Drug Monograph

Drug/Drug Class:	**Invokana® (canagliflozin) tablet / sodium-glucose cotransporter-two inhibitor**
Prepared for:	MO HealthNet
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☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Invokana® is available in two strengths of capsule; 100mg and 300mg canagliflozin. Janssen Pharmaceuticals, Inc. Titusville, NJ 08560 of Johnson & Johnson, Inc.
Summary of Findings:	Invokana, a novel SGLT2 inhibitor, is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. In clinical trials, improved glycemic control and body weight reductions were demonstrated when canagliflozin was studied both as monotherapy and as add-on dual or triple therapy with other antihyperglycemic agents.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☐ PDL Product
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Under Solicitation ☒ Appropriate Indications ☐ 15 Day First Fill Fiscal Edit

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction

Type 2 diabetes mellitus affects many Americans and improving glycemic control is vital. It improves long term outcomes and quality of life.

Dosage Form(s) [1]

Invokana® is available in two strengths of capsule; 100mg and 300mg canagliflozin.

Manufacturer

Janssen Pharmaceuticals, Inc. Titusville, NJ 08560 of Johnson & Johnson, Inc.

Indication(s) [1]

Invokana, a novel SGLT2 inhibitor, is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Clinical Efficacy[1-3] (mechanism of action/pharmacology, comparative efficacy)

PHARMACOLOGY (1)

Invokana inhibits the sodium-glucose cotransporter 2 (SGLT2), which is expressed in the proximal renal tubules and is primarily responsible for renal absorption of filtered glucose. Inhibition of SGLT2 decreases reabsorption of filtered glucose and lowers the renal threshold for glucose, thus promoting urinary glucose excretion.

PHARMACOKINETICS (1,2)

Invokana is 99% protein bound with a volume of distribution of 119L. It is metabolized by O-glucuronidation, excreated in both feces and urine with a half-life of 10.6 to 13.1 hours.

EFFICACY (1,2,3)

SUMMARY

The approval of Invokana was based on several randomized, double-blind, controlled phase 3 studies in which Invokana was used as monotherapy or as add-on therapy in patients with type 2 diabetes mellitus receiving either metformin, a sulfonylurea, metformin plus a sulfonylurea, metformin and a thiazolidinedione, or insulin (with or without other antihyperglycemic agents). C at daily doses of 100 mg and 300 mg significantly improved glycemic control, as measured by HbA1c, as well as led to reductions in body weight. Efficacy was also demonstrated in patients with type 2 diabetes mellitus and chronic stage 3 kidney disease in another study. In a 52-week,

double-blind study in patients with type 2 diabetes mellitus inadequately controlled on metformin and sulfonylurea combination therapy, the addition of Invokana 300 mg/day achieved greater reductions in HbA1c and body weight compared with adding sitagliptin 100 mg/day
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CONCLUSION (1,2)

Invokana at daily doses of 100 mg and 300 mg significantly improved glycemic control compared with placebo in adults with type 2 diabetes mellitus inadequately controlled with diet and exercise.

Cantata-M Study

STUDY DESIGN	Multinational, randomized, double-blind, placebo-controlled, phase 3 Invokana Treatment and Trial Analysis – Monotherapy (CANTATA-M) study.
INCLUSION CRITERIA	Adults aged 18 to 80 years with type 2 diabetes mellitus who met at least one of the following criteria were included: 1) not receiving antihyperglycemic therapy and with an HbA1c ranging between 7% to 10%, 2) either on antihyperglycemic monotherapy (excluding a peroxisome proliferator-activated receptor (PPAR) agonist) or combination therapy (metformin plus sulfonylurea) and with an HbA1C ranging between 6.5% to 9.5% at screening, and an HbA1c ranging between 7% to 10% and a fasting plasma glucose < 15 mmol/L at the start of the 2-week placebo run-in period.
EXCLUSION CRITERIA	Patients with repeated fasting plasma glucose levels of > 15 mmol/L; a history of type 1 diabetes; hereditary glucose-galactose malabsorption; primary renal glycosuria or cardiovascular disease; treatment with a PPAR agonist, insulin, another SGLT2 inhibitor, or any other antihyperglycemic agents not specified in the inclusion criteria; or an estimated GFR (eGFR) of < 50 mL/min/1.73 m(2).
TREATMENT REGIMEN	Following an antihyperglycemic therapy washout and diet/exercise period of up to 8 weeks for those on antihyperglycemic therapy, and a 2-week, single-blind, placebo run-in period (all patients), patients were randomized to receive either Invokana 100 mg (n=195) or 300 mg (n=197), or placebo (n=192) orally once daily for 26 weeks. The primary efficacy endpoint was the change from baseline in HbA1c at week 26. At baseline, the mean age was 44 years, the mean HbA1c was 8%, the mean eGFR was 87 mL/min/1.73 m(2), and the mean duration of type 2 diabetes was 4.4 years. Efficacy was analyzed in the modified intent-to-treat population, which included all randomized patients who received at least 1 dose of the study drug.
RESULTS	Both doses of Invokana were superior to placebo for the primary endpoint of change in baseline HbA1c. At week 26, relative to placebo, the change in baseline HbA1c was -0.91% (95% CI, -1.09% to -0.73%) in the Invokana 100 mg group and -1.16% (95% CI, -1.34% to -0.99%) in the Invokana 300 mg group ($p < 0.001$ for both). Among key secondary endpoints, more patients in the Invokana 100 mg and 300 mg groups (45% and 62%, respectively) achieved an HbA1c of less than 7% at week 26 compared with placebo (21%; $p < 0.001$ for both). Also, greater reductions in fasting plasma glucose occurred with Invokana 100 mg (-36 mg/dL; 95% CI, -42 to -29 mg/dL) and 300 mg (-43 mg/dL; 95% CI, -50 to -37 mg/dL) relative to placebo

