INVOKANA™ (canagliflozin) tablets, for oral use

Product Description (please also refer to full prescribing information and medication guide)

• INVOKANA is a sodium-glucose cotransporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).[1]
• INVOKANA reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, by inhibiting SGLT2 (responsible for reabsorbing the majority of glucose filtered by the kidney), thereby increasing urinary glucose excretion.[1-3]
• INVOKANA is available as film-coated, 100- and 300-mg oral tablets dosed once daily and taken before the first meal of the day. INVOKANA can be used alone or in combination with other antihyperglycemic agents (AHAs).[1] The recommended starting dose is 100 mg daily and can be increased to 300 mg daily if tolerating INVOKANA 100 mg, have an estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2, and require additional glycemic control. Limit to INVOKANA 100 mg daily in moderate renal impairment (eGFR ≥45 to <60 mL/min/1.73 m^2). Do not initiate or discontinue INVOKANA if eGFR is <45 mL/min/1.73 m^2.[1]
• If a UGT inducer (eg, rifampin, phenytoin, phenobarbital, ritonavir) must be coadministered with INVOKANA, consider increasing INVOKANA to 300 mg once daily if the patient tolerates INVOKANA 100 mg, has an eGFR ≥60 mL/min/1.73 m^2, and requires additional glycemic control.[1]

Efficacy in Clinical Studies

• INVOKANA was studied in 9 pivotal, phase 3, double-blind, randomized, controlled, multinational studies enrolling approximately 10,300 patients. INVOKANA was studied as monotherapy; in combination with metformin, a sulfonylurea (glimepiride), metformin and a sulfonylurea, and metformin and a thiazolidinedione (pioglitazone); and in combination with insulin (with or without other AHAs).
• The efficacy and safety of INVOKANA was compared to sitagliptin as add-on combination therapy with metformin and sulfonylurea. INVOKANA was compared to glimepiride as add-on combination therapy with metformin. INVOKANA was also evaluated in adults 55 to 80 years of age and in patients with moderate renal impairment (eGFR ≥30 to <50 mL/min/1.73 m2).

Placebo-Controlled Studies[1,4-11]

• Significant improvement in A1C versus placebo was reported with INVOKANA at 18 and 26 weeks ($p<0.001$).
• For prespecified secondary endpoints at 26 weeks, INVOKANA resulted in a greater proportion of patients achieving A1C <7%, and reductions in fasting plasma glucose (FPG) and body weight ($p<0.001$ for all vs. placebo).[4-9,11]
• Significant reductions in systolic blood pressure (BP) from baseline with INVOKANA were reported in 3 studies.[4,5,7]
• At 52 weeks, dose-related drops in A1C, FPG, body weight, and systolic BP were seen.[8,9]

Active-Controlled Studies (vs sitagliptin and vs glimepiride)[12-14]

• When added to metformin therapy, both INVOKANA doses were noninferior to glimepiride 6-8 mg (titrated) in A1C reduction from baseline at 52 weeks. INVOKANA 300 mg also demonstrated a statistically superior reduction in A1C versus glimepiride 6-8 mg (when added to metformin) and versus sitagliptin 100 mg (when added to metformin and sulfonylurea) at 52 weeks. At 104 weeks, A1C reductions were maintained, and reductions in FPG, body weight, and systolic BP were generally similar to 52 weeks.
• Among prespecified secondary efficacy endpoints at 52 weeks, INVOKANA 100- and 300-mg treatment arms provided significant improvements in percent body weight change, relative to glimepiride ($p<0.0001$ for both doses vs glimepiride). INVOKANA 300 mg provided significant improvement in percent body weight vs sitagliptin ($p<0.001$) at 52 weeks.
• A greater mean decrease from baseline in systolic blood pressure was seen INVOKANA compared with sitagliptin.

