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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use INVOKAMET® safely and effectively. See full prescribing information for INVOKAMET.

INVOKAMET (canagliflozin and metformin hydrochloride) tablets, for oral use
Initial U.S. Approval – 2014

WARNING: LACTIC ACIDOSIS

See full prescribing information for complete boxed warning.

- **Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as renal impairment, sepsis, dehydration, excess alcohol intake, hepatic impairment, and acute congestive heart failure (5.1)**
- **Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate (5.1)**
- **If acidosis is suspected, discontinue INVOKAMET and hospitalize the patient immediately (5.1)**

----------INDICATIONS AND USAGE----------

INVOKAMET is a sodium-glucose co-transporter 2 (SGLT2) inhibitor and biguanide combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing metformin or canagliflozin or in patients already being treated with both canagliflozin and metformin (1)

Limitation of use:
Not for treatment of type 1 diabetes or diabetic ketoacidosis (1)

----------DOSAGE AND ADMINISTRATION----------

- Individualize based on the patient's current regimen (2)
- Take twice daily with meals, with gradual dose escalation to reduce the gastrointestinal side effects due to metformin (2.1)
- Do not exceed a daily dose of metformin 2,000 mg and canagliflozin 300 mg; INVOKAMET is limited to canagliflozin 50 mg twice daily in patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 (2.1, 2.2)
- Assess renal function before initiating INVOKAMET. Do not initiate or continue INVOKAMET if creatinine levels are greater than or equal to 1.5 mg/dL for males or 1.4 mg/dL for females, or if eGFR is persistently below 45 mL/min/1.73 m^2 (2.2, 4)

----------DOSAGE FORMS AND STRENGTHS----------

Film-coated tablets:
- Canagliflozin 50 mg and metformin hydrochloride 500 mg
- Canagliflozin 50 mg and metformin hydrochloride 1,000 mg
- Canagliflozin 150 mg and metformin hydrochloride 500 mg
- Canagliflozin 150 mg and metformin hydrochloride 1,000 mg (3)

----------CONTRAINDICATIONS----------

- Renal impairment, ESRD, or on dialysis (4, 5.1, 5.3)
- Metabolic acidosis, including diabetic ketoacidosis (1, 4, 5.1)
- History of serious hypersensitivity reaction to canagliflozin or metformin (4, 5.8)

----------WARNINGS AND PRECAUTIONS----------

- Lactic acidosis: Warn against excessive alcohol use. INVOKAMET is not recommended in hepatic impairment or hypoxic states. Ensure normal renal function before initiating and at least annually thereafter (5.1, 5.3, 5.5, 5.10, 5.11)
- Hypotension: Before initiating INVOKAMET, assess volume status and correct hypovolemia in patients with renal impairment, the elderly, in patients with low systolic blood pressure, or on diuretics, ACEi, or ARB. Monitor for signs and symptoms during therapy (5.2)
- Impairment in Renal Function: Monitor renal function during therapy (5.3)
- Radiological Studies and Surgical Procedures: Temporarily discontinue for radiologic studies with intravascular administration of iodinated contrast materials or any surgical procedures necessitating restricted intake of food and fluids (5.3)
- Hyperkalemia: Monitor potassium levels in patients with impaired renal function and in patients predisposed to hyperkalemia (5.4)
- Hypoglycemia: Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination with INVOKAMET (5.6)
- Genital mycotic infections: Monitor and treat if indicated (5.7)
- Hypersensitivity reactions: Discontinue INVOKAMET and monitor until signs and symptoms resolve (5.8)
- Vitamin B_{12} deficiency: Metformin may lower vitamin B_{12} levels. Monitor hematologic parameters annually (5.9)
- Increased LDL-C: Monitor LDL-C and treat per standard of care (5.12)

----------ADVERSE REACTIONS----------

- Most common adverse reactions associated with canagliflozin (5% or greater incidence): female genital mycotic infections, urinary tract infection, and increased urination (6.1)
- Most common adverse reactions associated with metformin (5% or greater incidence) are diarrhea, nausea, vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-526-7736 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Cationic drugs: May reduce metformin elimination (7.1)
- UGT inducers (e.g., rifampin): Canagliflozin exposure is reduced. Consider increasing canagliflozin dose from 50 mg to 150 mg twice daily (2.3, 7.2)
- Digoxin: Monitor digoxin levels (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Use during pregnancy only if the potential benefit justifies the potential risk to the fetus (8.1)
- Nursing mothers: Discontinue drug or nursing (8.3)
- Geriatrics: Higher incidence of adverse reactions related to reduced intravascular volume (5.2, 6.1, 8.5)
- Renal impairment: Higher incidence of adverse reactions related to reduced intravascular volume and renal function (2.2, 5.3, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 03/2015

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FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS

- **Lactic acidosis is a rare but serious complication that can occur due to metformin accumulation. The risk increases with conditions such as renal impairment, sepsis, dehydration, excess alcohol intake, hepatic impairment, and acute congestive heart failure.**
- **The onset is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress.**
- **Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate.**
- **If lactic acidosis is suspected, INVOKAMET® should be discontinued and the patient hospitalized immediately *[see Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

INVOKAMET (canagliflozin and metformin hydrochloride) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing metformin or canagliflozin, or in patients who are already treated with both canagliflozin and metformin *[see Clinical Studies (14)]*.

Limitations of Use

INVOKAMET is not recommended in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

- Individualize the starting dose of INVOKAMET (canagliflozin and metformin hydrochloride) based on the patient's current regimen:
  - In patients on metformin, switch to INVOKAMET containing canagliflozin 50 mg with a similar total daily dose of metformin;
  - In patients on canagliflozin, switch to INVOKAMET containing metformin 500 mg with a similar total daily dose of canagliflozin;
  - In patients already treated with canagliflozin and metformin, switch to INVOKAMET containing the same total daily doses of each component.

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- Take INVOKAMET twice daily with meals, with gradual dose escalation to reduce the gastrointestinal side effects due to metformin *[see Dosage Forms and Strengths (3)]*.
- In patients with volume depletion not previously treated with canagliflozin, correct this condition before initiating INVOKAMET *[see Warnings and Precautions (5.2), Use in Specific Populations (8.5), (8.6), and Patient Counseling Information (17)]*.
- Adjust dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of metformin 2000 mg and canagliflozin 300 mg in patients with an eGFR of 60 mL/min/1.73 m^2 or greater *[see Dosage and Administration (2.2)]*.

2.2 Recommended Dosage for Patients with Renal Impairment

- Assess renal function before initiating INVOKAMET and periodically thereafter.
- Do not initiate or continue INVOKAMET in patients with serum creatinine levels greater than or equal to 1.5 mg/dL for males or 1.4 mg/dL for females. In patients who meet these serum creatinine levels, do not initiate or continue INVOKAMET if eGFR is persistently less than 45 mL/min/1.73 m^2 *[see Contraindications (4) and Warnings and Precautions (5.3)]*.
- No dose adjustment of INVOKAMET is needed in patients with mild renal impairment (eGFR of 60 mL/min/1.73 m^2 or greater).
- Limit the dose of INVOKAMET to canagliflozin 50 mg twice daily in patients with moderate renal impairment with an eGFR of 45 to less than 60 mL/min/1.73 m^2.

2.3 Concomitant Use with UDP-Glucuronosyl Transferase (UGT) Enzyme Inducers

If an inducer of UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) is co-administered with INVOKAMET, consider increasing the dose to canagliflozin 150 mg twice daily in patients currently tolerating 50 mg twice daily who have an eGFR of 60 mL/min/1.73 m^2 or greater and require additional glycemic control *[see Drug Interactions (7.2)]*.

Consider another antihyperglycemic agent in patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer.

3 DOSAGE FORMS AND STRENGTHS

INVOKAMET (canagliflozin and metformin hydrochloride) film-coated tablets for oral administration are available in the following strengths:

- Canagliflozin 50 mg and metformin hydrochloride 500 mg tablets are immediate-release, capsule-shaped, white film-coated tablets with “CM” on one side and “155” on the other side.

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- Canagliflozin 50 mg and metformin hydrochloride 1,000 mg tablets are immediate-release, capsule-shaped, beige, film-coated tablets with “CM” on one side and “551” on the other side.

