Invokana (canagliflozin)

FIRST LOOK: NEW INDICATION

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Introduction

- **Brand name:** Invokana
- **Generic name:** Canagliflozin
- **Pharmacologic class:** Sodium-glucose co-transporter 2 (SGLT2) inhibitor
- **Strength and Formulation:** 100mg, 300mg; tablets
- **Manufacturer:** Janssen
- **How supplied:** Bottles—30, 90, 500 tablets
- **Legal Classification:** Rx

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New Indication

- Canagliflozin is indicated to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria >300mg/day

CREDENCE Clinical Trial

- Approval based on Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation Trial (**CREDENCE**)
- Multinational, randomized, double-blind, placebo-controlled trial comparing canagliflozin with placebo in patients with type 2 diabetes, an eGFR ≥30 to <90mL/min/1.73 m^2 and albuminuria (urine albumin/creatinine >300 to ≤5000mg/g) receiving standard of care including maximum-tolerated, labeled daily dose of angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB)

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CREDENCE Clinical Trial

- Patients randomized to receive canagliflozin 100mg (n=2202) or placebo (n=2199); treatment continued until initiation of dialysis or renal transplantation
- At randomization:
  - Mean HbA1c: 8.3%
  - Median urine albumin/creatinine: 927mg/g
  - Mean eGFR: 56.2 mL/min/1.73m^2
  - 50% had prior CV disease, and 15% reported history of heart failure
  - Most frequent antihyperglycemic agents used at baseline: insulin (66%), biguanides (58%), sulfonylureas (29%)
  - 99.9% of patients on ACEi or ARB, approximately 60% taking antithrombotic agent (including aspirin); 69% were on statin

CREDENCE Clinical Trial

- **Primary composite endpoint**: time to first occurrence of end stage kidney disease (ESKD; defined as eGFR <15 mL/min/1.73 m^2, initiation of chronic dialysis or renal transplant), doubling of serum creatinine, and renal or CV death

- Median follow-up duration was 137 weeks

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CREDENCE Clinical Trial

- Canagliflozin 100mg significantly reduced risk of primary composite endpoint based on time-to-event analysis (hazard ratio [HR] 0.70; 95% CI, 0.59-0.82; *P* <.0001)
- Treatment effect reflected a reduction in progression to ESKD (HR 0.68; 95% CI, 0.54-0.86), doubling of serum creatinine (HR 0.60; 95% CI, 0.48-0.76) and cardiovascular death (HR 0.78; 95% CI, 0.61-1.00)
- Canagliflozin 100mg also significantly reduced risk of hospitalization for heart failure (HR 0.61; 95% CI, 0.47-0.80; *P* <.001]
- There were few renal deaths during the trial: 2 and 5 in the canagliflozin and placebo arms, respectively

CREDENCE Clinical Trial

- Rate of lower limb amputations associated with canagliflozin 100mg relative to placebo was 12.3 vs 11.2 events per 1000 patient-years, respectively
- Incidence rates of adjudicated events of diabetic ketoacidosis were 0.21 (0.5%, 12/2200) and 0.03 (0.1%, 2/2197) per 100 patient-years of follow-up with canagliflozin 100mg and placebo, respectively
- Incidence of acute kidney injury was similar between canagliflozin 100mg and placebo
- Incidence of hypotension was 2.8% and 1.5% on canagliflozin 100mg and placebo, respectively

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Other Indications

- **Also indicated for:**
  - 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

Limitations of Use

- Not recommended in patients with type 1 diabetes mellitus or for treatment of diabetic ketoacidosis

Dosage and Administration

- Take before first meal of the day
- Assess renal function before initiating and periodically thereafter:
  - **eGFR ≥60mL/min/1.73m^2**: Initially 100mg once daily; may increase to 300mg once daily for additional glycemic control
  - **eGFR 45–<60mL/min/1.73m^2**: 100mg once daily
  - **eGFR 30–<45mL/min/1.73m^2 with albuminuria >300mg/day**: 100mg once daily
- In patients already initiated on therapy who meet the criterion of eGFR <30mL/min/1.73m^2 with albuminuria >300mg/day, therapy can be continued at 100mg once daily

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Dosage and Administration

- **Concomitant UDP-Glucuronosyl Transferase (UGT) enzyme inducers**
  - *eGFR ≥60mL/min/1.73m^2*: increase to 200mg once daily in patients currently tolerating 100mg, may increase to 300mg once daily in those tolerating 200mg and require additional glycemic control
  - *eGFR <60mL/min/1.73m^2*: increase to 200mg once daily in patients currently tolerating 100mg, consider adding another antihyperglycemic agent if additional glycemic control required

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Considerations for Special Populations

