Brand Name 1,2,3,4: Invokana

Generic Name: canagliflozin

Manufacturer 1,2,3,4: Janssen Pharmaceuticals

Drug Class 1,2,3,4: Sodium-glucose co-transporter 2 (SGLT2) inhibitor

Labeled Uses 1,2,3,4: Type 2 diabetes mellitus (adjunct to diet and exercise)

Unlabeled Uses 1,2,3,4: None listed

**Mechanism of Action** <sup>1,2,3,4</sup>: Canagliflozin inhibits sodium-glucose co-transporter 2 (SGLT2). SGLT2 is a transporter which is expressed primarily in the proximal renal tubule and is responsible for the reabsorption of the majority (approximately 90%) of glucose filtered by the kidney. By inhibiting SGLT2, glucose reabsorption is decreased, urinary glucose excretion is increased, 24-hour and fasting plasma glucose is decreased, and beta cell function is improved.

## **Pharmacokinetics:**

### Absorption <sup>1,2,4</sup>:

T <sub>max</sub>	1-2 hours
Vd	119 L
t <sub>1/2</sub>	10.6-13.1 hours
Clearance	192 ml/min
Protein binding	Albumin: 99%
Bioavailability	65%

**Metabolism**<sup>1,2,4</sup>: Canagliflozin is extensively metabolized in the liver by Oglucuronidation via UGT1A9 and UGT2B4 to inactive metabolites. CYP3A4 metabolism is minimal (approximately 7%) in humans. Canagliflozin is a weak inhibitor and substrate of P-glycoprotein, and a substrate of drug transporter MRP2.

**Elimination** <sup>1,2,4</sup>: Canagliflozin and its metabolites are mainly eliminated in feces (41.5% as unchanged drug, 7% as hydroxylated metabolite, and 3.2% as O-glucuronide metabolite). Approximately 33% was excreted in urine, mainly as O-glucuronide metabolites (30.5%).

Efficacy:

# Rosenstock J, Aggarwal N, Polidori D, Yue Z, et al. Dose-Ranging Effects of Canagliflozin, a Sodium-Glucose Cotransporter 2 Inhibitor, as Add-On to Metformin in Subjects With Type 2 Diabetes. Diabetes Care. 2012;35:1232-1238.

**Study Design:** Multicenter, double-blind, placebo-controlled, parallel-group, dose-ranging study

**Description of Study:** *Methods*: Four-hundred-fifty-one patients who met eligibility criteria for Type 2 diabetes mellitus were randomized into one of seven treatment groups: canagliflozin at doses of 50, 100, 200, or 300 mg once daily or 300 mg twice daily; sitagliptin 100 mg once daily, or placebo for 12 weeks. Outcome measures include change in A1C, FPG, weight, and overnight urinary glucose to creatinine ratio. To determine safety, adverse event reports, vital signs, 12-lead electrocardiograms, physical exams, and laboratory data was evaluated. Outcome Results: Reductions in hemoglobin A1C in the canagliflozin groups ranged from 0.70-0.95%. The greatest reduction in A1C was observed in the canagliflozin 300 mg once daily (-0.92) and twice daily groups (-0.95). More patients in the canagliflozin 100 and 300 mg once daily and 300 mg twice daily were reported to attain an A1C < 6.5% than placebo. Fasting plasma glucose was most affected at the 200 mg once daily dose (-27.0). Body weight reduction was observed in all canagliflozin groups and was greatest in the 300 mg once daily and twice daily groups. A higher incidence of adverse events was observed in the 300 mg twice daily group (56% vs. 40% in placebo group). Genital infections were reported in 13-25% of female subjects in canagliflozin treatment groups, with most infections reported in the 100 mg once daily group (25%). A higher incidence of symptomatic hypoglycemic events was present in the canagliflozin 200 mg once daily group (6% of patients).

**Limitations:** The study was funded by the manufacturer of canagliflozin, Janssen Global Services. In addition, five out of eight authors are employees of Janssen and editorial assistance was provided by a Janssen supported communication company. This introduces a potential conflict of interest. It was unclear if patients were trained to self administer vaginal swabs and assess genital infections. The study did not account for diet and exercise. In addition, patients were required to be on stable metformin dose and it was unclear how this drug will work in patients on other antidiabetic meds. The authors did not provide statistical analysis of canagliflozin group with sitagliptin group.

**Conclusion:** The study showed that canagliflozin may be useful for reduction in hemoglobin A1C, reduction in fasting plasma glucose, as well as weight loss in Type 2 diabetes mellitus patients. Clinically, canagliflozin may be used for the management of Type 2 diabetes mellitus patients receiving metformin who are not at their target A1C and do not have a history of genital infections.