- Canagliflozin 150 mg and metformin hydrochloride 500 mg tablets are immediate-release, capsule-shaped, yellow, film-coated tablets with “CM” on one side and “215” on the other side.

- Canagliflozin 150 mg and metformin hydrochloride 1,000 mg tablets are immediate-release, capsule-shaped, purple, film-coated tablets with “CM” on one side and “611” on the other side.

4 CONTRAINDICATIONS

INVOKAMET is contraindicated in patients with:

- Renal impairment (e.g., serum creatinine levels greater than or equal to 1.5 mg/dL for males or 1.4 mg/dL for females, *or* eGFR is less than 45 mL/min/1.73 m^2) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia; end stage renal disease (ESRD) or patients on dialysis *[see Warnings and Precautions (5.1), (5.3) and Use in Specific Populations (8.6)]*.

- Acute or chronic metabolic acidosis, including diabetic ketoacidosis *[see Warnings and Precautions (5.1)]*.

- History of a serious hypersensitivity reaction to canagliflozin or metformin *[see Warnings and Precautions (5.8)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with INVOKAMET and is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (greater than 5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels greater than 5 mcg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin is approximately 0.03 cases/1000 patient-years (with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, particularly when

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accompanied by hypoperfusion and hypoxemia due to unstable or acute failure, are at increased risk of lactic acidosis.

The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in any patients unless measurement of creatinine clearance demonstrates that renal function is not reduced. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis.

Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should be avoided in patients with clinical or laboratory evidence of hepatic impairment. Patients should be cautioned against excessive alcohol intake when taking metformin, since alcohol potentiates the effects of metformin on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure necessitating restricted intake of food or fluids *[see Warnings and Precautions (5.3), (5.5), (5.10) and Clinical Pharmacology (12.3)]*.

The onset of lactic acidosis often is subtle, and accompanied by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. More severe acidosis may be associated with signs such as hypothermia, hypotension, and resistant bradyarrhythmias. Patients should be educated to recognize and promptly report these symptoms. If present, INVOKAMET should be discontinued until lactic acidosis is ruled out. Gastrointestinal symptoms in patients on a chronic, stable dose of metformin could be caused by lactic acidosis or other serious disease.

To rule out lactic acidosis, serum electrolytes, ketones, blood glucose, blood pH, lactate levels, and blood metformin levels may be useful. Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking metformin do not necessarily indicate impending lactic acidosis and may be due to other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling.

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia). Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted. Metformin is dialyzable (clearance of up to 170 mL/min under good hemodynamic conditions) and prompt hemodialysis is recommended to remove the accumulated metformin and correct the metabolic acidosis. Such management often results in prompt reversal of symptoms and recovery *[see Boxed Warning and Contraindications (4)]*.

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5.2 Hypotension

Canagliflozin causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKAMET *[see Adverse Reactions (6.1)]* particularly in patients with eGFR less than 60 mL/min/1.73 m^2, elderly patients, patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (e.g., angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKAMET in patients with one or more of these characteristics who were not already on canagliflozin, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.

5.3 Impairment in Renal Function

Canagliflozin increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating INVOKAMET *[see Adverse Reactions (6.1)]*.

Metformin is known to be substantially excreted by the kidney. The risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Therefore, INVOKAMET is contraindicated in patients with renal impairment *[see Contraindications (4), Warnings and Precautions (5.1), and Use in Specific Populations (8.6)]*.

Before initiation of INVOKAMET therapy and at least annually thereafter, assess renal function *[see Contraindications (4)]*. In patients in whom development of renal impairment is anticipated (e.g., elderly), assess renal function more frequently and discontinue INVOKAMET if evidence of renal impairment is present (e.g. serum creatinine levels greater than or equal to 1.5 mg/dL for males or 1.4 mg/dL for females, or eGFR is less than 45 mL/min/1.73 m^2).

Use of Concomitant Medications That May Affect Renal Function or Metformin Disposition

Monitor and adjust dose of INVOKAMET or concomitant drug in patients taking medication(s) that may affect renal function or result in a significant hemodynamic change or interfere with the disposition of metformin *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

Radiological Studies and Surgical Procedures

Radiologic studies involving the use of intravascular iodinated contrast materials (e.g., intravenous urogram, intravenous cholangiography, angiography, and computed tomography) can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such study is planned, temporarily discontinue INVOKAMET at the time of or prior to the procedure, and withhold for 48 hours subsequent to the procedure and reinstitute only after renal function has been confirmed to be normal.

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Temporarily discontinue INVOKAMET for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and restart after the patient's oral intake has resumed and renal function has been evaluated as normal.

5.4 Hyperkalemia

Canagliflozin can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia *[see Adverse Reactions (6.1)]*.

Monitor serum potassium levels periodically after initiating INVOKAMET in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.

5.5 Impaired Hepatic Function

Metformin use in patients with impaired hepatic function has been associated with some cases of lactic acidosis. Therefore, INVOKAMET is not recommended in patients with hepatic impairment *[see Warnings and Precautions (5.1)]*.

5.6 Hypoglycemia with Concomitant Use of Sulfonylurea or Insulin

Canagliflozin

Insulin and insulin secretagogues are known to cause hypoglycemia. Canagliflozin can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue *[see Adverse Reactions (6.1)]*. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKAMET.

Metformin

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication, are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs. Monitor for a need to lower the dose of INVOKAMET to minimize the risk of hypoglycemia in these patients.

5.7 Genital Mycotic Infections

Canagliflozin increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections *[see Adverse Reactions (6.1)]*. Monitor and treat appropriately.

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5.8 Hypersensitivity Reactions

Hypersensitivity reactions (e.g., generalized urticaria), some serious, were reported with canagliflozin treatment; these reactions generally occurred within hours to days after initiating canagliflozin. If hypersensitivity reactions occur, discontinue use of INVOKAMET; treat per standard of care and monitor until signs and symptoms resolve *[see Contraindications (4) and Adverse Reactions (6.1)]*.

5.9 Vitamin B_{12} Levels

In controlled, 29-week clinical trials of metformin, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of metformin-treated patients. Such decreases, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia or neurologic manifestations due to the short duration (less than 1 year) of the clinical trials. This risk may be more relevant to patients receiving long-term treatment with metformin and adverse hematologic and neurologic reactions have been reported postmarketing. The decrease in vitamin B_{12} levels appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Measure hematologic parameters on an annual basis in patients on INVOKAMET and investigate and treat if abnormalities occur. Patients with inadequate vitamin B_{12} or calcium intake or absorption may be predisposed to developing subnormal vitamin B_{12} levels, and routine serum vitamin B_{12} measurement at 2- to 3-year intervals is recommended in these patients.

5.10 Alcohol Intake

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving INVOKAMET *[see Warnings and Precautions (5.1)]*.

5.11 Hypoxic States

Cardiovascular collapse (shock) from whatever cause (e.g., acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia) have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, promptly discontinue INVOKAMET *[see Warnings and Precautions (5.1)]*.

5.12 Increases in Low-Density Lipoprotein (LDL-C)

Dose-related increases in LDL-C occur with canagliflozin *[see Adverse Reactions (6.1)]*. Monitor LDL-C and treat per standard of care after initiating INVOKAMET.

5.13 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with INVOKAMET or any other antidiabetic drug *[see Adverse Reactions (6.1)]*.

