinical trial and post-market cases of DKA, a serious life-threatening condition requiring urgent hospitalization, have been reported in patients with type 2 diabetes mellitus treated with INVOKANA® or other sodium-glucose co-transporter 2 (SGLT2) inhibitors. Fatal cases of DKA have been reported in patients taking INVOKANA®. A number of these cases have been atypical with blood glucose values below 13.9 mmol/L (250 mg/dL). The risk of DKA must be considered in the event of non-specific symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, anorexia, excessive thirst, and unusual fatigue or sleepiness. If these symptoms occur, regardless of blood glucose level, INVOKANA® treatment should be **immediately discontinued and patients should be assessed for DKA immediately**.
INVOKANA® should not be used for the treatment of DKA or in patients with a history of DKA. Nephropathy may increase the risk of DKA during treatment with INVOKANA®. INVOKANA® is not indicated, and should not be used, in patients with type 1 diabetes.

Lower Limb Amputation: An approximately 2-fold increased risk of lower limb amputations associated with INVOKANA® use was observed in CANVAS and CANVAS-R, two large, randomized, placebo-controlled trials in patients with type 2 diabetes who had established CVD or were at risk for CVD. Amputations of the toe and midfoot were most frequent; however, amputations involving the leg were also observed. Some patients had multiple amputations, some involving both limbs. Before initiating INVOKANA®, consider factors that may increase the risk of amputation, such as a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers.
Monitor patients receiving INVOKANA® for infection, new pain or tenderness, sores, or ulcers involving the lower limbs, and discontinue INVOKANA® if these complications occur.

Other relevant warnings and precautions:

- Risk of DKA, particularly in patients on a very low carbohydrate diet and patients with: conditions that lead to restricted food intake or severe dehydration; increased insulin requirement due to an acute medical illness, surgery, or alcohol abuse; low beta-cell function reserve (e.g., type 2 diabetes patients with low C-peptide or latent autoimmune diabetes in adults); pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis, or pancreatic surgery); insulin dose reduction (including insulin pump failure); history of ketoacidosis. Temporarily discontinue treatment in patients who are hospitalized for major surgical procedures, or will undergo scheduled surgery, and patients who are hospitalized for serious infections or acute serious medical illnesses. Monitor patients for DKA even if treatment was interrupted or discontinued; ensure risk factors are resolved prior to restarting INVOKANA®. Educate patients on signs and symptoms of DKA and instruct them to discontinue INVOKANA® and seek immediate medical attention if they occur.
- Risk of reduced intravascular volume may lead to postural dizziness, orthostatic hypotension, hypotension, or renal failure, particularly in patients on loop diuretics or medications that interfere with the renin-angiotensin-aldosterone system. (e.g., angiotensin-converting-enzyme inhibitors [ACEi], angiotensin receptor blockers [ARBs]), patients with low systolic blood pressure, patients with moderate renal impairment, and elderly patients. Not recommended for use in patients who are receiving loop diuretics or who are volume-depleted. Normalize volume before initiating INVOKANA®. Volume status should be assessed prior to treatment initiation and carefully monitored throughout therapy in those at risk.
- The effect of INVOKANA® on the ability to drive or use machinery has not been examined. Alert patients to the elevated risk of adverse reactions related to reduced intravascular volume, such as postural dizziness, and the risk of hypoglycemia.
- Risk of hypoglycemia in add-on therapy with other antihyperglycemic agents.
- Monitor for increases in LDL-C.
- Risk of genital mycotic infections and urinary tract infections.
- Risk of Fournier's gangrene (necrotizing fasciitis of the perineum), a rare but serious and potentially life-threatening infection requiring urgent treatment.
- Use with caution in patients with elevated hemoglobin/hematocrit.
- Risk of serious hypersensitivity reactions, including angioedema and anaphylaxis.
- Risk of bone fracture.
- Risk of increased serum creatinine, decreased eGFR (in a dose-dependent fashion), and renal function abnormalities and acute kidney injury including acute renal failure and decline in eGFR.
- Renal function should be assessed prior to initiation and regularly thereafter, with more frequent and intensive monitoring for glycemic and renal biomarkers and signs and symptoms of renal dysfunction in patients whose eGFR is <60 mL/min/1.73 m^2, especially if eGFR is <45 mL/min/1.73 m^2. The glucose-lowering benefit of INVOKANA® decreases with declining renal function and has not been demonstrated for patients with eGFR <30 mL/min/1.73 m^2.
- Do not use in pregnant and breastfeeding women.
- INVOKANA® may increase digoxin AUC and C_{max}; patients taking concomitant digoxin should therefore be monitored appropriately.
- Not recommended in patients with severe hepatic impairment.
- Monitor blood glucose and A1C.