Stenlof K, Cefalu WT, Kim KA, Alba M, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes, Obesity and Metabolism. 2013;15(4):372-382.

Study Design: Randomized, double-blind, placebo-controlled, phase 3 study

Description of Study: Methods: Two studies were performed simultaneously. The first study (the "main study") involved 584 patients who were given canagliflozin 100 mg, 300 mg, or placebo for 26 weeks. The second study (the "high glycemic control study") involved 91 patients whose glucose was severely elevated. To qualify for the study, the patient needed an HbA1c > 10.0 and  $\leq$  12.0% at screening or week -1 and fasting plasma glucose ≤ 19.4 mmol/l at week -1. These patients received canagliflozin 100 mg or 300 mg for 26 weeks. Metformin therapy was initiated during the double-blind treatment period if fasting plasma glucose was > 15.0 mmol/l between day 1 to week 6, > 13.3 mmol/l between week 6 and week 12, or > 11.1 mmol/l between week 12 and week 26. Safety was evaluated based upon adverse event reports, laboratory tests, vital signs, physical examinations, and 12-lead electrocardiograms. Outcome Results: At week 26, the least square mean changes for HbA1c in patients treated with canagliflozin 100 mg and 300 mg were -0.91 and -1.16% respectively compared to placebo. The most significant decrease in HbA1c occurred during the first 12 weeks of canagliflozin therapy. When evaluating fasting plasma glucose, the least square mean changes were -2.0 mmol/l and -2.4 mmol/l for canagliflozin 100 mg and 300 mg respectively at week 26, p < 0.001 compared to placebo. During the first 6 weeks of therapy, there was a significant reduction in fasting plasma glucose as well as weight loss. In the high glycemic study, HbA1c was reduced by -2.13% for canagliflozin 100 mg and -2.56% for canagliflozin 300 mg. There was an increased risk of mycotic infections in male and female patients taking canagliflozin as compared to placebo.

**Limitations:** Five out of eight authors are full-time research and development employees of Janssen, the manufacturer of canagliflozin. This introduces a potential conflict of interest due to their participation in study conduct, data collection, data analysis, and writing of the manuscript. In the main study, higher rates of discontinuation were reported with placebo than canagliflozin doses. This could be due to unblinding either by appearance of placebo or by self-monitoring of blood glucose. Diet and exercise were not evaluated. In addition, only metformin was used; therefore, the results cannot be generalized to patients taking other antidiabetic medications.

**Conclusion:** The study showed that canagliflozin may assist Type 2 diabetes mellitus patients with weight loss as well as reduce systolic/diastolic blood pressure, fasting plasma glucose, and HbA1c. Canagliflozin was also shown to be generally well tolerated with a low incidence of hypoglycemia. Clinically, canagliflozin may be useful in Type 2 diabetes patients with normal renal function who are not currently at their disease state goals. Future studies should account for patients diet and exercise levels and include patients using additional antidiabetic agents.

Schernthaner G, Gross JL, Rosenstock J, Guarisco M, et al. Canagliflozin Compared With Sitagliptin for Patients With Type 2 Diabetes Who Do Not Have Adequate Glycemic Control With Metformin Plus Sulfonylurea. Diabetes Care. 2013;1-9.

Study Design: Randomized, double-blind, active-control, phase 3 study

**Description of Study:** *Methods*: Seven-hundred-fifty-six patients were randomized to receive either sitagliptin 100 mg or canagliflozin 300 mg for 52 weeks. Subjects were required to be on maximum doses of metformin or sulfonylurea. *Outcome Results*: Of the 378 patients who received sitagliptin, 14 discontinued the study due to adverse events; while 21 of the 378 patients in the canagliflozin arm discontinued due to adverse events. Canagliflozin 300 mg was shown to be noninferior to sitagliptin 100 mg in A1C reduction (least square mean change of -1.03% (-11.3 mmol/mol) for canagliflozin, -0.66% (-7.2 mmol/mol) for sitagliptin; difference in least square means of -0.37% (95% Cl, -0.50 to -0.25)). Fasting plasma glucose was significantly reduced in the canagliflozin group as compared to the sitagliptin group (-1.7 mmol/L (-28.7 mg/dL), -0.3 mmol/L (-2.2 mg/dL), respectively). Canagliflozin also resulted in a least square mean change weight loss of -2.5% or -2.3 kg; while sitagliptin resulted in a least square mean change weight gain of 0.3% or 0.1 kg. Canagliflozin was also associated with higher rates of genital mycotic infection than sitagliptin.