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6 ADVERSE REACTIONS

The following adverse reactions are also discussed elsewhere in the labeling:

- Lactic Acidosis *[see Boxed Warning and Warnings and Precautions (5.1), (5.3), (5.5), (5.10), (5.11)]*
- Hypotension *[see Warnings and Precautions (5.2)]*
- Impairment in Renal Function *[see Warnings and Precautions (5.3)]*
- Hyperkalemia *[see Warnings and Precautions (5.4)]*
- Impaired Hepatic Function *[see Warnings and Precautions (5.5)]*
- Hypoglycemia with Concomitant Use of Sulfonylurea or Insulin *[see Warnings and Precautions (5.6)]*
- Genital Mycotic Infections *[see Warnings and Precautions (5.7)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.8)]*
- Vitamin B_{12} Deficiency *[see Warnings and Precautions (5.9)]*
- Increases in Low-Density Lipoprotein (LDL-C) *[see Warnings and Precautions (5.12)]*

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Pool of Placebo-Controlled Trials

Canagliflozin

The data in Table 1 is derived from four 26-week placebo-controlled trials. In one trial canagliflozin was used as monotherapy and in three trials canagliflozin was used as add-on therapy with metformin (with or without other agents) *[see Clinical Studies (14)]*. These data reflect exposure of 1667 patients to canagliflozin and a mean duration of exposure to canagliflozin of 24 weeks with 1275 subjects exposed to a combination of canagliflozin and metformin. Patients received canagliflozin 100 mg (N=833), canagliflozin 300 mg (N=834) or placebo (N=646) once daily. The mean daily dose of metformin was 2138 mg (SD 337.3) for the 1275 subjects in the three placebo-controlled metformin add-on studies. The mean age of the population was 56 years and 2% were older than 75 years of age. Fifty percent (50%) of the population was male and 72% were Caucasian, 12% were Asian, and 5% were Black or African American. At baseline the population had diabetes for an average of 7.3 years, had a mean HbA1C of 8.0% and 20% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 88 mL/min/1.73 m^2).

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Table 1 shows common adverse reactions associated with the use of canagliflozin. These adverse reactions were not present at baseline, occurred more commonly on canagliflozin than on placebo, and occurred in at least 2% of patients treated with either canagliflozin 100 mg or canagliflozin 300 mg.

Table 1: Adverse Reactions From Pool of Four 26−Week Placebo-Controlled Studies Reported in ≥ 2% of Canagliflozin-Treated Patients*

Adverse Reaction	Placebo N=646	Canagliflozin 100 mg N=833	Canagliflozin 300 mg N=834
Female genital mycotic infections†	3.2%	10.4%	11.4%
Urinary tract infections‡	4.0%	5.9%	4.3%
Increased urination§	0.8%	5.3%	4.6%
Male genital mycotic infections¶	0.6%	4.2%	3.7%
Vulvovaginal pruritus	0.0%	1.6%	3.0%
Thirst#	0.2%	2.8%	2.3%
Constipation	0.9%	1.8%	2.3%
Nausea	1.5%	2.2%	2.3%

* The four placebo-controlled trials included one monotherapy trial and three add-on combination trials with metformin, metformin and sulfonylurea, or metformin and pioglitazone.

† Female genital mycotic infections include the following adverse reactions: Vulvovaginal candidiasis, Vulvovaginal mycotic infection, Vulvovaginitis, Vaginal infection, Vulvitis, and Genital infection fungal. Percentages calculated with the number of female subjects in each group as denominator: placebo (N=312), canagliflozin 100 mg (N=425), and canagliflozin 300 mg (N=430).

‡ Urinary tract infections include the following adverse reactions: Urinary tract infection, Cystitis, Kidney infection, and Urosepsis.

§ Increased urination includes the following adverse reactions: Polyuria, Pollakiuria, Urine output increased, Micturition urgency, and Nocturia.

¶ Male genital mycotic infections include the following adverse reactions: Balanitis or Balanoposthitis, Balanitis candida, and Genital infection fungal. Percentages calculated with the number of male subjects in each group as denominator: placebo (N=334), canagliflozin 100 mg (N=408), and canagliflozin 300 mg (N=404).

Thirst includes the following adverse reactions: Thirst, Dry mouth, and Polydipsia.

Abdominal pain was also more commonly reported in patients taking canagliflozin 100 mg (1.8%), 300 mg (1.7%) than in patients taking placebo (0.8%).

Canagliflozin and Metformin

The incidence and type of adverse reactions in the three 26-week placebo-controlled metformin add-on studies, representing a majority of data from the four 26-week placebo-controlled trials, was similar to the adverse reactions described in Table 1. There were no additional adverse reactions identified in the pooling of these three placebo-controlled studies that included metformin relative to the four placebo-controlled studies.

Pool of Placebo- and Active-Controlled Trials - Canagliflozin

The occurrence of adverse reactions for canagliflozin was evaluated in a larger pool of patients participating in placebo- and active-controlled trials.

The data combined eight clinical trials and reflect exposure of 6177 patients to canagliflozin. The mean duration of exposure to canagliflozin was 38 weeks with 1832 individuals exposed to

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canagliflozin for greater than 50 weeks. Patients received canagliflozin 100 mg (N=3092), canagliflozin 300 mg (N=3085) or comparator (N=3262) once daily. The mean age of the population was 60 years and 5% were older than 75 years of age. Fifty-eight percent (58%) of the population was male and 73% were Caucasian, 16% were Asian, and 4% were Black or African American. At baseline, the population had diabetes for an average of 11 years, had a mean HbA1C of 8.0% and 33% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 81 mL/min/1.73 m^2).

The types and frequency of common adverse reactions observed in the pool of eight clinical trials were consistent with those listed in Table 1. In this pool, canagliflozin was also associated with the adverse reactions of fatigue (1.7% with comparator, 2.2% with canagliflozin 100 mg, and 2.0% with canagliflozin 300 mg) and loss of strength or energy (i.e., asthenia) (0.6% with comparator, 0.7% with canagliflozin 100 mg, and 1.1% with canagliflozin 300 mg).

In the pool of eight clinical trials, the incidence rate of pancreatitis (acute or chronic) was 0.9, 2.7, and 0.9 per 1000 patient-years of exposure to comparator, canagliflozin 100 mg, and canagliflozin 300 mg, respectively.

In the pool of eight clinical trials with a longer mean duration of exposure to canagliflozin (68 weeks), the incidence rate of bone fracture was 14.2, 18.7, and 17.6 per 1000 patient years of exposure to comparator, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. Upper extremity fractures occurred more commonly on canagliflozin than comparator.

In the pool of eight clinical trials, hypersensitivity-related adverse reactions (including erythema, rash, pruritus, urticaria, and angioedema) occurred in 3.0%, 3.8%, and 4.2% of patients receiving comparator, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. Five patients experienced serious adverse reactions of hypersensitivity with canagliflozin, which included 4 patients with urticaria and 1 patient with a diffuse rash and urticaria occurring within hours of exposure to canagliflozin. Among these patients, 2 patients discontinued canagliflozin. One patient with urticaria had recurrence when canagliflozin was re-initiated.

Photosensitivity-related adverse reactions (including photosensitivity reaction, polymorphic light eruption, and sunburn) occurred in 0.1%, 0.2%, and 0.2% of patients receiving comparator, canagliflozin 100 mg, and canagliflozin 300 mg, respectively.

Other adverse reactions occurring more frequently on canagliflozin than on comparator were:

Volume Depletion-Related Adverse Reactions

Canagliflozin results in an osmotic diuresis, which may lead to reductions in intravascular volume. In clinical studies, treatment with canagliflozin was associated with a dose-dependent increase in the incidence of volume depletion-related adverse reactions (e.g., hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration). An increased incidence was observed in patients on the 300 mg dose. The three factors associated with the largest increase in volume depletion-related adverse reactions were the use of loop diuretics, moderate

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renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2), and age 75 years and older (Table 2) *[see Dosage and Administration (2.2), Warnings and Precautions (5.2), and Use in Specific Populations (8.5), (8.6)]*.

Table 2: Proportion of Patients With at Least One Volume Depletion-Related Adverse Reaction (Pooled Results from 8 Clinical Trials)

Baseline Characteristic	Comparator Group* %	Canagliflozin 100 mg %	Canagliflozin 300 mg %
Overall population	1.5%	2.3%	3.4%
75 years of age and older†	2.6%	4.9%	8.7%
eGFR less than 60 mL/min/1.73 m^2†	2.5%	4.7%	8.1%
Use of loop diuretic†	4.7%	3.2%	8.8%

* Includes placebo and active-comparator groups
† Patients could have more than 1 of the listed risk factors

Impairment in Renal Function

Canagliflozin is associated with a dose-dependent increase in serum creatinine and a concomitant fall in estimated GFR (Table 3). Patients with moderate renal impairment at baseline had larger mean changes.