	($p < 0.001$ for both). Both doses of Invokana also significantly reduced the 2-hour postprandial glucose, body weight, and systolic blood pressure compared with placebo.
SAFETY	The following adverse events occurred at a higher incidence in the Invokana groups (100 mg, 300 mg) compared with placebo: urinary tract infections (7.2% and 5.1% vs 4.2%), female genital mycotic infections (8.8% and 7.4% vs 3.8%), male genital mycotic infections (2.5% and 5.6% vs 0%), and increased urinary frequency (2.6% and 3% vs 0.5%). The incidence of documented hypoglycemia was similar across the Invokana (100 mg, 300 mg) and placebo patient groups (3.6% and 3% vs 2.6%, respectively), with no occurrences of severe hypoglycemia.

Type 2 Diabetes – CKD

CONCLUSION (3)
Invokana at daily doses of 100 mg and 300 mg significantly improved glycemic control compared with placebo in adults with type 2 diabetes mellitus and chronic stage 3 kidney disease.

STUDY DESIGN	Randomized, double-blind, placebo-controlled, phase 3 study.
INCLUSION CRITERIA	Adults 25 years of age or older with type 2 diabetes mellitus, an HbA1c ranging between 7% to 10.5%, and stage 3 chronic kidney disease (eGFR between 30 to 50 mL/min/1.73 m(2)). Patients were either not on antihyperglycemic therapy or receiving stable monotherapy or combination therapy with approved antihyperglycemic agents, including insulin for at least 8 weeks (12 weeks with pioglitazone), prior to study entry.
EXCLUSION CRITERIA	Patients with a fasting plasma glucose of > 270 mg/dL; a history of type 1 diabetes; renal disease requiring immunosuppressive therapy, dialysis, or transplant; nephrotic syndrome or inflammatory renal disease; NYHA Class III to IV cardiovascular disease; a myocardial infarction, unstable angina, a revascularization procedure or cerebrovascular accident in prior 3 months; or a hemoglobin level of < 10 g/dL.
TREATMENT REGIMEN	Following an antihyperglycemic therapy adjustment period of up to 12 weeks and a 2-week, single-blind, placebo run-in period, patients were randomized to receive either Invokana 100 mg (n=90) or 300 mg (n=89), or placebo (n=90) orally once daily for 26 weeks. The primary efficacy endpoint was the change from baseline in HbA1c at week 26. At baseline, the mean age was 68.5 years, the mean HbA1c was 8%, the mean baseline eGFR was 39.4 mL/min/1.73 m(2), and the mean duration of type 2 diabetes was 16.3 years. Among 98% of patients who were receiving stable background antihyperglycemic therapy, insulin (74%) and sulfonylureas (31%) were the most commonly used agents. Efficacy was analyzed in the modified intent-to-treat population, which included all randomized patients who received at least 1 dose of the study drug.

