

Invokamet (Canagliflozin plus Metformin HCl): First Fixed-Dose Combination with an SGLT2 Inhibitor Approved for the Treatment of Patients with Type 2 Diabetes

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Diabetes is a chronic disease that affects an estimated 29.1 million individuals in the United States—approximately 9.3% of the US population.¹ In addition, a staggering 37% of US adults have prediabetes, placing them at a high risk for diabetes.¹ Coinciding with the aging of the US population, the prevalence of diabetes is projected to increase dramatically over the next few decades, from approximately 1 in 10 adults today to approximately 1 in 3 adults by 2050.² Approximately 90% to 95% of all cases of diabetes are type 2 diabetes mellitus, a disease that is characterized by insulin resistance and a gradual decline in the ability of the pancreas to produce insulin.¹

Diabetes is associated with multiple comorbidities, as well as microvascular, macrovascular, and neuropathic complications that impact the quality of life.¹ The seventh leading cause of mortality in the United States, diabetes is a major cause of stroke and heart disease and is the leading cause of kidney failure, new cases of blindness, and nontraumatic lower-limb amputations. Furthermore, individuals with diabetes are at an increased risk for nerve disease, nonalcoholic fatty liver disease, periodontal disease, erectile dysfunction, hearing loss, depression, and pregnancy complications compared with individuals without diabetes.¹

In 2012, diabetes accounted for \$245 billion in total US healthcare costs, including \$176 billion in direct medical costs and \$69 billion in indirect costs (eg, increased absenteeism, reduced productivity, lost productivity, and disability).³ These estimated economic costs of diagnosed diabetes represent a 41% increase from the estimated medical expenditures in 2007.³ Overall, the medical expenditures for individuals with diabetes are approximately 2.3 times higher than the medical expenditures for individuals without diabetes. In fact, more than 1 in 5 US healthcare dollars is spent on the care of patients with diabetes.³

The management of diabetes requires glycemic control, as well as multiple risk-reduction strategies, including lifestyle and behavioral changes, ongoing medical care, patient education and self-management, and ongoing patient monitoring and support.⁴

Improvements in glycemic control have been shown

to reduce the morbidity and mortality associated with type 2 diabetes mellitus by decreasing chronic complications. Lowering hemoglobin (Hb) A_{1c} levels to $\leq 7\%$ is associated with a reduction in diabetes-related microvascular complications (ie, diabetic neuropathy, nephropathy, and retinopathy).⁴ In its 2013 position statement, the American Diabetes Association (ADA) recommends a general HbA_{1c} target goal of $< 7\%$ for adult patients with diabetes, acknowledging that more stringent or less stringent goals may be appropriate for individual patients.⁴ According to the ADA, the target goal should be individualized based on the patient's duration of diabetes, age, comorbidities, known cardiovascular or advanced microvascular complications, and other patient factors.⁴

The American Association of Clinical Endocrinologists recommends an HbA_{1c} target goal of $< 6.5\%$ for the majority of patients with type 2 diabetes mellitus, acknowledging that this goal may be too aggressive for some patients and not aggressive enough for other patients (ie, younger patients for whom a lower target may prevent subsequent complications).⁵

Although the number of individuals in the United States who achieve the target HbA_{1c} levels of $< 7\%$ has been increasing in recent years, further strategies are needed to improve the achievement of glycemic-control targets and overall outcomes for individuals with diabetes or those at risk for diabetes.⁴

The New SGLT2 Inhibitors

The kidney plays a key role in maintaining glucose homeostasis. Evidence suggests that in patients with type 2 diabetes mellitus, there is an increase in the amount of renal glucose that is released, thereby implicating the kidneys' contribution to hyperglycemia.⁶ In hyperglycemia, excess glucose is reabsorbed by the kidneys—a process that increases the renal glucose threshold and creates a cycle of chronic hyperglycemia, along with associated microvascular complications.⁶ The sodium-glucose cotransporter 2 (SGLT2), a cotransporter that is expressed in the proximal renal tubules, mediates the active transport of glucose

against a concentration gradient via cotransport with sodium. SGLT2 is responsible for reabsorbing 90% of the glucose that is filtered at the glomerulus.⁶ SGLT2 inhibitors represent a novel class of drugs that lower the renal threshold for glucose, thereby increasing urinary glucose excretion.^{6,7} Combined with diet and exercise, these agents have a promising role in improving glycemic control in patients with type 2 diabetes mellitus.