Table 3: Changes in Serum Creatinine and eGFR Associated with Canagliflozin in the Pool of Four Placebo-Controlled Trials and Moderate Renal Impairment Trial

			Placebo N=646	Canagliflozin 100 mg N=833	Canagliflozin 300 mg N=834
Pool of Four Placebo-Controlled Trials	Baseline	Creatinine (mg/dL)	0.84	0.82	0.82
		eGFR (mL/min/1.73 m^2)	87.0	88.3	88.8
	Week 6 Change	Creatinine (mg/dL)	0.01	0.03	0.05
		eGFR (mL/min/1.73 m^2)	-1.6	-3.8	-5.0
	End of Treatment Change*	Creatinine (mg/dL)	0.01	0.02	0.03
		eGFR (mL/min/1.73 m^2)	-1.6	-2.3	-3.4
			Placebo N=90	**Canagliflozin 100 mg N=90**	**Canagliflozin 300 mg N=89**
Moderate Renal Impairment Trial	Baseline	Creatinine (mg/dL)	1.61	1.62	1.63
		eGFR (mL/min/1.73 m^2)	40.1	39.7	38.5
	Week 3 Change	Creatinine (mg/dL)	0.03	0.18	0.28
		eGFR (mL/min/1.73 m^2)	-0.7	-4.6	-6.2
	End of Treatment Change*	Creatinine (mg/dL)	0.07	0.16	0.18
		eGFR (mL/min/1.73 m^2)	-1.5	-3.6	-4.0

* Week 26 in mITT LOCF population

In the pool of four placebo-controlled trials where patients had normal or mildly impaired baseline renal function, the proportion of patients who experienced at least one event of significant renal function decline, defined as an eGFR below 80 mL/min/1.73 m^2 and 30% lower than baseline, was 2.1% with placebo, 2.0% with canagliflozin 100 mg, and 4.1% with

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canagliflozin 300 mg. At the end of treatment, 0.5% with placebo, 0.7% with canagliflozin 100 mg, and 1.4% with canagliflozin 300 mg had a significant renal function decline.

In a trial carried out in patients with moderate renal impairment with a baseline eGFR of 30 to less than 50 mL/min/1.73 m^2 (mean baseline eGFR 39 mL/min/1.73 m^2), the proportion of patients who experienced at least one event of significant renal function decline, defined as an eGFR 30% lower than baseline, was 6.9% with placebo, 18% with canagliflozin 100 mg, and 22.5% with canagliflozin 300 mg. At the end of treatment, 4.6% with placebo, 3.4% with canagliflozin 100 mg, and 2.2% with canagliflozin 300 mg had a significant renal function decline.

In a pooled population of patients with moderate renal impairment (N=1085) with baseline eGFR of 30 to less than 60 mL/min/1.73 m^2 (mean baseline eGFR 48 mL/min/1.73 m^2), the overall incidence of these events was lower than in the dedicated trial but a dose-dependent increase in incident episodes of significant renal function decline compared to placebo was still observed. Use of canagliflozin has been associated with an increased incidence of renal-related adverse reactions (e.g., increased blood creatinine, decreased glomerular filtration rate, renal impairment, and acute renal failure), particularly in patients with moderate renal impairment.

In the pooled analysis of patients with moderate renal impairment, the incidence of renal-related adverse reactions was 3.7% with placebo, 8.9% with canagliflozin 100 mg, and 9.3% with canagliflozin 300 mg. Discontinuations due to renal-related adverse events occurred in 1.0% with placebo, 1.2% with canagliflozin 100 mg, and 1.6% with canagliflozin 300 mg *[see Warnings and Precautions (5.3)]*.

Genital Mycotic Infections

In the pool of four placebo-controlled clinical trials, female genital mycotic infections (e.g., vulvovaginal mycotic infection, vulvovaginal candidiasis, and vulvovaginitis) occurred in 3.2%, 10.4%, and 11.4% of females treated with placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections on canagliflozin. Female patients who developed genital mycotic infections on canagliflozin were more likely to experience recurrence and require treatment with oral or topical antifungal agents and anti-microbial agents. In females, discontinuation due to genital mycotic infections occurred in 0% and 0.7% of patients treated with placebo and canagliflozin, respectively *[see Warnings and Precautions (5.7)]*.

In the pool of four placebo-controlled clinical trials, male genital mycotic infections (e.g., candidal balanitis, balanoposthitis) occurred in 0.6%, 4.2%, and 3.7% of males treated with placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. Male genital mycotic infections occurred more commonly in uncircumcised males and in males with a prior history of balanitis or balanoposthitis. Male patients who developed genital mycotic infections on canagliflozin were more likely to experience recurrent infections (22% on canagliflozin versus none on placebo), and require treatment with oral or topical antifungal agents and anti-microbial agents than patients on comparators. In males, discontinuations due to genital mycotic infections

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occurred in 0% and 0.5% of patients treated with placebo and canagliflozin, respectively. In the pooled analysis of 8 controlled trials, phimosis was reported in 0.3% of uncircumcised male patients treated with canagliflozin and 0.2% required circumcision to treat the phimosis *[see Warnings and Precautions (5.7)]*.

Hypoglycemia

In canagliflozin clinical trials, hypoglycemia was defined as any event regardless of symptoms, where biochemical hypoglycemia was documented (any glucose value below or equal to 70 mg/dL). Severe hypoglycemia was defined as an event consistent with hypoglycemia where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained). In individual clinical trials *[see Clinical Studies (14.6)]*, episodes of hypoglycemia occurred at a higher rate when canagliflozin was co-administered with insulin or sulfonylureas (Table 4) *[see Warnings and Precautions (5.6)]*.

Table 4: Incidence of Hypoglycemia* in Controlled Clinical Studies

Monotherapy (26 weeks)	**Placebo (N=192)**	**Canagliflozin 100 mg (N=195)**	**Canagliflozin 300 mg (N=197)**
Overall [N (%)]	5 (2.6)	7 (3.6)	6 (3.0)
In Combination with Metformin (26 weeks)	**Placebo + Metformin (N=183)**	**Canagliflozin 100 mg + Metformin (N=368)**	**Canagliflozin 300 mg + Metformin (N=367)**
Overall [N (%)]	3 (1.6)	16 (4.3)	17 (4.6)
Severe [N (%)]†	0 (0)	1 (0.3)	1 (0.3)
In Combination with Metformin (18 weeks) ‡	**Placebo (N=93)**	**Canagliflozin 100 mg (N=93)**	**Canagliflozin 300 mg (N=93)**
Overall [N (%)]	3 (3.2)	4 (4.3)	3 (3.2)
In Combination with Metformin + Sulfonylurea (26 weeks)	**Placebo + Metformin + Sulfonylurea (N=156)**	**Canagliflozin 100 mg + Metformin + Sulfonylurea (N=157)**	**Canagliflozin 300 mg + Metformin + Sulfonylurea (N=156)**
Overall [N (%)]	24 (15.4)	43 (27.4)	47 (30.1)
Severe [N (%)]†	1 (0.6)	1 (0.6)	0
In Combination with Metformin + Pioglitazone (26 weeks)	**Placebo + Metformin + Pioglitazone (N=115)**	**Canagliflozin 100 mg + Metformin + Pioglitazone (N=113)**	**Canagliflozin 300 mg + Metformin + Pioglitazone (N=114)**
Overall [N (%)]	3 (2.6)	3 (2.7)	6 (5.3)
In Combination with Insulin (18 weeks)	**Placebo (N=565)**	**Canagliflozin 100 mg (N=566)**	**Canagliflozin 300 mg (N=587)**
Overall [N (%)]	208 (36.8)	279 (49.3)	285 (48.6)
Severe [N (%)]†	14 (2.5)	10 (1.8)	16 (2.7)
In Combination with Insulin and Metformin (18 weeks) §	**Placebo (N=145)**	**Canagliflozin 100 mg**	**Canagliflozin 300 mg**

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Table 4: Incidence of Hypoglycemia* in Controlled Clinical Studies

		(N=139)	(N=148)
Overall [N (%)]	66 (45.5)	58 (41.7)	70 (47.3)
Severe [N (%)][†]	4 (2.8)	1 (0.7)	3 (2.0)

* Number of patients experiencing at least one event of hypoglycemia based on either biochemically documented episodes or severe hypoglycemic events in the intent-to-treat population

† Severe episodes of hypoglycemia were defined as those where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained)

‡ Phase 2 clinical study with twice daily dosing (50 mg or 150 mg twice daily in combination with metformin)

§ Subgroup of patients (N=287) from insulin substudy on canagliflozin in combination with metformin and insulin (with or without other antiglycemic agents)

Metformin

The most common adverse reactions (5% or greater incidence) due to initiation of metformin are diarrhea, nausea, vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache.

