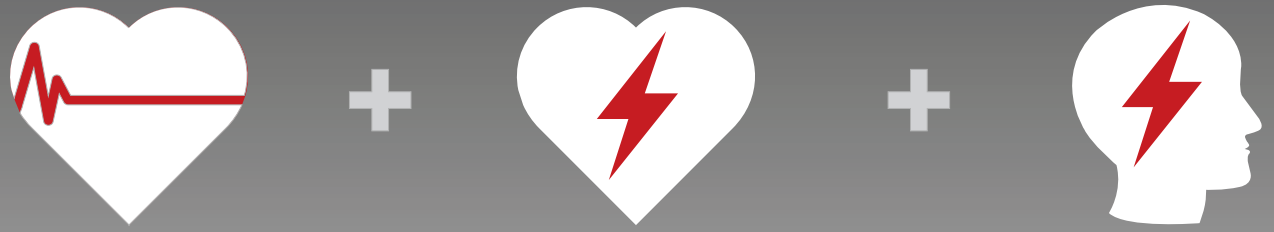
MAJOR ADVERSE CARDIOVASCULAR EVENTS[1]

MACE includes **ALL** of these outcomes:[1]



CV death + **Nonfatal MI** + **Nonfatal stroke**

CV=cardiovascular; MI=myocardial infarction.

As an adjunct to diet, exercise and standard-of-care therapy in adults with T2D and established CVD...

INVOKANA® CAN:

CV DEATH + STROKE + MI

Help reduce the risk of MACE
(CV death, nonfatal MI and nonfatal stroke).[2]

INVOKANA® is 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.[2]

T2D=type 2 diabetes; CVD=cardiovascular disease.

References: 1. Diabetes Canada. 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Can J Diabetes* 2018;42(suppl 1):S1–S325. **2.** INVOKANA® Product Monograph. Janssen Inc. May 20, 2020.

Pr Invokana® canagliflozin tablets

Pr Invokana® canagliflozin tablets

Indications not previously discussed:

INVOKANA® (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus:

As a monotherapy in patients for whom metformin is inappropriate due to contraindications or intolerance.

In combination with metformin or a sulfonylurea when diet and exercise plus monotherapy with one of these agents do not provide adequate glycemic control.

In combination with metformin and either a sulfonylurea or pioglitazone when diet, exercise and dual therapy (with metformin plus either a sulfonylurea or pioglitazone) do not provide adequate glycemic control.

In combination with metformin and sitagliptin when diet, exercise and dual therapy (with metformin and sitagliptin) do not provide adequate glycemic control.

In combination with insulin (with or without metformin) when diet, exercise and insulin therapy do not provide adequate glycemic control.

INVOKANA® (canagliflozin) is also 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 CV death in adult patients with type 2 diabetes mellitus and diabetic nephropathy with albuminuria (>33.9 mg/mmol).

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 HbA1C 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 [ACEis], angiotensin receptor blockers [ARBs]), patients with low systolic blood pressure, patients with moderate renal impairment, and patients ≥75 years of age. Not recommended for use in patients who are volume-depleted. Volume status should be assessed prior to treatment initiation and carefully monitored throughout therapy in those at risk.
- 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. In patients with eGFR <60 mL/min/1.73 m^2, more intensive monitoring for glycemic and renal biomarkers and signs and symptoms of renal dysfunction is recommended, 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/products 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.

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