Placebo-Controlled Studies in Specific Populations (55 to 80 years of age and moderate renal impairment)[15-17]

• In older patients (55 to 80 years), INVOKANA 100 mg and 300 mg significantly improved A1C levels compared with placebo ($p<0.05$ for 100 mg versus placebo; $p<0.001$ for 300 mg versus placebo) at 26 weeks.
• In patients with moderate renal impairment (eGFR ≥30 to <50 mL/min/1.73 m^2), both INVOKANA doses significantly improved A1C levels compared with placebo ($p<0.001$) at 26 weeks; reductions in A1C levels were seen at 52 weeks.
• Analyses of CV outcomes are ongoing in patients with or at high risk for CV disease on INVOKANA (as add-on to insulin +/- AHAs and as add-on to a sulfonylurea).

Overall Safety

In 4 pooled placebo-controlled studies[4-7], the most common AEs (≥5% with either INVOKANA 100 mg or 300 mg) were female genital mycotic infections, urinary tract infections, and increased urination.[1] Other AEs that occurred in ≥2% of patients treated with INVOKANA were male genital mycotic infection, vulvovaginal pruritus, thirst, constipation, and nausea.[1] In a larger pool of 8, placebo- and active-controlled studies[4-7,10,11,14-16], the types and frequency of common AEs were consistent with the 4 pooled placebo-controlled studies.[1] INVOKANA results in an osmotic diuresis, which may lead to reductions in intravascular volume. In the 8 pooled studies, patients on loop diuretics, patients with moderate renal impairment (eGFR, 30 to <60 mL/min/1.73 m^2), and patients ≥75 years of age had the largest increase in volume depletion-related AEs. INVOKANA was associated with a dose-dependent increase in the incidence of volume depletion-related AEs (eg, hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration).[1] INVOKANA is associated with a dose-dependent increase in serum creatinine and a concomitant decrease in eGFR; patients with

moderate renal impairment at baseline had larger mean changes.[1] In monotherapy or in combination with metformin, the incidence of hypoglycemia observed with INVOKANA was similar to the incidence with placebo. Hypoglycemia occurred at a higher rate when INVOKANA was co-administered with insulin or a sulfonylurea.[1] In 4 pooled placebo-controlled studies, dose-related increases in LDL-C and non-HDL-C with INVOKANA were observed. Mean changes from baseline in LDL-C relative to placebo were 4.4 mg/dL (100 mg) and 8.2 mg/dL (300 mg); mean changes from baseline in non-HDL-C relative to placebo were 2.1 mg/dL (100 mg) and 5.1 mg/dL (300 mg). Refer to Section 6 of the full PI for more information. (*Note: the sitagliptin-controlled study was not included in pooled analyses of adverse reactions.*)

Clinical Value, Place in Therapy, and Cost Effectiveness

• In clinical studies of INVOKANA given as monotherapy or given adjunctively with metformin, patients who received active treatment had significantly better control over their glucose levels than those who received placebo.[4,5]
• INVOKANA 300 mg provided statistically superior A1C reduction from baseline to 52 weeks versus sitagliptin 100 mg in combination with background metformin and a sulfonylurea.[13] In combination with metformin, INVOKANA 100 mg and 300 mg were noninferior to glimepiride and 300 mg was statistically superior in A1C reduction from baseline at 52 weeks.[12]
• INVOKANA has also been shown to be effective in lowering glucose levels in triple-combination regimens with metformin and either a sulfonylurea or pioglitazone.[6,7,13]
• Glycemic control was also significantly better with both doses of INVOKANA than with placebo when added to stable insulin therapy alone or in combination with other AHAs.[11]
• Significant reductions in A1C were seen INVOKANA in older patients and patients with moderate renal impairment.[15,16]
• Greater reductions in A1C relative to placebo were observed in patients with higher baseline A1C or eGFR values.[1] In addition, INVOKANA has been associated with blood pressure reduction and body weight reduction in clinical studies and has shown improvements in β-cell function indices.[1,4-7,11,16]
• The place in therapy of INVOKANA is as an oral treatment option for adults with T2DM as monotherapy and as an add-on agent to metformin in patients requiring additional glycemic control. Additionally, INVOKANA can be used as monotherapy for patients intolerant to metformin, or in triple therapy, including insulin, to achieve glycemic control.
• Based on the active-comparator randomized controlled trial, INVOKANA 300 mg (a) demonstrated cost savings and superior cost efficiency as compared with sitagliptin in a 1-year cost and cost-efficiency analysis and (b) was found to dominate (ie, is more effective and less costly than) sitagliptin, showing an increase in QALYs and lower costs than sitagliptin over 10-, 20-, and 30-year time horizons in the longer-term cost-effectiveness model.