Fixed-Dose Combination for Type 2 Diabetes

On August 8, 2014, the combination of canagliflozin (Invokana) plus metformin hydrochloride (Invokamet; Janssen Pharmaceuticals) in a single tablet was approved by the US Food and Drug Administration (FDA) for the treatment of patients with type 2 diabetes mellitus.⁸ The combination of canagliflozin, an SGLT2 inhibitor, and metformin hydrochloride (metformin), a biguanide, is not indicated for the treatment of type 1 diabetes or for the treatment of diabetic ketoacidosis. Canagliflozin plus metformin is the first fixed-dose combination of an SGLT2 inhibitor with metformin to receive FDA approval in the United States.⁸

Canagliflozin, the first SGLT2 inhibitor available in the United States, was approved by the FDA in 2013 for type 2 diabetes.⁹ Metformin, often prescribed in the early treatment of type 2 diabetes mellitus, has been available in the United States for nearly 20 years.

Richard B. Aguilar, MD, Medical Director of Diabetes Nation, said, “Invokamet™ combines, in one tablet, two complementary therapeutic approaches proven effective for managing type 2 diabetes. Canagliflozin works with the kidney to promote the loss of glucose in the urine, whereas metformin decreases the production of glucose in the liver and improves the body’s response to insulin.”⁸

Mechanism of Action

Canagliflozin plus metformin combines 2 oral antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes mellitus—canagliflozin, an SGLT2 inhibitor, and metformin, a member of the biguanide class.¹⁰

SGLT2, expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. By inhibiting SGLT2, canagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, thereby increasing urinary glucose excretion.¹⁰ Metformin is an antihyperglycemic agent that improves glucose tolerance in patients with type 2 diabetes by lowering basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.¹⁰

Dosing

The dosing of canagliflozin plus metformin is individualized based on the patient’s current antidiabetes drug regimen.¹⁰ The combination of canagliflozin plus metformin is taken twice daily with meals, with gradual dose escalation to reduce metformin-related gastrointestinal side effects.¹⁰ The daily dose of metformin should not exceed 2000 mg, and the daily dose of canagliflozin should not exceed 300 mg in patients with an estimated glomerular filtration rate (eGFR) of ≥ 60 mL/min/1.73 m². Canagliflozin plus metformin is limited to canagliflozin 50 mg twice daily in patients with an eGFR of 45 mL/min/1.73 m² to < 60 mL/min/1.73 m².¹⁰

Before starting treatment with canagliflozin plus metformin, renal function should be assessed.¹⁰ Canagliflozin plus metformin should not be initiated or continued if creatinine levels are ≥ 1.5 mg/dL for males or 1.4 mg/dL for females, or if eGFR is < 45 mL/min/1.73 m².

The combination of canagliflozin plus metformin is available as film-coated tablets in 4 strengths—canagliflozin 50 mg/metformin 500 mg, canagliflozin 50 mg/metformin 1000 mg, canagliflozin 150 mg/metformin 500 mg, and canagliflozin 150 mg/metformin 1000 mg.¹⁰

Clinical Trials

Although no clinical efficacy studies have been conducted on the combination of canagliflozin plus metformin, the bioequivalence of canagliflozin plus metformin to canagliflozin and metformin coadministered as individual tablets has been demonstrated in healthy individuals.¹⁰

Treatment with canagliflozin plus metformin demonstrated clinically significant improvements in HbA_{1c} levels compared with placebo in patients with type 2 diabetes. These reductions were observed across subgroups, including age, sex, race, and baseline body mass index.^{7,10,11}

Studies have been conducted on canagliflozin in combination with metformin alone, metformin and sulfonylurea, metformin and a thiazolidinedione (ie, pioglitazone), and metformin and insulin (with or without other antihyperglycemic agents).¹⁰ In addition, the efficacy of canagliflozin was compared with a dipeptidyl peptidase-4 inhibitor (sitagliptin) and with a sulfonylurea (glimepiride).^{7,10,11}