**Limitations:** Janssen (manufacturer of canagliflozin) supported the study. Five out of nine authors are full-time employees of Janssen research and development. In addition, one author has received grants or research support from Janssen. This introduces a potential conflict of interest. Patients monitored their glucose during the study; therefore, there is a potential for unblinding if the patient would realize their fasting blood glucose is not improving. In addition, diet and exercise were not accounted for.

**Conclusion:** Canagliflozin may be a suitable option as an adjunct for additional glycemic control in patients with Type 2 diabetes mellitus. The medication has a low risk of hypoglycemia, is associated with weight loss, reduction of hemoglobin A1C, and reduction of fasting plasma glucose. Due to adverse events, such as mycotic infections, comorbidities should be taken into account before initiation of this medication therapy.

## Contraindications <sup>1,2,3,4</sup>:

**Canagliflozin Hypersensitivity:** Hypersensitivity reactions (e.g., urticaria) to canagliflozin usually occur within hours to days after initiation of therapy. Do not administer the medication in patients with a history of canagliflozin hypersensitivity and discontinue therapy if hypersensitivity occurs.

**Severe Renal Impairment, End Stage Renal Failure, or Dialysis:** Efficacy and safety studies evaluated patients with moderate renal impairment (eGFR 30-50

ml/min/1.73m<sup>2</sup>). As compared to patients with normal or mild renal dysfunction (eGFR  $\geq$  60 ml/min/1.73m<sup>2</sup>), the moderate renal impairment patients had less glycemic efficacy, increased rate of adverse events, and decreased eGFR. Therefore, canagliflozin is not expected to be effective in patients with severe renal impairment (eGFR < 30 ml/min/1.73m<sup>2</sup>).

## Precautions 1,2,3,4:

**Genital Mycotic Infection:** Use with caution in patients with a history of genital mycotic infection due to increased risk of genital fungal infection during canagliflozin therapy.

**Geriatrics:** Elderly patients are associated with a higher incidence of adverse reactions related to decreased intravascular volume (e.g., hypotension, orthostatic hypotension, dehydration).

**Hepatic Impairment:** Use of canagliflozin has not been evaluated in patients with severe hepatic disease (Child-Pugh Class C), therefore it is not recommended. No dosage adjustments are needed in patients with mild to moderate (Child-Pugh Class A, B) hepatic impairment.

**Hyperkalemia:** Impaired renal function, canagliflozin doses of 300 mg/day or more, potassium-sparing diuretics, and medications that interfere with the renin-angiotensinaldosterone system are associated with an increase in potassium. Monitor serum potassium levels periodically in these patients.

**Hypoglycemia:** Increased risk when combined with insulin or an insulin secretagogue (e.g., sulfonylureas). Dose reduction of insulin or sulfonylurea may be required.

**Hypotension:** Patients who are have low systolic blood pressure, elderly, dehydrated, hypovolemic, impaired renal function (eGFR < 60 ml/min/1.73m<sup>2</sup>), or taking concurrent medications that interfere with the renin-angiotensin-aldosterone system are at increased risk. Monitor for signs and symptoms upon initiation of therapy.

**Increased Low-density Lipoprotein:** Increases in LDL-C are dose related and may require adjustment of therapy.

Pediatrics: Safety and efficacy in children less than 18 has not been evaluated.

**Renal Impairment:** Assess renal function in all patients prior to initiation of therapy and periodically thereafter. Canagliflozin should be discontinued if eGFR is persistently < 45 ml/min/1.73m<sup>2</sup>.

**Type 1 Diabetes Mellitus:** Canagliflozin should not be used in these patients or for treatment of diabetic ketoacidosis.

