

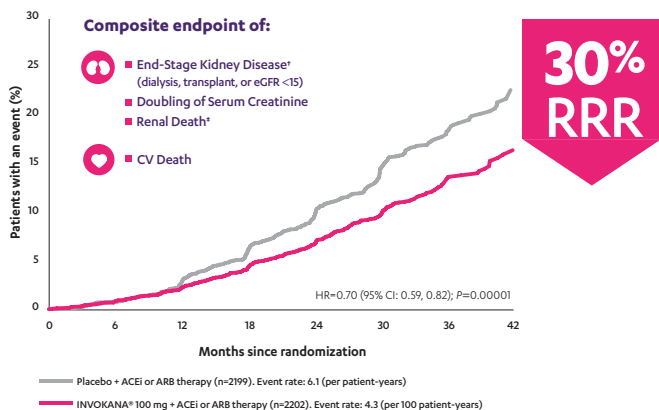
INVOKANA®: The FIRST therapy for diabetic nephropathy (ie, DKD) in T2D approved by the FDA in ~20 years^{1,2}

INVOKANA® : the FIRST T2D therapy indicated to reduce the risk of ESKD, doubling of serum creatinine, CV death, and hospitalization for heart failure in adults who have T2D and diabetic nephropathy with albuminuria >300 mg/day³

In adults with DKD* and T2D who were taking a maximum tolerated dose of an ACEi or ARB⁴:

- Mean baseline eGFR of 56.2
- Median urinary albumin-to-creatinine ratio of 927 mg/g

Primary endpoint⁴:



*With albuminuria >300 mg/day.

[†]End-stage kidney disease was defined as dialysis for ≥30 days, kidney transplantation, or an eGFR <15 mL/min/1.73 m² sustained for ≥30 days.

[‡]There were not enough events to evaluate the risk of renal death (placebo, n=5; INVOKANA®, n=2).
INVOKANA® is not indicated to reduce the risk of renal death.

INDICATIONS

INVOKANA® (canagliflozin) is indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- 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)
- to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria greater than 300 mg/day

Limitations of Use

INVOKANA® is not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.

INVOKANA® is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 30 mL/min/1.73 m².

INVOKANA® is likely to be ineffective in this setting based upon its mechanism of action.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- Serious hypersensitivity reaction to INVOKANA®, such as anaphylaxis or angioedema
- Patients on dialysis

WARNINGS AND PRECAUTIONS

- **Lower-Limb Amputation:** An increased risk of lower-limb amputations associated with INVOKANA® use versus placebo was observed in CANVAS (5.9 vs 2.8 events per 1000 patient-years) and CANVAS-R (7.5 vs 4.2 events per 1000 patient-years), two randomized, placebo-controlled trials evaluating patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease. The risk of lower-limb amputations was observed at both the 100-mg and 300-mg once-daily dosage regimens. Amputations of the toe and midfoot (99 out of 140 patients with amputations receiving INVOKANA® in the two trials) were the most frequent; however, amputations involving the leg, below and above the knee, were also observed (41 out of 140 patients with amputations receiving INVOKANA® in the two trials). Some patients had multiple amputations, some involving both lower limbs. Lower-limb infections, gangrene, and diabetic foot ulcers were the most

Proven safety profile in adults with an eGFR of 30 to <90^{3,4}

- Similar overall AEs with INVOKANA® vs placebo (35.1 vs 37.9 per 100 patient-years). Male GMI incidence was 0.84% vs 0.09% per 100 patient-years, respectively. DKA incidence was 0.22% vs 0.02% per 100 patient-years, respectively. No imbalance in fracture or amputation. Hypotension incidence was 2.8% vs 1.5%, respectively.³ Hypoglycemia incidence was 4.43 vs 4.89 per 100 patient-years, respectively.⁴

INVOKANA® 100 mg : the FIRST SGLT2i approved for use in adults with DKD* and T2D with an eGFR as low as 30^{3,5-7}

- Patients already on INVOKANA® whose eGFR declines below 30, with albuminuria >300 mg/day, can continue on the 100-mg dose unless dialysis is initiated³

INVOKANA® is contraindicated in patients with serious hypersensitivity reaction to INVOKANA® and patients on dialysis.³

ACEi=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; CV=cardiovascular; DKD=diabetic kidney disease; ESKD=end-stage kidney disease; HR=hazard ratio; RRR=relative risk reduction; T2D=type 2 diabetes. eGFR is measured in mL/min/1.73 m².

common precipitating medical events leading to the need for an amputation. The risk of amputation was highest in patients with a baseline history of prior amputation, peripheral vascular disease, and neuropathy.