RESULTS	Both doses of Invokana were superior to placebo for the primary endpoint of change in baseline HbA1c. At week 26, relative to placebo, the change in baseline HbA1c was -0.3% (95% CI, -0.5% to -0.1%; p < 0.05) in the Invokana 100 mg group and -0.4% (95% CI, -0.6% to -0.2%; p < 0.001) in the Invokana 300 mg group. Among key secondary endpoints, more patients in the Invokana 100 mg and 300 mg groups (27.3% and 32.6%, respectively) achieved an HbA1c of less than 7% at week 26 compared with placebo (17.2%). Also, relative to placebo, greater reductions in fasting plasma glucose occurred with Invokana 100 mg (-15.4 mg/dL; 95% CI, -28.5 to -2.3 mg/dL) and 300 mg (-12.2 mg/dL; 95% CI, -25.4 to 1 mg/dL) at week 26.
SAFETY	The following adverse events occurred at a higher incidence in the Invokana groups (100 mg, 300 mg) compared with placebo: female genital mycotic infections (3.1% and 2.4% vs 0%), male genital mycotic infections (1.7% and 2.1% vs 0%), and increased urinary frequency (2.2% and 4.5% vs 1.1%). Decreases in baseline eGFR occurred more frequently in the Invokana 100 mg and 300 mg groups (-9.1% and -10.1%, respectively) compared with placebo (-4.5%). Among patients receiving concomitant therapy with insulin or sulfonylureas, there were more documented hypoglycemic episodes in patients receiving Invokana 100 mg and 300 mg (52.9% and 51.2%, respectively) compared with placebo (36.4%); 6 patients experienced severe hypoglycemic episodes (4 and 1 vs 1 patient, respectively).

Contraindications[1]

- Serious hypersensitivity to Invokana
- Severe renal impairment (estimated GFR < 30 mL/min/1.73 m(2)), ESRD or dialysis patients

Warnings and Precautions[1]

- Symptomatic hypotension has been reported, particularly in elderly patients, those with low systolic blood pressure or impaired renal function (estimated GFR < 60 mL/min/1.73 m(2), or those receiving diuretics or medications affecting the renin-angiotensin-aldosterone system; correct hypovolemia prior to therapy initiation and monitor during treatment.
- Hyperkalemia may occur; increased risk in patients with moderate renal impairment and those receiving medications that either interfere with potassium excretion or the renin-angiotensin-aldosterone system; monitor serum potassium levels periodically in patients with increased risk.
- Increased risk of hypoglycemia when used in combination with insulin or insulin secretagogues; may require dose reduction of insulin or insulin secretagogues.
- Genital mycotic infections have been reported; increased risk in patients with a prior history of such infections and in uncircumcised males.
- Serious hypersensitivity reactions, occurring within hours to days after initiating therapy, have been reported; discontinue therapy if such reactions occur.
- LDL-C increases have been reported; monitoring LDL-C is recommended.

Adverse Effects[1]

Most common, >= 2%, pooled data (4 trials)	Invokana 100 mg (n=833)	Invokana 300 mg (n=834)
Female genital mycotic infections	10.4%	11.4%
Urinary tract infections	5.9%	4.3%
Increased urination	5.3%	4.6%
Male genital mycotic infections	4.2%	3.7%

Drug Interactions[1]

- Digoxin
- Uridine diphosphate glucuronosyltransferase (UGT) enzyme inducers: rifampin, phenytoin, phenobarbital, ritonavir

Dosage and Administration[1]

The recommended adult starting dose is 100 mg orally once daily, taken before the first meal of the day. If additional glycemic control is required, the dose may be increased to 300 mg once daily if the 100 mg dose is tolerated and the estimated GFR is >= 60 mL/min/1.73 m(2).

Cost Comparisons (at commonly used dosages)

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST/ MONTH
Canagliflozin	Invokana	Janssen	100 mg tablets	1 tablet daily	$ 263.10
			300 mg tablets	1 tablet daily	$ 263.10

*Wholesale Acquisition Cost (WAC)

Conclusion

Invokana, a novel SGLT2 inhibitor, is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. In clinical trials, improved glycemic control and body weight reductions were demonstrated when Invokana was studied both as monotherapy and as add-on dual or triple therapy with other antihyperglycemic agents, including insulin; similar outcomes were also observed in patients with type 2 diabetes mellitus and stage 3 chronic kidney disease. As add-on therapy in a comparative study, Invokana also achieved greater reductions in HbA1c and body weight compared with add-on sitagliptin in patients with type 2 diabetes mellitus who were inadequately controlled on metformin and sulfonylurea combination therapy. Adverse events include urinary tract infections, female and male genital mycotic infections, and increased urinary frequency. Hypovolemia should be corrected prior to therapy initiation, and monitoring of serum potassium is recommended in

patients at increased risk for hyperkalemia. Dosage increases may be warranted in patients receiving concomitant therapy with UGT enzyme inducers.

Recommendation

The Division recommends this product be considered placed in a clinical edit.

References

1. Product Information: Invokana™, canagliflozin tablets. Janssen Pharmaceuticals Inc, Titusville, NJ, 03/2013.

2. Stenlop K, Cefalu WT, Kim K-A et al: Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab 2013; 15(4):372-382.

3. Yale J-F, Bakris G, Cariou B et al: Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. Diabetes Obes Metab 2013; 15(5):463-473.

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Date: August 26, 2013