#### Adverse Effects 1,2,4:

# Occurring in > 10% of patients Endocrine/Metabolic Hyperkalemia (100 mg/day 12.4%, 300 mg/day 27%) Reproductive Female genital mycosis (100 mg/day 10.4%, 300 mg/day 11.4%) Occurring in < 10% to > 1% of patients Cardiovascular Hypovolemia (e.g., hypotension) (100 mg/day 2.3%, 300 mg/day 3.4%) Central Nervous System Fatigue (100 mg/day 2.2%, 300 mg/day 2%) Endocrine/Metabolic Hypermagnesemia (100 mg/day 8.1%, 300 mg/day 9.3%) Hyperphosphatemia (100 mg/day 3.6%, 300 mg/day 5.1%) Hypoglycemia (e.g., $\leq$ 70 mg/dL) (100 mg/day 3.6%, 300 mg/day 3%) Increased LDL-C (100 mg/day 4.5%, 300 mg/day 8%) Thirst, xerostomia (100 mg/day 2.8%, 300 mg/day 2.3%) Gastrointestinal Abdominal pain (100 mg/day 1.8%, 300 mg/day 1.7%) Constipation (100 mg/day 1.8%, 300 mg/day 2.3%) Nausea (100 mg/day 2.2%, 300 mg/day 2.3%) Hematologic Increased hemoglobin (100 mg/day 3.5%, 300 mg/day 3.8%) Immunologic Hypersensitivity (100 mg/day 3.8%, 300 mg/day 4.2%) Renal Increased SCr, decreased eGFR (100 mg/day 8.9%, 300 mg/day 9.3%) Increased urinary frequency (100 mg/day 5.3%, 300 mg/day 4.6%) Urinary tract infection (100 mg/day 5.9%, 300 mg/day 4.3%) Reproductive Male genital mycosis (100 mg/day 4.2%, 300 mg/day 3.7%) Vulvovaginal pruritis (100 mg/day 1.6%, 300 mg/day 3%) Occurring in < 1% of patients Dermatologic Photosensitivity, sunburn (100 mg/day 0.2%, 300 mg/day 0.2%)

## Drug Interactions <sup>1,2,3,4</sup>:

Co-administration with drugs that interfere with renin-angiotensin-aldosterone system Symptomatic hypotension may occur with concomitant therapy.
Diabetic agents
Co-administration has resulted in an increased risk of hypoglycemia.
Digoxin
Co-administration has resulted in increased AUC and C <sub>max</sub> of digoxin.
Diuretics
Symptomatic hypotension may occur with concomitant therapy.
Gatifloxacin
Contraindicated in diabetes mellitus patients due to alterations in blood glucose.
UGT Enzyme Inducers (rifampin, ritonavir, phenobarbital, phenytoin)
Canagliflozin is a UGT substrate; thus, UGT induction may result in decreased
levels of canagliflozin. Consider increasing the dose of canagliflozin to 300 mg
PO once daily in patients with adequate renal function ( $\geq 60 \text{ ml/min}/1.73 \text{m}^2$ ).

## Dosing/Administration <sup>1,2,3,4</sup>:

Adults	100 mg PO once daily, taken before first meal of the day
	May increase to 300 mg PO once daily for additional glycemic control
	if the 100 mg dose is tolerated and eGFR $\geq$ 60 ml/min/1.73m <sup>2</sup> .
	Maximum dosage limit: 300 mg/day PO
Pediatrics	Safety and efficacy have not been established.
Geriatrics	Maximum dosage limit: 300 mg/day PO
Hepatic	No dosage adjustment needed for mild to moderate impairment.
Impairment	Not recommended in patients with severe impairment due to lack of
	literature.
Renal	eGFR ≥ 60 ml/min/1.73m <sup>2</sup> : No dosage adjustment needed
Impairment	eGFR 45-59 ml/min/1.73m <sup>2</sup> : Do not exceed 100 mg/day PO
	eGFR < 45 ml/min/1.73m <sup>2</sup> : Do not initiate therapy or discontinue

## Use in Special Circumstances <sup>1,2,3,4</sup>:

**Pregnancy:** Canagliflozin is an FDA pregnancy risk category C medication. There are no adequate or well-controlled human pregnancy studies at this time. In animal studies, when given to juvenile rats, renal development and maturation issues were observed. Insulin is recommended as the therapy of choice to maintain blood glucose during pregnancy in patients with Type 1 or 2 diabetes mellitus.

**Lactation:** It is unknown if canagliflozin is excreted in human milk and there is concern about its effect on the developing kidney during maturation. A study involving lactating

rats showed canagliflozin was secreted into the milk and resulted in renal pelvic and tubular dilations. If oral hypoglycemics are utilized during breast feeding, monitor the infant for signs of hypoglycemia (e.g., fussiness, somnolence).

**Conclusion:** Canagliflozin is a useful medication for Type 2 diabetes mellitus patients. It has been shown to reduce hemoglobin A1C, fasting plasma glucose, as well as result in weight loss for this patient population. Clinically, canagliflozin may be used for the management of Type 2 diabetes mellitus patients who are not at their target A1C, are interested in losing weight, and do not have a history of genital infections. In addition, patients who are initiated on canagliflozin should be educated about signs and symptoms associated with a genital infection as well as monitored for incidence. This medication is not suitable for patients with renal impairment, Type 1 diabetes mellitus, children, pregnant women, or breastfeeding mothers. Further studies are needed to determine canagliflozin's role in relation to other antidiabetic medications.

## **Recommended References:**

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