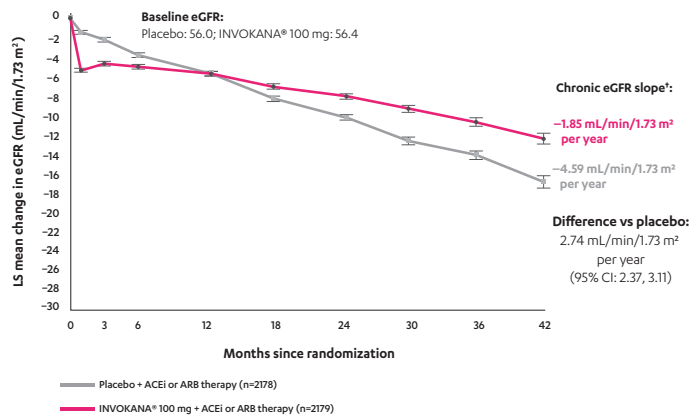
Before initiating INVOKANA®, consider factors in the patient history that may predispose to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers. Counsel patients about the importance of routine preventative foot care. Monitor patients for signs and symptoms of infection (including osteomyelitis), new pain or tenderness, sores, or ulcers involving the lower limbs, and discontinue if these complications occur.

- **Volume Depletion:** INVOKANA® can cause intravascular volume contraction, which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine. There have been postmarketing reports of acute kidney injury which are likely related to volume depletion, some requiring hospitalizations and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including INVOKANA®. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m²), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating INVOKANA® in patients with one or more of these characteristics,

Please read additional Important Safety Information on the following page. Please read full [Prescribing Information and Medication Guide](#) for INVOKANA®.

In patients with DKD* and T2D,

Exploratory endpoint: Mean change from baseline in eGFR⁴ eGFR over 3.5 years with INVOKANA® vs placebo⁴



LS=least squares.

eGFR is measured in mL/min/1.73 m².

*With albuminuria >300 mg/day.

[†]From week 3 to month 42.

Study design

CREDESCENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) was a randomized, double-blind, placebo-controlled, parallel group, multicenter, event-driven clinical trial. The trial compared the effects of INVOKANA® 100 mg vs placebo in 4401 men and women with type 2 diabetes and diabetic kidney disease (described as chronic kidney disease with eGFR 30 to <90 mL/min/1.73 m² and albuminuria [ratio of albumin to creatinine >300 to 5000 mg/g]) who were already taking a stable, maximum-tolerated, or labeled dose (for ≥4 weeks prior to randomization) of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). The mean eGFR of patients was 56.2 mL/min/1.73 m² and the median urinary albumin-to-creatinine ratio was 927 mg/g. The primary efficacy outcome was the composite of end-stage kidney disease (dialysis, transplant, or eGFR <15 mL/min/1.73 m²), doubling of serum creatinine, or renal or cardiovascular (CV) death. Prespecified secondary outcomes included a composite of CV death or hospitalization for heart failure; a composite of heart attack, stroke, or CV death; hospitalization for heart failure; and a composite of end-stage kidney disease, doubling of the serum creatinine level, or renal death.⁴

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Volume Depletion (cont'd):** assess and correct volume status. Monitor for signs and symptoms of volume depletion after initiating therapy.
- **Ketoacidosis:** Ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, has been identified in patients with type 1 and 2 diabetes mellitus receiving SGLT2 inhibitors, including INVOKANA®. In placebo-controlled trials of patients with type 1 diabetes, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. The risk of ketoacidosis may be greater with higher doses. Fatal cases of ketoacidosis have been reported in patients taking INVOKANA®. Before initiating INVOKANA®, consider factors in patient history that may predispose to ketoacidosis. For patients who undergo scheduled surgery, consider temporarily discontinuing INVOKANA® for at least 3 days prior to surgery. Monitor for ketoacidosis and temporarily discontinue in other clinical situations known to predispose to ketoacidosis. Ensure risk factors for ketoacidosis are resolved prior to restarting therapy. Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue INVOKANA® and seek medical attention immediately if signs and symptoms occur.
- **Urosepsis and Pyelonephritis:** Serious urinary tract infections, including urosepsis and pyelonephritis, requiring hospitalization have been reported in patients receiving SGLT2 inhibitors, including INVOKANA®. Treatment with SGLT2 inhibitors increases this risk. Evaluate for signs and symptoms and treat promptly.
- **Hypoglycemia With Concomitant Use With Insulin and Insulin Secretagogues:** Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA® may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA®.
- **Necrotizing Fasciitis of the Perineum (Fournier's Gangrene):** Necrotizing fasciitis of the perineum, a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, has been identified in postmarketing surveillance in female and male patients with diabetes mellitus receiving SGLT2 inhibitors, including INVOKANA®. Serious outcomes have included hospitalization, multiple surgeries, and death. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue INVOKANA®.
- **Genital Mycotic Infections:** INVOKANA® increases risk of genital mycotic infections, especially in uncircumcised males or patients with prior infections. Monitor and treat appropriately.

