Canagliflozin Label Summary Reference Card

Selected Product Information: Invokana® (canagliflozin) Tablets (Napp Pharmaceuticals Limited)

Information is selected from the SPC for Invokana (SPC updated April 30, 2019).
The full SPC should be consulted for additional information.

Therapeutic Indications

Invokana is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:

- As monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- In addition to other medicinal products for the treatment of diabetes

Posology and Method of Administration

The recommended starting dose of canagliflozin is 100 mg once daily. In patients tolerating canagliflozin 100 mg once daily who have an estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2 or CrCl ≥60 mL/min and need tighter glycaemic control, the dose can be increased to 300 mg once daily orally.

When canagliflozin is used as add-on therapy with insulin or an insulin secretagogue (e.g., sulphonylurea), a lower dose of insulin or the insulin secretagogue may be considered to reduce the risk of hypoglycaemia.

Invokana should be taken orally once a day, preferably before the first meal of the day. Tablets should be swallowed whole. If a dose is missed, it should be taken as soon as the patient remembers; however, a double dose should not be taken on the same day.

Undesirable Effects

The most frequently reported adverse reactions (≥1/10) include:

- Hypoglycaemia in combination with insulin or sulphonylurea
- Vulvovaginal candidiasis

Commonly reported adverse reactions (≥1/100 to <1/10) include:

- Gastrointestinal disorders: constipation, thirst, nausea
- Renal and urinary disorders: polyuria or pollakiuria; urinary tract infection (pyelonephritis and urosepsis have been reported postmarketing)
- Reproductive and breast disorders: balanitis or balanoposthitis
- Investigations: dyslipidemia; hematocrit increased

Special Warnings and Precautions for Use

Renal impairment

The canagliflozin dose should be limited to 100 mg once daily in patients with an eGFR <60 mL/min/1.73 m^2 or CrCl <60 mL/min and canagliflozin should not be used in patients with an eGFR <45 mL/min/1.73 m^2 or CrCl <45 mL/min. Canagliflozin has not been studied in severe renal impairment (eGFR <30 mL/min/1.73 m^2 or CrCl <30 mL/min) or ESRD. Monitor renal function during treatment.

Special Warnings and Precautions for Use

Use in patients at risk for adverse reactions related to volume depletion

Caution should be exercised in patients for whom a canagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients with an eGFR <60 mL/min/1.73 m^2, patients on anti-hypertensive therapy with a history of hypotension, patients on diuretics, or elderly patients (≥65 years of age).

Diabetic ketoacidosis (DKA)

In patients where DKA is suspected or diagnosed, treatment with canagliflozin should be discontinued immediately. Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. In both cases, treatment with canagliflozin may be restarted once the patient's condition has stabilised.

Elevated haematocrit

Haematocrit increase was observed with canaglifozin treatment.

Genital mycotic infections

Vulvovaginal candidiasis in females and balanitis or balanoposthitis in males were reported in clinical trials with canagliflozin.

Lower limb amputations

In long-term clinical studies of canagliflozin in type 2 diabetes patients with established cardiovascular disease (CVD) or at least 2 risk factors for CVD, an approximately 2-fold increased risk of lower limb amputation (primarily of the toe and midfoot) has been observed in patients treated with canagliflozin. Consideration should be given to carefully monitoring patients with a higher risk for amputation events. Consideration may also be given to stopping treatment with Invokana in patients who develop events which may precede amputation such as lower-extremity skin ulcer, infection, osteomyelitis, or gangrene.

Contraindications

Canagliflozin is contraindicated in patients who are hypersensitive to the active substance or to any of the excipients.

Canagliflozin Label Summary Reference Card

Selected Product Information: Invokana® (canagliflozin) Tablets (Napp Pharmaceuticals Limited)

Information is selected from the SPC for Invokana (SPC updated April 30, 2019).
The full SPC should be consulted for additional information.

Cardiovascular Outcomes

The CANVAS (CANagliflozin cardioVascular Assessment Study) Program

A total of 10,134 patients were treated (4,327 in CANVAS and 5,807 in CANVAS-R; total of 4,344 randomly assigned to placebo and 5,790 to canagliflozin) and exposed for a mean of 149 weeks. Vital status was obtained for 99.6% of subjects across the studies. The mean age was 63 years and 64% were male. Sixty-six percent of subjects had a history of established CVD, with 56% having a history of coronary disease, 19% with cerebrovascular disease, and 21% with peripheral vascular disease; 14% had a history of heart failure.

- The mean HbA1c at baseline was 8.2% and mean duration of diabetes was 13.5 years.
- Baseline renal function was normal or mildly impaired in 80% of patients and moderately impaired in 20% of patients (mean eGFR 77 mL/min/1.73 m^2). At baseline, patients were treated with one or more antidiabetic medications including metformin (77%), insulin (50%), and sulfonylurea (43%).
- The primary endpoint in the CANVAS Program was the time to first occurrence of a MACE. Secondary endpoints within a sequential conditional hypothesis testing were all-cause mortality and cardiovascular mortality.
- Patients in the pooled canagliflozin groups (pooled analysis of canagliflozin 100 mg, canagliflozin 300 mg, and canagliflozin up-titrated from 100 mg to 300 mg) had a lower rate of MACE as compared to placebo: 2.69 versus 3.15 patients per 100 patient-years (HR of the pooled analysis: 0.86; 95% CI [0.75, 0.97]; *P* = 0.0158 for superiority).

Special Populations

Renal impairment

For patients with an eGFR 60 mL/min/1.73 m^2 to <90 mL/min/1.73 m^2 or CrCl 60 mL/min to <90 mL/min, no dose adjustment is needed. Canagliflozin should not be initiated in patients with an eGFR <60 mL/min/1.73 m^2 or CrCl <60 mL/min. In patients tolerating canagliflozin whose eGFR falls persistently below 60 mL/min/1.73 m^2 or CrCl 60 mL/min, the dose of canagliflozin should be adjusted to or maintained at 100 mg once daily. Canagliflozin should be discontinued when eGFR is persistently <45 mL/min/1.73 m^2 or CrCl is persistently <45 mL/min. Canagliflozin should not be used in patients with end stage renal disease (ESRD) or in patients on dialysis.

Hepatic impairment

For patients with mild or moderate hepatic impairment, no dose adjustment is required. Canagliflozin has not been studied in patients with severe hepatic impairment and is not recommended for use in these patients.

Elderly (≥65 years old)

Renal function and risk of volume depletion should be taken into account.

Paediatric population

The safety and efficacy of canagliflozin in children under 18 years of age have not yet been established. No data are available.

Clinical Efficacy

Placebo-controlled studies

In general, canagliflozin produced clinically and statistically significant (*P* < 0.001) results relative to placebo in glycaemic control, including HbA1c, the percentage of patients achieving HbA1c <7%, change from baseline fasting plasma glucose (FPG), and 2-hour postprandial glucose (PPG). In addition, reductions in body weight and systolic blood pressure relative to placebo were observed.