Long-term treatment with metformin has been associated with a decrease in vitamin B_{12}, which may very rarely result in clinically significant vitamin B_{12} deficiency (e.g., megaloblastic anemia) *[see Warnings and Precautions (5.9)]*.

Laboratory Tests

Increases in Serum Potassium

In pooled data from four placebo-controlled trials with canagliflozin, the mean percent change in serum potassium levels was 0.5% and 1.0% with canagliflozin 100 mg and canagliflozin 300 mg, respectively, compared to 0.6% with placebo. Episodes of elevated serum potassium (greater than 5.4 mEq/L and 15% above baseline) were seen in 4.4% of patients treated with canagliflozin 100 mg, 7.0% of patients treated with canagliflozin 300 mg, and 4.8% of patients treated with placebo. Dose-related, transient mean increases in serum potassium were observed early after initiation of canagliflozin (i.e., within 3 weeks) in a trial of patients with moderate renal impairment. In this trial, increases in serum potassium of greater than 5.4 mEq/L and 15% above baseline occurred in 16.1%, 12.4%, and 27.0% of patients treated with placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. More severe elevations (i.e., equal or greater than 6.5 mEq/L) occurred in 1.1%, 2.2%, and 2.2% of patients treated with placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. In patients with moderate renal impairment, increases in potassium were more commonly seen in those with elevated potassium at baseline and in those using medications that reduce potassium excretion, such as potassium-sparing diuretics, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor blockers *[see Warnings and Precautions (5.3), (5.4)]*.

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Increases in Serum Magnesium

Dose-related increases in serum magnesium were observed early after initiation of canagliflozin (within 6 weeks) and remained elevated throughout treatment. In the pool of four placebo-controlled trials, the mean percent change in serum magnesium levels was 8.1% and 9.3% with canagliflozin 100 mg and canagliflozin 300 mg, respectively, compared to -0.6% with placebo. In a trial of patients with moderate renal impairment, serum magnesium levels increased by 0.2%, 9.2%, and 14.8% with placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively.

Increases in Serum Phosphate

Dose-related increases in serum phosphate levels were observed with canagliflozin. In the pool of four placebo-controlled trials, the mean percent change in serum phosphate levels were 3.6% and 5.1% with canagliflozin 100 mg and canagliflozin 300 mg, respectively, compared to 1.5% with placebo. In a trial of patients with moderate renal impairment, the mean serum phosphate levels increased by 1.2%, 5.0%, and 9.3% with placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively.

Increases in Low-Density Lipoprotein Cholesterol (LDL-C) and non-High-Density Lipoprotein Cholesterol (non-HDL-C)

In the pool of four placebo-controlled trials, dose-related increases in LDL-C with canagliflozin were observed. Mean changes (percent changes) from baseline in LDL-C relative to placebo were 4.4 mg/dL (4.5%) and 8.2 mg/dL (8.0%) with canagliflozin 100 mg and canagliflozin 300 mg, respectively. The mean baseline LDL-C levels were 104 to 110 mg/dL across treatment groups *[see Warnings and Precautions (5.12)]*.

Dose-related increases in non-HDL-C with canagliflozin were observed. Mean changes (percent changes) from baseline in non-HDL-C relative to placebo were 2.1 mg/dL (1.5%) and 5.1 mg/dL (3.6%) with canagliflozin 100 mg and 300 mg, respectively. The mean baseline non-HDL-C levels were 140 to 147 mg/dL across treatment groups.

Increases in Hemoglobin

In the pool of four placebo-controlled trials, mean changes (percent changes) from baseline in hemoglobin were -0.18 g/dL (-1.1%) with placebo, 0.47 g/dL (3.5%) with canagliflozin 100 mg, and 0.51 g/dL (3.8%) with canagliflozin 300 mg. The mean baseline hemoglobin value was approximately 14.1 g/dL across treatment groups. At the end of treatment, 0.8%, 4.0%, and 2.7% of patients treated with placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively, had hemoglobin levels above the upper limit of normal.

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7 DRUG INTERACTIONS

7.1 Drug Interactions with Metformin

Cationic Drugs

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of INVOKAMET and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis and may increase the risk of lactic acidosis. Monitor for signs and symptoms of acidosis when these drugs are used concomitantly with INVOKAMET *[see Warnings and Precautions (5.1)]*.

Drugs Affecting Glycemic Control

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid. When such drugs are administered to a patient receiving INVOKAMET, monitor for loss of blood glucose control. When such drugs are withdrawn from a patient receiving INVOKAMET, monitor for hypoglycemia.

7.2 Drug Interactions with Canagliflozin

UGT Enzyme Inducers

Rifampin: Rifampin lowered canagliflozin exposure which may reduce the efficacy of INVOKAMET. If an inducer of UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) must be co-administered with INVOKAMET, consider increasing the dose to canagliflozin 150 mg twice daily if patients are currently tolerating INVOKAMET with 50 mg canagliflozin twice daily, have an eGFR greater than 60 mL/min/1.73 m^2, and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer and require additional glycemic control *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

Digoxin

Canagliflozin increased digoxin exposure. Digoxin, as a cationic drug, also has the potential to compete with metformin for common renal tubular transport systems *[see Drug Interactions*

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(7.1)]. Monitor patients taking INVOKAMET with concomitant digoxin for a need to adjust dose of either drug.

Drug/Laboratory Test Interference

Positive Urine Glucose Test

Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay

Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category C:

INVOKAMET

There are no adequate and well-controlled studies in pregnant women with INVOKAMET or its individual components. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. INVOKAMET should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Canagliflozin

Based on results from rat studies, canagliflozin may affect renal development and maturation. In a juvenile rat study, increased kidney weights and renal pelvic and tubular dilatation were evident at greater than or equal to 0.5 times clinical exposure from a 300 mg dose *[see Nonclinical Toxicology (13.2)]*.

These outcomes occurred with drug exposure during periods of animal development that correspond to the late second and third trimester of human development.

Metformin

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the maximum recommended human daily dose of 2,000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

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8.3 Nursing Mothers

INVOKAMET

No studies in lactating animals have been conducted with the combined components of INVOKAMET.

Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from INVOKAMET, a decision should be made whether to discontinue nursing or to discontinue INVOKAMET, taking into account the importance of the drug to the mother *[see Nonclinical Toxicology (13.2)]*.

Canagliflozin

It is not known if canagliflozin is excreted in human milk. Canagliflozin is secreted in the milk of lactating rats reaching levels 1.4 times higher than that in maternal plasma. Data in juvenile rats directly exposed to canagliflozin showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.

Metformin

Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. It is not known whether metformin is secreted in human milk.

8.4 Pediatric Use

Safety and effectiveness of INVOKAMET in pediatric patients under 18 years of age have not been established.

8.5 Geriatric Use

INVOKAMET

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, monitor renal function more frequently after initiating INVOKAMET in the elderly and then adjust dose based on renal function *[see Dosage and Administration (2.2) and Warnings and Precautions (5.1), (5.3)]*.

Canagliflozin

Two thousand thirty-four (2034) patients 65 years and older, and 345 patients 75 years and older were exposed to canagliflozin in nine clinical studies of canagliflozin. Of these patients, 1334 patients 65 years and older and 181 patients 75 years and older were exposed to the combination of canagliflozin and metformin *[see Clinical Studies (14)]*. Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with canagliflozin (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300 mg daily dose, compared to younger patients; a more prominent

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increase in the incidence was seen in patients who were 75 years and older *[see Dosage and Administration (2.1) and Adverse Reactions (6.1)]*. Smaller reductions in HbA1C with canagliflozin relative to placebo were seen in older (65 years and older; -0.61% with canagliflozin 100 mg and -0.74% with canagliflozin 300 mg relative to placebo) compared to younger patients (-0.72% with canagliflozin 100 mg and -0.87% with canagliflozin 300 mg relative to placebo).

