

# Invokana (canagliflozin)



**NEW INDICATION REVIEW**

**MPR**

# Introduction

- **Brand name:** Invokana
- **Generic name:** Canagliflozin
- **Pharmacological class:** Sodium-glucose co-transporter 2 (SGLT2) inhibitor
- **Strength and Formulation:** 100mg, 300mg; tabs
- **Manufacturer:** Janssen Pharmaceuticals
- **How supplied:** Tabs—30, 90, 100 (10x10 blister cards), 500
- **Legal Classification:** Rx

# Invokana



# New Indication

- To reduce the risk of major cardiovascular (CV) events (eg, CV death, nonfatal MI and stroke) in adults with type 2 diabetes mellitus (T2DM) and established CV disease

# Other Indication

- Also indicated for:
  - Adjunct to diet and exercise to improve glycemic control in adults with T2DM
  - **Limitations of use:** Not for treating type 1 diabetes or diabetic ketoacidosis

# Dosage & Administration

- Take before first meal of the day
- Initially 100mg once daily
  - If tolerated, and with eGFR  $\geq 60$  mL/min/1.73m<sup>2</sup> and need additional glycemic control; may increase to 300mg once daily

# Dosage & Administration

- **Renal impairment:**
  - eGFR 45–<60mL/min/1.73m<sup>2</sup>: 100mg once daily
  - eGFR <45mL/min/1.73m<sup>2</sup>: do not initiate
- **Concomitant UGT inducers:**
  - eGFR ≥60mL/min/1.73m<sup>2</sup>: consider increase to 300mg once daily
  - eGFR 45–<60mL/min/1.73m<sup>2</sup>: consider other antihyperglycemics

# Considerations for Special Populations

- **Pediatric:** <18yrs: not established
- **Pregnancy:** Risk to fetus during the 2<sup>nd</sup> and 3<sup>rd</sup> trimesters: not recommended
- **Nursing mothers:** Not recommended
- **Elderly:** Higher incidence of adverse reactions related to intravascular volume
- **Renal impairment:** See Dosing
- **Hepatic impairment:** Severe: not recommended

# Contraindications

- Severe renal impairment (eGFR  $<30\text{mL}/\text{min}/1.73\text{m}^2$ ), ESRD, or on dialysis

# Boxed Warning

- In patients with T2DM who have established CVD or at risk for CVD, Invokana has been associated with **lower limb amputations**, most frequently of the toe and midfoot; some also involved the leg

# Warnings/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

# Warnings/Precautions

- Monitor for symptomatic **hypotension** in renal impairment, elderly, low systolic BP, concomitant diuretics or drugs that interfere with the RAA system (eg, ACEIs, ARBs)
- 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)

# Warnings/Precautions

- Evaluate **renal function** prior to starting and monitor periodically thereafter; more frequently if eGFR  $<60\text{mL}/\text{min}/1.73\text{m}^2$
- Risk of **acute kidney injury** in hypovolemia, chronic renal insufficiency, CHF, and concomitant drugs (eg, diuretics, ACEIs, ARBs, NSAIDs)

# Warnings/Precautions

- Consider temporarily discontinuing in reduced oral intake or fluid losses; monitor for acute kidney injury; discontinue and treat if occurs
- Discontinue if hypersensitivity reactions occur; monitor until resolved

# Warnings/Precautions

- Consider bone fracture risks before initiation
- Necrotizing fasciitis of the perineum (Fournier's gangrene); discontinue and treat immediately if suspected (give antibiotics and/or surgical debridement, if needed)
- Monitor for genital mycotic infections, UTIs, increases in LDL-C; treat if needed

# Interactions

- Antagonized by **UGT inducers** (eg, rifampin, phenytoin, phenobarbital, ritonavir): see Dosing
- 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-AG assay; use alternative methods to monitor glycemic control

# Adverse Reactions

- Female genital mycotic infections
- Urinary tract infection
- Increased urination

# Mechanism of Action

- Sodium-glucose co-transporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen
- Canagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion

# Clinical Studies

- The **CANVAS** and **CANVAS-R trials** were multicenter, multi-national, randomized, double-blind, parallel group studies (N=10,134) that evaluated patients:
  - Aged  $\geq 30$  yrs who had established, stable, CV, cerebrovascular, peripheral artery disease or;
  - Aged  $\geq 50$  yrs who had 2 or more other specified risk factors for CV disease

# Clinical Studies

- In **CANVAS**, patients were randomized to receive canagliflozin 100mg, canagliflozin 300mg, or matching placebo
- In **CANVAS-R**, patients were randomized to receive canagliflozin 100mg, or matching placebo, and titration to 300mg was permitted after Week 13 based on need

# Clinical Studies

- The **primary endpoint**, Major Adverse Cardiovascular Event (MACE), was the time to first occurrence of a 3-part composite outcome which included CV death, non-fatal myocardial infarction (MI), and non-fatal stroke

# Clinical Studies

- Compared with placebo, treatment with canagliflozin lowered the risk of MACE by **14%** overall (hazard ratio [HR] 0.86, 95% CI, 0.75, 0.97;  $P=0.0158$  for superiority)
- For more clinical trial data, see full labeling

# Product Monograph

- For more information view the product monograph available at:

<http://www.empr.com/invokana/drug/8308/>