Canagliflozin as Add-On to Metformin

A 26-week, double-blind, placebo-controlled phase 3 clinical trial evaluated the efficacy and safety of canagliflozin in combination with metformin.⁷ This study included 1284 patients with type 2 diabetes mellitus that was inadequately controlled with metformin monotherapy (≥ 2000 mg daily or ≥ 1500 mg daily if a higher dose was not tolerated). The patients’ mean age was 55 years; 47% were men, and the mean baseline eGFR was 89 mL/min/1.73 m².¹⁰

The primary end point of this study was the change

from baseline in HbA_{1c} levels at 26 weeks. The secondary end points included changes in HbA_{1c} levels, fasting plasma glucose (FPG) levels at 52 weeks, body weight, and systolic blood pressure at 26 and 52 weeks.^{7,10}

A total of 1009 patients who were already receiving the required metformin dose were randomized after completing a 2-week, single-blind, placebo run-in period. In addition, 275 patients who were taking less than the required metformin dose or who were receiving metformin in combination with another antihyperglycemic agent were switched to metformin monotherapy for at least 8

weeks before entering the 2-week, single-blind, placebo run-in period. After the placebo run-in period, all patients were randomized to canagliflozin 100 mg, canagliflozin 300 mg, sitagliptin 100 mg, or to placebo, administered once daily as add-on therapy to metformin.¹⁰

At the end of the 26-week treatment period, 100-mg and 300-mg doses of canagliflozin administered once daily as add-on therapy to metformin demonstrated a significant improvement in HbA_{1c} levels ($P < .001$ for both doses) compared with placebo (Table 1). Furthermore, canagliflozin 100 mg and canagliflozin 300 mg once daily also resulted in a greater proportion of patients who achieved HbA_{1c} levels of $<7\%$, a significant reduction in FPG levels, improved postprandial glucose, and greater percent body weight reduction compared with placebo when added to metformin. The mean changes from baseline in systolic blood pressure compared with placebo were significant: -5.4 mm Hg for canagliflozin 100 mg and -6.6 mm Hg for canagliflozin 300 mg ($P < .001$ for both doses).¹⁰

At week 52, canagliflozin 100 mg was noninferior to sitagliptin at lowering HbA_{1c} levels, and canagliflozin 300 mg was superior to sitagliptin at lowering HbA_{1c} levels. Canagliflozin 100 mg and canagliflozin 300 mg also showed a significant reduction in body weight compared with sitagliptin at 52 weeks ($P < .001$).⁷

Canagliflozin versus Glimepiride

In a 52-week, double-blind, active-controlled study, the efficacy and safety of canagliflozin plus metformin versus glimepiride plus metformin were evaluated in 1450 patients with type 2 diabetes that was inadequately controlled with metformin monotherapy (≥ 2000 mg daily or ≥ 1500 mg daily if a higher dose was not tolerated).¹¹ The patients' mean age was 56 years; 56% were men, and the mean baseline eGFR was 90 mL/min/1.73 m².¹⁰

The primary end point was the change from baseline in HbA_{1c} levels at 52 weeks (0.3% noninferiority margin for comparing each of the canagliflozin doses vs glimepiride).¹¹ The secondary end point was changes in percent body weight at week 52.¹¹ A total of 928 patients who tolerated the maximally required metformin dose were randomized after completing a 2-week, single-blind, placebo run-in period. In addition, 522 patients were switched to metformin monotherapy for at least 10 weeks, and then completed a 2-week single-blind run-in period. After the 2-week run-in period, all the patients were randomized to receive canagliflozin 100 mg, canagliflozin 300 mg, or glimepiride (6 mg or 8 mg, allowed throughout the 52-week study period), administered once daily as add-on therapy to metformin.¹⁰

At the end of the treatment period, canagliflozin 100 mg demonstrated similar reductions in HbA_{1c} levels from baseline compared with glimepiride when added to

Table 1 Canagliflozin plus Metformin: Results from a 26-Week, Placebo-Controlled Clinical Trial