Metformin

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and younger patients. The initial and maintenance dosing of metformin should be conservative in patients with advanced age due to the potential for decreased renal function in this population. Any dose adjustment should be based on a careful assessment of renal function *[see Contraindications (4), Warnings and Precautions (5.3), and Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

Canagliflozin

The efficacy and safety of canagliflozin were evaluated in a study that included patients with moderate renal impairment (eGFR 30 to less than 50 mL/min/1.73 m^2). These patients had less overall glycemic efficacy and had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR greater than or equal to 60 mL/min/1.73 m^2); patients treated with canagliflozin 300 mg were more likely to experience increases in potassium *[see Dosage and Administration (2.2), Contraindications (4), Warnings and Precautions (5.2), (5.3), (5.4), and Adverse Reactions (6.1)]*.

The efficacy and safety of canagliflozin have not been established in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), with ESRD, or receiving dialysis. Canagliflozin is not expected to be effective in these patient populations *[see Contraindications (4) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

In the event of an overdose with INVOKAMET, contact the Poison Control Center. Employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful partly for removal of accumulated metformin from patients in whom INVOKAMET overdosage is suspected.

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Canagliflozin

There were no reports of overdose during the clinical development program of canagliflozin.

Metformin

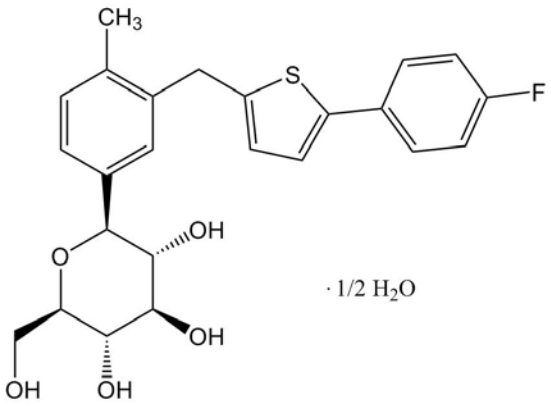
Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases *[see Warnings and Precautions (5.1)]*.

11 DESCRIPTION

INVOKAMET (canagliflozin and metformin hydrochloride) tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: canagliflozin and metformin hydrochloride.

Canagliflozin

Canagliflozin is an inhibitor of sodium-glucose co-transporter 2 (SGLT2), the transporter responsible for reabsorbing the majority of glucose filtered by the kidney. Canagliflozin is chemically known as (1*S*)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol hemihydrate and its molecular formula and weight are $C_{24}H_{25}FO_5S \bullet 1/2\ H_2O$ and 453.53, respectively. The structural formula for canagliflozin is:



Canagliflozin is practically insoluble in aqueous media from pH 1.1 to 12.9.

Metformin Hydrochloride

Metformin hydrochloride is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Metformin hydrochloride is chemically known as 1,1-Dimethylbiguanide hydrochloride and its molecular formula and weight are $C_4H_{11}N_5 \bullet HCl$ and 165.62, respectively. The structural formula for metformin hydrochloride is:

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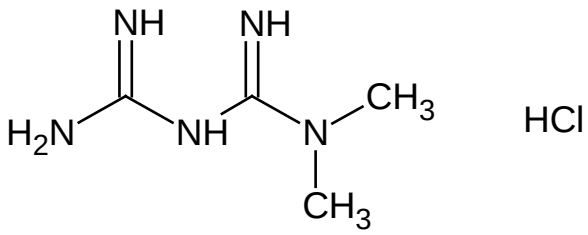

INVOKAMET

INVOKAMET is supplied as film-coated tablets for oral administration. Each 50 mg/500 mg tablet and 50 mg/1,000 mg tablet contains 51 mg of canagliflozin equivalent to 50 mg canagliflozin (anhydrous) and 500 mg or 1,000 mg metformin hydrochloride. Each 150 mg/500 mg tablet and 150 mg/1,000 mg tablet contains 153 mg of canagliflozin equivalent to 150 mg canagliflozin (anhydrous) and 500 mg or 1,000 mg metformin hydrochloride.

Inactive ingredients of the core tablet are croscarmellose sodium, hypromellose, magnesium stearate, and microcrystalline cellulose. The magnesium stearate is vegetable-sourced. The tablets are finished with a commercially available film-coating consisting of the following excipients: Macrogol/PEG, polyvinyl alcohol (partially hydrolyzed), talc, titanium dioxide, iron oxide yellow, (50 mg/1,000 mg and 150 mg/500 mg tablets only), iron oxide red, (50 mg/1,000 mg, 150 mg/500 mg and 150 mg/1,000 mg tablets only), and iron oxide black (150 mg/1,000 mg tablets only).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

INVOKAMET

INVOKAMET (canagliflozin and metformin hydrochloride) combines two oral antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: canagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, and metformin hydrochloride, a member of the biguanide class.

Canagliflozin

Sodium-glucose co-transporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Canagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, canagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose (RT_G), and thereby increases urinary glucose excretion (UGE).

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Metformin

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both 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. Metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects except in special circumstances *[see Warnings and Precautions (5.6)]* and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

12.2 Pharmacodynamics

Canagliflozin

Following single and multiple oral doses of canagliflozin in patients with type 2 diabetes, dose-dependent decreases in RT_G and increases in urinary glucose excretion were observed. From a starting RT_G value of approximately 240 mg/dL, canagliflozin at 100 mg and 300 mg once daily suppressed RT_G throughout the 24-hour period. Maximal suppression of mean RT_G over the 24-hour period was seen with the 300 mg daily dose to approximately 70 to 90 mg/dL in patients with type 2 diabetes in Phase 1 studies. The reductions in RT_G led to increases in mean UGE of approximately 100 g/day in subjects with type 2 diabetes treated with either 100 mg or 300 mg of canagliflozin. The 24-h mean RT_G at steady state was similar following once daily and twice daily dosing regimens at the same total daily dose of 100 mg or 300 mg. In patients with type 2 diabetes given 100 to 300 mg once daily over a 16-day dosing period, reductions in RT_G and increases in urinary glucose excretion were observed over the dosing period. In this study, plasma glucose declined in a dose-dependent fashion within the first day of dosing.

Cardiac Electrophysiology

In a randomized, double-blind, placebo-controlled, active-comparator, 4-way crossover study, 60 healthy subjects were administered a single oral dose of canagliflozin 300 mg, canagliflozin 1,200 mg (4 times the maximum recommended dose), moxifloxacin, and placebo. No meaningful changes in QTc interval were observed with either the recommended dose of 300 mg or the 1,200 mg dose.

12.3 Pharmacokinetics

INVOKAMET

The results of a bioequivalence study in healthy subjects demonstrated that INVOKAMET 50 mg/500 mg, 50 mg/1,000 mg, 150 mg/500 mg and 150 mg/1,000 mg combination tablets are bioequivalent to co-administration of corresponding doses of canagliflozin and metformin hydrochloride as individual tablets under fed conditions.

Administration of INVOKAMET 150 mg/1,000 mg fixed-dose combination with food resulted in no change in overall exposure of canagliflozin. There was no change in metformin AUC; however, the mean peak plasma concentration of metformin was decreased by 16% when

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administered with food. A delayed time to peak plasma concentration was observed for both components (a delay of 2 hours for canagliflozin and 1 hour for metformin) under fed conditions. These changes are not likely to be clinically meaningful.

Canagliflozin

The pharmacokinetics of canagliflozin is essentially similar in healthy subjects and patients with type 2 diabetes. Following single-dose oral administration of 100 mg and 300 mg of canagliflozin, peak plasma concentrations (median T_{max}) of canagliflozin occurs within 1 to 2 hours post-dose. Plasma C_{max} and AUC of canagliflozin increased in a dose-proportional manner from 50 mg to 300 mg. The apparent terminal half-life ($t_{1/2}$) was 10.6 hours and 13.1 hours for the 100 mg and 300 mg doses, respectively. Steady-state was reached after 4 to 5 days of once-daily dosing with canagliflozin 100 mg to 300 mg. Canagliflozin does not exhibit time-dependent pharmacokinetics and accumulated in plasma up to 36% following multiple doses of 100 mg and 300 mg. The mean systemic exposure (AUC) at steady state was similar following once daily and twice daily dosing regimens at the same total daily dose of 100 mg or 300 mg.