Summary

INVOKANA, the first in a new class, is an SGLT2 inhibitor, resulting in increased urinary glucose excretion. INVOKANA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.[1] INVOKANA improved glycemic control relative to placebo when given as monotherapy, as initial combination therapy with metformin or a sulfonylurea, in combination with metformin and a sulfonylurea, metformin and pioglitazone, or in combination with insulin (+/- AHAs) at 18, 26, and 52 weeks.[4-11] INVOKANA 300 mg resulted in statistically superior reductions from baseline in A1C levels than glimepiride at 52 weeks (on background metformin) or sitagliptin at 52 weeks (on background metformin and sulfonylurea).[12,13] Prespecified secondary endpoints showed reductions in percent change in body weight and systolic blood pressure at 26 weeks in placebo-controlled studies.[4-7] In study extension periods (up to 52 weeks[5,8-9,18] or 104 weeks[14]), both doses maintained reductions in A1C, FPG, body weight, and systolic BP, with small increases in HDL-C and LDL-C vs comparator. The most commonly reported AEs with INVOKANA were female genital mycotic infections, urinary tract infections, and increased urination.[1] Hypoglycemia occurred at a higher rate when co-administered with insulin or a sulfonylurea.[1]

References

1. INVOKANA™ (canagliflozin) [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc. **2.** Liang Y, et al. *PLoS One*. 2012;7:e30555. **3.** Rosenstock J, et al. *Diabetes Care.* 2012;35:1232-1238. **4.** Stenlöf K, et al. *Diabetes Obes Metab.* 2013;15:372-382. **5.** Lavalle-Gonzalez F, et al. *Diabetologia*. 2013 Sep 13. published ahead of print, DOI: 10.1007/s00125-013-3039-1. **6.** Wilding J, et al. *Intl J Clin Pract.* 2013 Oct 13. published ahead of print, DOI: 10.1111/ijcp.12322. **7.** Forst T, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes on metformin and pioglitazone. Poster presented at CODHy 2012. **8.** Stenlöf K, et al. *Curr Med Res Opin*. 2013, DOI: 10.1185/03007995.2013.850066. **9.** Forst T, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes mellitus on metformin and pioglitazone over 52 weeks. Poster presented at ADA 2013. **10.** Fulcher G, et al. Canagliflozin in subjects with type 2 diabetes mellitus inadequately controlled on sulfonylurea monotherapy: A CANVAS substudy. Poster presented at ADA 2013. **11.** Matthews D, et al. Efficacy and safety of canagliflozin, an inhibitor of sodium glucose co-transporter 2, added on to insulin therapy with or without oral agents in type 2 diabetes. Poster presented at EASD 2012.**12.** Cefalu WT, et al. *Lancet*. 2013;382:941-950. **13.** Schernthaner G, et al. *Diabetes Care*. 2013;36:2508-2515. **14.** Cefalu WT, et al. Canagliflozin demonstrates durable glycemic improvements over 104 weeks versus glimepiride in subjects with type 2 diabetes mellitus on metformin. Poster presented at ADA 2013**. 15.** Bode B, et al. *Hosp Pract*. 2013;41(2):72-84. **16.** Yale J, et al. *Diabetes Obes Metab*. 2013;15:463-473. **17.** Neal B, et al. *Am Heart J.* 2013;166:217-223. **18.** Yale J, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes mellitus and chronic kidney disease over 52 weeks. Poster presented at ADA 2013.