Efficacy parameter	Placebo + metformin (N = 183)	Canagliflozin 100 mg + metformin (N = 368)	Canagliflozin 300 mg + metformin (N = 367)
HbA_{1c} level			
Baseline, mean, %	7.96	7.94	7.95
Change from baseline, adjusted mean, %	-0.17	-0.79	-0.94
Difference from placebo, adjusted mean, ^a %		-0.62 ^b (95% CI, -0.76 to -0.48)	-0.77 ^b (95% CI, -0.91 to -0.64)
Patients achieving HbA _{1c} $<7\%$, %	30	46 ^b	58 ^b
Fasting plasma glucose			
Baseline, mean, mg/dL	164	169	173
Change from baseline, adjusted mean, mg/dL	2	-27	-38
Difference from placebo, adjusted mean, ^a mg/dL		-30 ^b (95% CI, -36 to -24)	-40 ^b (95% CI, -46 to -34)
2-hour postprandial glucose			
Baseline, mean, mg/dL	249	258	262
Change from baseline, adjusted mean, mg/dL	-10	-48	-57
Difference from placebo, adjusted mean, ^a mg/dL		-38 ^b (95% CI, -49 to -27)	-47 ^b (95% CI, -58 to -36)
Body weight			
Baseline, mean, kg	86.7	88.7	85.4
Change from baseline, adjusted mean, %	-1.2	-3.7	-4.2
Difference from placebo, adjusted mean, ^a kg		-2.5 ^b (95% CI, -3.1 to -1.9)	-2.9 ^b (95% CI, -3.5 to -2.3)

^aLeast squares mean adjusted for baseline value and stratification factors.

^b $P < .001$.

CI indicates confidence interval.

Source: Invokamet (canagliflozin and metformin hydrochloride) tablets prescribing information; August 2014.

metformin therapy (Table 2).¹⁰ Furthermore, canagliflozin 300 mg demonstrated a greater reduction from baseline in HbA_{1c} levels compared with glimepiride, and the relative treatment difference was -0.12% (95% confidence interval, -0.22 to -0.02). Treatment with canagliflozin 100 mg and canagliflozin 300 mg daily also demonstrated greater reductions in percent body weight than treatment with glimepiride.¹⁰

Safety

The most common adverse reactions (≥5%) associated with the use of canagliflozin are female genital mycotic infections, urinary tract infection, and increased urination. The most common adverse reactions (≥5%) associated with the use of metformin are diarrhea, nausea, vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache.¹⁰

Contraindications

The combination of canagliflozin plus metformin is contraindicated in patients with renal impairment (eg, serum creatinine levels ≥1.5 mg/dL for males or 1.4 mg/dL for females, or eGFR <45 mL/min/1.73 m²), which may also result from conditions such as cardiovascular collapse, acute myocardial infarction, or septicemia; end-stage renal disease; or patients on dialysis.¹⁰ Canagliflozin plus metformin is also contraindicated in patients with acute or chronic metabolic acidosis, including diabetic ketoacidosis, or in patients with a history of a hypersensitivity reaction to canagliflozin or to metformin.¹⁰

Drug Interactions

Cationic drugs. Cationic drugs (eg, amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) may compete with metformin for common renal tubular transport systems and may inhibit metformin elimination.¹⁰

Uridine 5'-diphospho-glucuronosyltransferase (UGT) enzyme inducers. The concomitant use of a UGT inducer (eg, rifampin, phenytoin, phenobarbital, ritonavir) with canagliflozin plus metformin may reduce the exposure of canagliflozin; consider increasing the canagliflozin dose from 50 mg to 150 mg twice daily.¹⁰

Digoxin. Canagliflozin increases digoxin exposure. Patients who take canagliflozin plus metformin with concomitant digoxin should be monitored for a need to adjust the dose of either drug.¹⁰

Warnings and Precautions

Boxed warning. The prescribing information for canagliflozin plus metformin contains a boxed warning stating that lactic acidosis can occur as a result of metformin accumulation. This risk increases in patients with renal

Efficacy parameter	Canagliflozin 100 mg + metformin (N = 483)	Canagliflozin 300 mg + metformin (N = 485)	Glimepiride (titrated) + metformin (N = 482)
HbA_{1c} level			
Baseline, mean, %	7.78	7.79	7.83
Change from baseline, adjusted mean, %	-0.82	-0.93	-0.81
Difference from glimepiride, adjusted mean, ^a %	-0.01 ^b (95% CI, -0.11 to 0.09)	-0.12 ^b (95% CI, -0.22 to -0.02)	
Patients achieving HbA _{1c} <7%, %	54	60	56
Fasting plasma glucose			
Baseline, mean, mg/dL	165	164	166
Change from baseline, adjusted mean, mg/dL	-24	-28	-18
Difference from glimepiride, adjusted mean, ^a mg/dL	-6 (95% CI, -10 to -2)	-9 (95% CI, -13 to -5)	
Body weight			
Baseline, mean, kg	86.8	86.6	86.6
Change from baseline, adjusted mean, %	-4.2	-4.7	1.0
Difference from glimepiride, adjusted mean, ^a kg	-5.2 ^c (95% CI, -5.7 to -4.7)	-5.7 ^c (95% CI, -6.2 to -5.1)	
^a Least squares mean adjusted for baseline value and stratification factors.			
^b Canagliflozin plus metformin is considered noninferior to glimepiride plus metformin, because the upper limit of this confidence interval is less than the prespecified noninferiority margin of <0.3%.			
^c P <.001.			
CI indicates confidence interval.			
Source: Invokamet (canagliflozin and metformin hydrochloride) tablets prescribing information; August 2014.			