Absorption

Canagliflozin

The mean absolute oral bioavailability of canagliflozin is approximately 65%.

Metformin

The absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of metformin hydrochloride 500 to 1,500 mg, and 850 to 2,550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination.

Distribution

Canagliflozin

The mean steady-state volume of distribution of canagliflozin following a single intravenous infusion in healthy subjects was 119 L, suggesting extensive tissue distribution. Canagliflozin is extensively bound to proteins in plasma (99%), mainly to albumin. Protein binding is independent of canagliflozin plasma concentrations. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment.

Metformin

The apparent volume of distribution (V/F) of metformin following single oral doses of metformin hydrochloride 850 mg tablets averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin tablets, steady-state plasma concentrations of metformin are

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reached within 24 to 48 hours and are generally less than 1 mcg/mL. During controlled clinical trials of metformin, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

Metabolism

Canagliflozin

O-glucuronidation is the major metabolic elimination pathway for canagliflozin, which is mainly glucuronidated by UGT1A9 and UGT2B4 to two inactive *O*-glucuronide metabolites. CYP3A4-mediated (oxidative) metabolism of canagliflozin is minimal (approximately 7%) in humans.

Metformin

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion.

Excretion

Canagliflozin

Following administration of a single oral [^{14}C] canagliflozin dose to healthy subjects, 41.5%, 7.0%, and 3.2% of the administered radioactive dose was recovered in feces as canagliflozin, a hydroxylated metabolite, and an *O*-glucuronide metabolite, respectively. Enterohepatic circulation of canagliflozin was negligible.

Approximately 33% of the administered radioactive dose was excreted in urine, mainly as *O*−glucuronide metabolites (30.5%). Less than 1% of the dose was excreted as unchanged canagliflozin in urine. Renal clearance of canagliflozin 100 mg and 300 mg doses ranged from 1.30 to 1.55 mL/min.

Mean systemic clearance of canagliflozin was approximately 192 mL/min in healthy subjects following intravenous administration.

Metformin

Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Specific Populations

Studies characterizing the pharmacokinetics of canagliflozin and metformin after administration of INVOKAMET were not conducted in patients with renal and hepatic impairment. Descriptions of the individual components in this patient population are described below.

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Renal Impairment

Canagliflozin

A single-dose, open-label study evaluated the pharmacokinetics of canagliflozin 200 mg in subjects with varying degrees of renal impairment (classified using the MDRD-eGFR formula) compared to healthy subjects.

Renal impairment did not affect the C_{max} of canagliflozin. Compared to healthy subjects (N=3; eGFR greater than or equal to 90 mL/min/1.73 m^2), plasma AUC of canagliflozin was increased by approximately 15%, 29%, and 53% in subjects with mild (N=10), moderate (N=9), and severe (N=10) renal impairment, respectively, (eGFR 60 to less than 90, 30 to less than 60, and 15 to less than 30 mL/min/1.73 m^2, respectively) but was similar for ESRD (N=8) subjects and healthy subjects. Increases in canagliflozin AUC of this magnitude are not considered clinically relevant. The pharmacodynamic response to canagliflozin declines with increasing severity of renal impairment *[see Contraindications (4) and Warnings and Precautions (5.3)]*.

Canagliflozin was negligibly removed by hemodialysis.

Metformin

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance *[see Contraindications (4) and Warnings and Precautions (5.3)]*.

Hepatic Impairment

Canagliflozin

Relative to subjects with normal hepatic function, the geometric mean ratios for C_{max} and AUC_{∞} of canagliflozin were 107% and 110%, respectively, in subjects with Child-Pugh class A (mild hepatic impairment) and 96% and 111%, respectively, in subjects with Child-Pugh class B (moderate hepatic impairment) following administration of a single 300 mg dose of canagliflozin.

These differences are not considered to be clinically meaningful. There is no clinical experience in patients with Child-Pugh class C (severe) hepatic impairment *[see Warnings and Precautions (5.5)]*.

Metformin

No pharmacokinetic studies of metformin have been conducted in patients with hepatic insufficiency *[see Warnings and Precautions (5.5)]*.

Pharmacokinetic Effects of Age, Body Mass Index (BMI)/Weight, Gender and Race

Canagliflozin

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Based on the population PK analysis with data collected from 1526 subjects, age, body mass index (BMI)/weight, gender, and race do not have a clinically meaningful effect on the pharmacokinetics of canagliflozin *[see Use in Specific Populations (8.5)]*.

Metformin

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analyzed according to gender.

No studies of metformin pharmacokinetic parameters according to race have been performed.

Geriatric

INVOKAMET

Studies characterizing the pharmacokinetics of canagliflozin and metformin after administration of INVOKAMET in geriatric patients have not been performed *[see Warnings and Precautions (5.1), (5.3) and Use in Specific Populations (8.5)]*.

Canagliflozin

Age had no clinically meaningful effect on the pharmacokinetics of canagliflozin based on a population pharmacokinetic analysis *[see Adverse Reactions (6.1) and Use in Specific Populations (8.5)]*.

Metformin

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared with healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Pediatric

Studies characterizing the pharmacokinetics of canagliflozin and metformin after administration of INVOKAMET in pediatric patients have not been performed.

Drug-Drug Interactions

INVOKAMET

Pharmacokinetic drug interaction studies with INVOKAMET have not been performed; however, such studies have been conducted with the individual components canagliflozin and metformin hydrochloride.

Co-administration of multiple doses of canagliflozin (300 mg) and metformin (2,000 mg) given once daily did not meaningfully alter the pharmacokinetics of either canagliflozin or metformin in healthy subjects.

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Canagliflozin

In Vitro Assessment of Drug Interactions

Canagliflozin did not induce CYP450 enzyme expression (3A4, 2C9, 2C19, 2B6, and 1A2) in cultured human hepatocytes. Canagliflozin did not inhibit the CYP450 isoenzymes (1A2, 2A6, 2C19, 2D6, or 2E1) and weakly inhibited CYP2B6, CYP2C8, CYP2C9, and CYP3A4 based on *in vitro* studies with human hepatic microsomes. Canagliflozin is a weak inhibitor of P-gp.

Canagliflozin is also a substrate of drug transporters P-glycoprotein (P-gp) and MRP2.

In Vivo Assessment of Drug Interactions

Table 5: Effect of Co−Administered Drugs on Systemic Exposures of Canagliflozin

Co-Administered Drug	**Dose of Co-Administered Drug***	**Dose of Canagliflozin***	**Geometric Mean Ratio (Ratio With/Without Co-Administered Drug) No Effect = 1.0**	
			AUC† (90% CI)	**C_{max} (90% CI)**
***See Drug Interactions (7.2)* for the clinical relevance of the following:**				
Rifampin	600 mg QD for 8 days	300 mg	0.49 (0.44; 0.54)	0.72 (0.61; 0.84)
No dose adjustments of canagliflozin required for the following:				
Cyclosporine	400 mg	300 mg QD for 8 days	1.23 (1.19; 1.27)	1.01 (0.91; 1.11)
Ethinyl estradiol and levonorgestrel	0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel	200 mg QD for 6 days	0.91 (0.88; 0.94)	0.92 (0.84; 0.99)
Hydrochlorothiazide	25 mg QD for 35 days	300 mg QD for 7 days	1.12 (1.08; 1.17)	1.15 (1.06; 1.25)
Metformin	2,000 mg	300 mg QD for 8 days	1.10 (1.05; 1.15)	1.05 (0.96; 1.16)
Probenecid	500 mg BID for 3 days	300 mg QD for 17 days	1.21 (1.16; 1.25)	1.13 (1.00; 1.28)

* Single dose unless otherwise noted
† AUC_{inf} for drugs given as a single dose and AUC_{24h} for drugs given as multiple doses
QD = once daily; BID = twice daily