For more information:

Please consult the Product Monograph available at www.janssen.com/canada/our-medicines for important information relating to adverse reactions, drug interactions, and dosage and administration that has not been discussed in this piece. The Product Monograph is also available by calling us at 1-800-567-3331.

CREDENCE study parameters: A randomized, double-blind, placebo-controlled clinical trial to examine the effects of INVOKANA® in adults with type 2 diabetes (T2D) and diabetic nephropathy on a background of standard-of-care therapy. Following a 2-week single-blind, placebo run-in period, participants were randomized to receive either INVOKANA® 100 mg (n=2202) or placebo (n=2199). Treatment with INVOKANA® was continued until the initiation of dialysis or renal transplantation. Mean exposure was 115 weeks. The primary endpoint was the time to first occurrence of one of end-stage kidney disease, doubling of serum creatinine, and renal or cardiovascular (CV) death.[1,4]

CANVAS Program study parameters: Two multicentre, multi-national, randomized, double-blind, placebo-controlled, parallel-group studies that examined the effect of INVOKANA® on CV risk in adults with T2D who had established cardiovascular disease (CVD) or were at risk for CVD (≥2 CV risk factors). The primary endpoint was the time to first occurrence of a major adverse cardiovascular event, which was defined as a composite of CV death, nonfatal myocardial infarction (MI), and nonfatal stroke. A total of 10,134 patients were treated with INVOKANA® (n=5790) or placebo (n=4344) in addition to standard-of-care treatments for diabetes and atherosclerotic CVD. The mean duration of treatment was 149.2 weeks. In CANVAS, subjects were randomly assigned 1:1:1 to INVOKANA® 100 mg, INVOKANA® 300 mg, or matching placebo. In CANVAS-R, subjects were randomly assigned 1:1 to INVOKANA® 100 mg or matching placebo, and titration to 300 mg was permitted at the investigator's discretion (based on tolerability and glycemic needs) at Week 13 or later visits. Concomitant antidiabetic and atherosclerotic therapies could be adjusted, at the discretion of investigators, to ensure participants were treated according to the standard care for these diseases.[1]

References: 1. INVOKANA® (canagliflozin) Product Monograph. Janssen Inc. February 16, 2023. **2.** Data on file, Janssen Inc **3.** Scherntha ner G, Gross JL, Rosenstock J, *et al.* Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week randomized trial. *Diabetes Care* 2013;36(9):2508–2515. **4.** Perkovic V, Jardine MJ, Neal B, *et al.* Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019;380(24):2295–2306. **5.** Neal B, Perkovic V, Mahaffey KW, *et al.* Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;377(7):644–657.

Pr Invokana® canagliflozin tablets

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ALL ABOUT INVOKANA®

Pr Invokana® canagliflozin tablets

In 2014, INVOKANA® became the FIRST-TO-MARKET SGLT2i* with an indication:

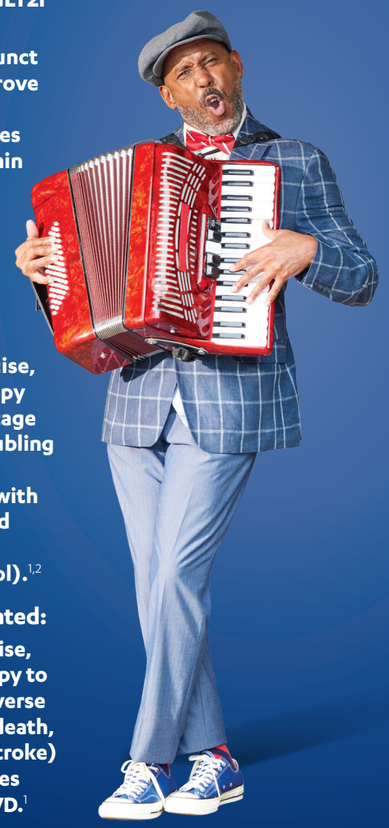
For monotherapy as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus for whom metformin is inappropriate due to contraindications or intolerance.[1,2]