impairment, sepsis, dehydration, excess alcohol intake, hepatic impairment, and acute congestive heart failure.¹⁰

The symptoms associated with lactic acidosis include malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH levels, increased anion gap, and elevated blood lactate levels. If lactic acidosis is suspected, the combination of canagliflozin plus metformin should be discontinued, and the patient should be hospitalized immediately.

Lactic acidosis. Patients should be cautioned against excessive alcohol use. The use of canagliflozin plus metformin is not recommended in patients with hepatic

impairment or with hypoxic states. Patients should be checked for normal renal function before treatment is initiated and at least annually thereafter.¹⁰

Hypotension. Before the combination of canagliflozin plus metformin combination treatment is initiated, the volume status and correct hypovolemia should be assessed in patients with renal impairment; the elderly; patients with low systolic blood pressure; or those receiving diuretics, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers. Patients should be monitored for signs and symptoms of hypotension during therapy.¹⁰

Renal function. Potential impairment in renal function should be monitored during therapy.¹⁰

Radiologic studies/surgical procedures. Canagliflozin plus metformin should be temporarily discontinued for radiologic studies with intravascular administration of iodinated contrast materials or any surgical procedures that necessitate the restricted intake of food and fluids.¹⁰

Hyperkalemia. Potassium levels should be monitored in patients with impaired renal function and in patients who are predisposed to hyperkalemia.¹⁰

Hypoglycemia. When used in combination with canagliflozin plus metformin, a lower dose of insulin or the insulin secretagogue should be considered to reduce the risk of developing hypoglycemia.¹⁰

Genital mycotic infections. Patients should be monitored and treated for genital mycotic infections.¹⁰

Hypersensitivity reactions. Canagliflozin plus metformin should be discontinued in patients with hypersensitivity reactions, and patients should be monitored until the signs and symptoms of hypersensitivity resolve.¹⁰

Vitamin B₁₂ deficiency. Metformin may lower vitamin B₁₂ levels; hematologic parameters should be measured annually.¹⁰

Increased low-density lipoprotein cholesterol (LDL-C) levels. Dose-related increases in LDL-C levels may occur with canagliflozin. LDL-C levels should be monitored and treated per standard of care after the combination of canagliflozin plus metformin is initiated.¹⁰

Use in Specific Populations

Pregnancy. Canagliflozin plus metformin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.¹⁰

Nursing mothers. A decision should be made whether to discontinue nursing or to suspend the use of canagliflozin plus metformin, taking into account the importance of the drug to the mother.¹⁰

Geriatric use. Because renal function abnormalities

can occur after initiating canagliflozin, metformin is substantially excreted by the kidney, and aging can be associated with reduced renal function, renal function should be monitored more frequently after initiating canagliflozin plus metformin in the elderly, and the dose should be adjusted based on renal function.¹⁰

Renal impairment. The efficacy and safety of canagliflozin were evaluated in a study that included patients with moderate renal impairment. These patients had a higher incidence of adverse reactions that were related to reduced intravascular volume and renal function compared with patients with mild renal impairment or patients with normal renal function.¹⁰

Conclusion

The recent FDA approval of the combination of canagliflozin plus metformin marks the availability of a novel SGLT2 and biguanide combination therapy in a single tablet for the treatment of patients with type 2 diabetes. Phase 3 studies demonstrated that this new combination improved HbA_{1c} levels in patients with type 2 diabetes. In addition, canagliflozin plus metformin resulted in greater reductions in body weight and systolic blood pressure compared with metformin alone. ■

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