- **Pregnancy:** not recommended during second and third trimesters
- **Nursing mothers**: not recommended while breastfeeding
- **Pediatric**: safety and effectiveness have not been established in patients less than 18 years of age
- **Geriatric:** ≥65 years: higher incidence of adverse reactions related to reduced intravascular volume (particularly with 300mg dose); smaller reductions in HbA1c compared with younger patients

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Considerations for Special Populations

- **Renal impairment**:
  - Moderate impairment (eGFR 30 to <50mL/min/1.73m^2): patients had less overall glycemic efficacy; 300mg dose associated with increases in potassium
  - Patients with renal impairment using canagliflozin for glycemic control may also be more likely to experience hypotension and may be at higher risk of acute kidney injury
  - Studies did not enroll patients with ESKD on dialysis or patients with eGFR <30mL/min/1.73m^2
  - Contraindicated in patients with ESKD on dialysis
- **Hepatic impairment**: not recommended in patients with severe impairment

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Contraindications

- Patients with severe renal impairment (eGFR <30mL/min/1.73m^2) who are being treated for glycemic control
- Patients on dialysis

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Boxed Warnings

- **Lower limb amputation**
  - Increased risk in patients with T2D who have established cardiovascular disease (CVD) or at risk of CVD
  - Toe and midfoot most frequent; some involved leg
  - Consider factors that may increase amputation risk
  - Monitor for infections or ulcers of lower limbs; discontinue use if occurs

Warnings and Precautions

- Increased risk of **lower limb amputations**; monitor for infection, new pain or tenderness, sores or ulcers in lower limbs, and discontinue if occur
- Consider risk factors for amputation (eg, prior amputation, peripheral vascular disease, neuropathy, diabetic foot ulcers) before initiation
- Correct **volume depletion** before starting therapy
- Monitor for **symptomatic hypotension** in renal impairment, elderly, low systolic BP, concomitant diuretics or drugs that interfere with the RAA system (eg, ACEIs, ARBs)

Warnings and Precautions

- Assess for **ketoacidosis** in presence of signs/symptoms of metabolic acidosis, regardless of blood glucose levels; discontinue if suspected, evaluate and treat; consider risk factors before initiation (eg, pancreatic insulin deficiency, caloric restriction, alcohol abuse)
- Consider temporarily discontinuing prior to **scheduled surgery** (for 3 days) or other clinical situations (eg, prolonged fasting due to acute illness or post-surgery)

Warnings and Precautions

- Evaluate **renal function** prior to starting and monitor periodically thereafter
- Risk of acute kidney injury in hypovolemia, chronic renal insufficiency, congestive heart failure, and concomitant drugs (eg, diuretics, ACEIs, ARBs, NSAIDs)
- Consider temporarily discontinuing in the setting of reduced oral intake or fluid losses; monitor for acute kidney injury; discontinue and treat if occurs

Warnings and Precautions

- Discontinue if hypersensitivity reactions occur; monitor until resolved
- Consider **bone fracture** risks before initiation
- Necrotizing fasciitis of the perineum (**Fournier gangrene**); discontinue and treat immediately if suspected; use alternative antidiabetic
- Monitor for **genital mycotic infections**, UTIs; treat if needed

Interactions

- Antagonized by **UGT inducers** (eg, rifampin, phenytoin, phenobarbital, ritonavir): see Dosage and Administration
- Concomitant digoxin: monitor
- Consider a lower dose of concomitant insulin/insulin secretagogue to reduce risk of hypoglycemia
- May cause false (+) urine glucose tests or unreliable measurements of 1,5-anhydroglucitol assay; use alternative methods to monitor glycemic control

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Adverse Reactions

- **Most common (5% or greater incidence)**: female genital mycotic infections, urinary tract infection, increased urination

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Mechanism of Action

- Canagliflozin is an inhibitor of sodium-glucose co-transporter 2 (SGLT2)
- By inhibiting SGLT2, canagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion
- Canagliflozin increases delivery of sodium to distal tubule by blocking SGLT2-dependent glucose and sodium reabsorption
  - This is believed to increase tubuloglomerular feedback and reduce intraglomerular pressure

Pharmacokinetics

- Terminal half-life: 10.6 hours and 13.1 hours for 100mg and 300mg doses, respectively
- Steady-state reached after 4-5 days of once-daily dosing with canagliflozin 100mg to 300mg
- Protein binding: 99%
- Metabolism:
  - O-glucuronidation is the major metabolic elimination pathway for canagliflozin, which is mainly glucuronidated by UGT1A9 and UGT2B4 to 2 inactive O-glucuronide metabolites
  - Minimal CYP3A4-mediated (oxidative) metabolism
- Excretion: Fecal, renal

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New Product Monograph

- For more information view the product monograph available at:

  https://www.empr.com/drug/invokana/