In 2020, INVOKANA® became the FIRST SGLT2i* with an indication:

As an adjunct to diet, exercise, and standard-of-care therapy to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, and CV death in adult patients with type 2 diabetes mellitus and diabetic nephropathy with albuminuria (>33.9 mg/mmol).[1,2]

INVOKANA® is also indicated:

As an adjunct to diet, exercise, and standard-of-care therapy to reduce the risk of major adverse cardiovascular events (CV death, nonfatal MI, and nonfatal stroke) in adults with type 2 diabetes mellitus and established CVD.[1]

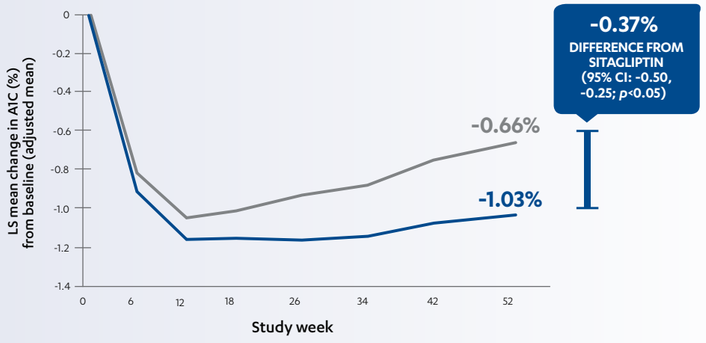


SGLT2i=sodium-glucose co-transporter 2 inhibitor; CV=cardiovascular; MI=myocardial infarction; CVD=cardiovascular disease.
* Comparative clinical significance has not been established.

In a study comparing INVOKANA® 300 mg to sitagliptin 100 mg as add-on therapy with metformin and a sulfonylurea in a general population of patients with T2D

Patients treated with **INVOKANA® achieved a mean decrease in A1C of 1.03%** at 52 weeks (vs. a mean decrease of 0.66% with sitagliptin)[1,3*]

MEAN CHANGE IN A1C FROM BASELINE[1,3]



Adapted from Schernthaner G, *et al.*, 2013[3]

>> **35% more patients reached glycemic target** than with sitagliptin.[1,3*]
47.6% vs. 35.3% of patients achieved an A1C <7% (secondary endpoint).

INVOKANA® is also 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.[1]

T2D=type 2 diabetes; A1C=glycated hemoglobin; LS=least squares; CI=confidence interval.
* Randomized, double-blind, active-controlled, parallel-group, multicentre trial over 52 weeks. 755 adults with type 2 diabetes were randomized to INVOKANA® 300 mg/day + metformin + a sulfonylurea (n=377) or sitagliptin 100 mg/day + metformin + a sulfonylurea (n=378). Baseline (mean) A1C values were 8.12% for INVOKANA® 300 mg and 8.13% for sitagliptin 100 mg.

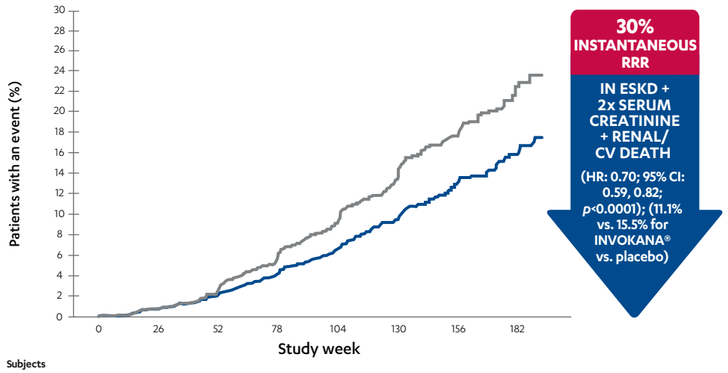
In CREDENCE, **all patients were adults with T2D and diabetic nephropathy** with an eGFR ≥30 to <90 mL/min/1.73 m² and albuminuria (>33.9 to ≤565.6 mg/mmol of creatinine) **receiving standard-of-care therapy** at baseline[1]

INVOKANA® demonstrated a **30% instantaneous RRR in the first occurrence of the primary composite endpoint (end-stage kidney disease, doubling of serum creatinine, and renal or CV death)** vs. placebo (HR: 0.70; 95% CI: 0.59, 0.82; *p*<0.0001); (11.1% vs. 15.5%)[1*]

CV death was not statistically significant.