- **Hypersensitivity Reactions:** Hypersensitivity reactions, including angioedema and anaphylaxis, were reported with INVOKANA®; these reactions generally occurred within hours to days after initiation. If reactions occur, discontinue INVOKANA®, treat, and monitor until signs and symptoms resolve.
- **Bone Fracture:** Increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed in patients using INVOKANA®. Prior to initiation, consider factors that contribute to fracture risk.

DRUG INTERACTIONS

- **UGT Enzyme Inducers:** Co-administration with rifampin lowered INVOKANA® exposure, which may reduce the efficacy of INVOKANA®. For patients with eGFR ≥60 mL/min/1.73 m², if an inducer of UGTs (eg, rifampin, phenytoin, phenobarbital, ritonavir) is co-administered with INVOKANA®, increase the dose to 200 mg (taken as two 100 mg tablets) once daily in patients currently tolerating INVOKANA® 100 mg. The dose may be increased to 300 mg once daily in patients currently tolerating INVOKANA® 200 mg and who require additional glycemic control.
- For patients with eGFR <60 mL/min/1.73 m², if an inducer of UGTs is co-administered with INVOKANA®, increase the dose to 200 mg (taken as two 100 mg tablets) once daily in patients currently tolerating INVOKANA® 100 mg. Consider adding another antihyperglycemic agent in patients who require additional glycemic control.
- **Digoxin:** There was an increase in the AUC and mean peak drug concentration of digoxin when co-administered with INVOKANA® 300 mg. Monitor appropriately.
- **Positive Urine Glucose Test:** Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
- **Interference With 1,5-Anhydroglucitol (1,5-AG) Assay:** Monitoring glycemic control with 1,5-AG assay is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** INVOKANA® is not recommended in pregnant women, especially during the second and third trimesters.
- **Lactation:** INVOKANA® is not recommended while breastfeeding.
- **Pediatric Use:** Safety and effectiveness in patients <18 years of age have not been established.
- **Geriatric Use:** Patients ≥65 years had a higher incidence of adverse reactions related to reduced intravascular volume, particularly with the 300-mg dose; more prominent increase in the incidence was seen in patients who were ≥75 years. Smaller reductions in HbA1c relative to placebo were seen in patients ≥65 years.
- **Renal Impairment:** The efficacy and safety of INVOKANA® for glycemic control were evaluated in a trial that included patients with moderate renal impairment (eGFR 30 to <50 mL/min/1.73 m²). These patients had less overall glycemic efficacy, and patients treated with 300 mg per day had increases in serum potassium, which were transient and similar by the end of the study. Patients with renal impairment using INVOKANA® for glycemic control may be more likely to experience hypotension and may be at a higher risk for acute kidney injury. INVOKANA® is contraindicated in patients with ESKD on dialysis.
- **Hepatic Impairment:** INVOKANA® has not been studied in patients with severe hepatic impairment and is not recommended in this population.

OVERDOSAGE

- In the event of an overdose, contact the Poison Control Center and employ the usual supportive measures.

ADVERSE REACTIONS

- The most common adverse reactions associated with INVOKANA® (5% or greater incidence) were female genital mycotic infections, urinary tract infections, and increased urination.

Please read full Prescribing Information and Medication Guide for INVOKANA®.

References: 1. Cozaar® [prescribing information]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. 2. Avapro® [prescribing information]. Bridgewater, NJ: Sanofi-Aventis U.S. LLC, a Sanofi company. 3. INVOKANA® [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc. 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. Jardiance® [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. 6. Farxiga® [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP. 7. Steglatro™ [prescribing information]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

Janssen Pharmaceuticals, Inc.

Canagliflozin is licensed from Mitsubishi Tanabe Pharma Corporation.

© Janssen Pharmaceuticals, Inc. 2021

June 2021

cp-149253v4