>> Results were achieved **on top of standard-of-care therapy**, including maximally tolerated labelled dose of an ACEi or an ARB.[1]

TIME TO FIRST OCCURRENCE OF THE PRIMARY COMPOSITE ENDPOINT IN CREDENCE[1]



Subjects								
placebo	2199	2178	2132	2047	1725	1129	621	170
INVOKANA®	2202	2181	2145	2081	1786	1211	646	196

INVOKANA® placebo

Adapted from the INVOKANA® Product Monograph[1]

The curves began to separate by Week 52 and continued to diverge thereafter.[1]

NNT=22 Number needed to treat with INVOKANA® over 2.5 years to prevent one of these events[4]

See back page for CREDENCE study parameters.

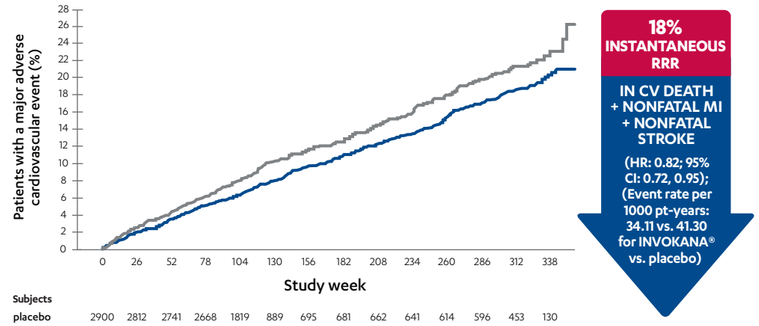
RRR=relative risk reduction; CV=cardiovascular; HR=hazard ratio; CI=confidence interval; T2D=type 2 diabetes; eGFR=estimated glomerular filtration rate; ACEi=angiotensin-converting-enzyme inhibitor; ARB=angiotensin receptor blocker; ESKD=end-stage kidney disease; NNT=number needed to treat.
* Intent-to-treat (ITT) analysis. HR and 95% CI estimated using a stratified Cox proportional hazards regression model with treatment as the explanatory variable and stratified by eGFR at screening.[1]

In the CANVAS Program, **all patients were adults with T2D who had established cardiovascular disease (CVD) or were at risk for CVD** (≥2 CV risk factors)[1]

INVOKANA® demonstrated a **14% instantaneous RRR in the first occurrence of a major adverse cardiovascular event** (HR: 0.86; 95% CI: 0.75, 0.97; *p*=0.0158 for superiority)[1*]

The reduction in the composite of CV death + nonfatal MI + nonfatal stroke was accounted for by the subgroup of patients with **established CVD** (HR: 0.82; 95% CI: 0.72, 0.95)[1]

TIME TO FIRST OCCURRENCE OF A MAJOR ADVERSE CARDIOVASCULAR EVENT IN PATIENTS WITH ESTABLISHED CVD IN THE INTEGRATED POPULATION OF THE CANVAS PROGRAM (ITT ANALYSIS SET)[1]



Subjects													
placebo	2900	2812	2741	2668	1819	889	695	681	662	641	614	596	453	130
INVOKANA®	3756	3661	3583	3493	2675	1708	1459	1431	1400	1374	1329	1291	974	261

INVOKANA® placebo

Adapted from the INVOKANA® Product Monograph[1]

>> Of all patients in the CANVAS Program, 66% had established CVD. The subgroup of patients with only risk factors for CVD at baseline (34% of all patients) had an HR of 0.98 (95% CI: 0.74, 1.30).[1†]

>> INVOKANA® is not indicated to reduce the risk of major adverse cardiovascular events in patients at risk for CVD.

See back page for study parameters of the CANVAS Program.

RRR=relative risk reduction; HR=hazard ratio; CI=confidence interval; CV=cardiovascular; MI=myocardial infarction; CVD=cardiovascular disease; ITT=intent-to-treat; pt=patient.
* HR and 95% CI estimated using a stratified Cox proportional hazards regression model with stratification by study and by established CVD.[1]
† The subgroup of patients at risk for CVD had ≥2 of the following CVD risk factors: duration of diabetes ≥10 years, systolic blood pressure >140 mmHg while on ≥1 antihypertensive agent, current smoker, microalbuminuria or macroalbuminuria, high-density lipoprotein (HDL) cholesterol <1 mmol/L.[5]

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