Table 6: Effect of Canagliflozin on Systemic Exposure of Co-Administered Drugs

Co-Administered Drug	**Dose of Co-Administered Drug***	**Dose of Canagliflozin***	**Geometric Mean Ratio (Ratio With/Without Co-Administered Drug) No Effect = 1.0**	
				AUC† (90% CI)	**C_{max} (90% CI)**

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Table 6: Effect of Canagliflozin on Systemic Exposure of Co-Administered Drugs

Co-Administered Drug	Dose of Co-Administered Drug*	Dose of Canagliflozin*	Geometric Mean Ratio (Ratio With/Without Co-Administered Drug) No Effect = 1.0		
				AUC† (90% CI)	C_{max} (90% CI)
***See Drug Interactions (7.2)* for the clinical relevance of the following:**					
Digoxin	0.5 mg QD first day followed by 0.25 mg QD for 6 days	300 mg QD for 7 days	digoxin	1.20 (1.12; 1.28)	1.36 (1.21; 1.53)
No dose adjustments of co-administered drug required for the following:					
Acetaminophen	1,000 mg	300 mg BID for 25 days	acetaminophen	1.06‡ (0.98; 1.14)	1.00 (0.92; 1.09)
Ethinyl estradiol and levonorgestrel	0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel	200 mg QD for 6 days	ethinyl estradiol	1.07 (0.99; 1.15)	1.22 (1.10; 1.35)
			levonorgestrel	1.06 (1.00; 1.13)	1.22 (1.11; 1.35)
Glyburide	1.25 mg	200 mg QD for 6 days	glyburide	1.02 (0.98; 1.07)	0.93 (0.85; 1.01)
			3-cis-hydroxy-glyburide	1.01 (0.96; 1.07)	0.99 (0.91; 1.08)
			4-trans-hydroxy-glyburide	1.03 (0.97; 1.09)	0.96 (0.88; 1.04)
Hydrochloro-thiazide	25 mg QD for 35 days	300 mg QD for 7 days	Hydrochloro-thiazide	0.99 (0.95; 1.04)	0.94 (0.87; 1.01)
Metformin	2,000 mg	300 mg QD for 8 days	metformin	1.20 (1.08; 1.34)	1.06 (0.93; 1.20)
Simvastatin	40 mg	300 mg QD for 7 days	simvastatin	1.12 (0.94; 1.33)	1.09 (0.91; 1.31)
			simvastatin acid	1.18 (1.03; 1.35)	1.26 (1.10; 1.45)
Warfarin	30 mg	300 mg QD for 12 days	(R)-warfarin	1.01 (0.96; 1.06)	1.03 (0.94; 1.13)
			(S)-warfarin	1.06 (1.00; 1.12)	1.01 (0.90; 1.13)
			INR	1.00 (0.98; 1.03)	1.05 (0.99; 1.12)

* Single dose unless otherwise noted
† AUC_{inf} for drugs given as a single dose and AUC_{24h} for drugs given as multiple doses
‡ $AUC_{0\text{-}12h}$
QD = once daily; BID = twice daily; INR = International Normalized Ratio

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Metformin

Table 7: Effect of Co−Administered Drugs on Plasma Metformin Systemic Exposures

Co-Administered Drug	Dose of Co-Administered Drug*	Dose of Metformin*	Geometric Mean Ratio (Ratio With/Without Co-Administered Drug) No Effect = 1.00	
			AUC†	C_{max}
No dose adjustments required for the following:				
Glyburide	5 mg	500 mg‡	0.98§	0.99§
Furosemide	40 mg	850 mg	1.09§	1.22§
Nifedipine	10 mg	850 mg	1.16	1.21
Propranolol	40 mg	850 mg	0.90	0.94
Ibuprofen	400 mg	850 mg	1.05§	1.07§
Cationic drugs eliminated by renal tubular secretion may reduce metformin elimination: use with caution *[see Warnings and Precautions (5) and Drug Interactions (7)]*				
Cimetidine	400 mg	850 mg	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis: use with caution *[see Warnings and Precautions (5) and Drug Interactions (7)]*				
Topiramate¶	100 mg	500 mg	1.25#	1.18

* Single dose unless otherwise noted
† AUC = $AUC_{0-\infty}$
‡ Metformin hydrochloride extended-release tablets 500 mg
§ Ratio of arithmetic means
¶ Healthy volunteer study at steady state with topiramate 100 mg every 12 hours and metformin 500 mg every 12 hours for 7 days. Study conducted to assess pharmacokinetics only
# Steady state AUC_{0-12h}.

Table 8: Effect of Metformin on Co−Administered Drug Systemic Exposures

Co-Administered Drug	Dose of Co-Administered Drug*	Dose of Metformin*	Geometric Mean Ratio (Ratio With/Without Co-Administered Drug) No Effect = 1.00	
			AUC†	C_{max}
No dose adjustments required for the following:				
Glyburide	5 mg	500 mg‡	0.78§	0.63§
Furosemide	40 mg	850 mg	0.87§	0.69§
Nifedipine	10 mg	850 mg	1.10‡	1.08
Propranolol	40 mg	850 mg	1.01‡	0.94
Ibuprofen	400 mg	850 mg	0.97¶	1.01¶
Cimetidine	400 mg	850 mg	0.95‡	1.01

* Single dose unless otherwise noted
† AUC = $AUC_{0-\infty}$
‡ $AUC_{0-24\ hr}$ reported
§ Ratio of arithmetic means, p-value of difference <0.05
¶ Ratio of arithmetic means.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid.

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13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

INVOKAMET

No animal studies have been conducted with the combined products in INVOKAMET to evaluate carcinogenesis, mutagenesis, or impairment of fertility. The following data are based on findings in studies with canagliflozin and metformin individually.

Canagliflozin

Carcinogenesis

Carcinogenicity was evaluated in 2-year studies conducted in CD1 mice and Sprague-Dawley rats. Canagliflozin did not increase the incidence of tumors in mice dosed at 10, 30, or 100 mg/kg (less than or equal to 14 times exposure from a 300 mg clinical dose).

Testicular Leydig cell tumors, considered secondary to increased luteinizing hormone (LH), increased significantly in male rats at all doses tested (10, 30, and 100 mg/kg). In a 12-week clinical study, LH did not increase in males treated with canagliflozin.

Renal tubular adenoma and carcinoma increased significantly in male and female rats dosed at 100 mg/kg, or approximately 12-times exposure from a 300 mg clinical dose. Also, adrenal pheochromocytoma increased significantly in males and numerically in females dosed at 100 mg/kg. Carbohydrate malabsorption associated with high doses of canagliflozin was considered a necessary proximal event in the emergence of renal and adrenal tumors in rats. Clinical studies have not demonstrated carbohydrate malabsorption in humans at canagliflozin doses of up to 2-times the recommended clinical dose of 300 mg.

Mutagenesis

Canagliflozin was not mutagenic with or without metabolic activation in the Ames assay. Canagliflozin was mutagenic in the *in vitro* mouse lymphoma assay with but not without metabolic activation. Canagliflozin was not mutagenic or clastogenic in an *in vivo* oral micronucleus assay in rats and an *in vivo* oral Comet assay in rats.

Impairment of Fertility

Canagliflozin had no effects on the ability of rats to mate and sire or maintain a litter up to the high dose of 100 mg/kg (approximately 14 times and 18 times the 300 mg clinical dose in males and females, respectively), although there were minor alterations in a number of reproductive parameters (decreased sperm velocity, increased number of abnormal sperm, slightly fewer corpora lutea, fewer implantation sites, and smaller litter sizes) at the highest dosage administered.

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Metformin

Carcinogenesis

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

Mutagenesis

There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Impairment of Fertility

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 3 times the maximum recommended human daily dose based on body surface area comparisons.

13.2 Animal Toxicology and/or Pharmacology

Canagliflozin

In a juvenile toxicity study in which canagliflozin was dosed directly to young rats from postnatal day (PND) 21 until PND 90 at doses of 4, 20, 65, or 100 mg/kg, increased kidney weights and a dose-related increase in the incidence and severity of renal pelvic and renal tubular dilatation were reported at all dose levels. Exposure at the lowest dose tested was greater than or equal to 0.5 times the maximum clinical dose of 300 mg. The renal pelvic dilatations observed in juvenile animals did not fully reverse within the 1-month recovery period. Similar effects on the developing kidney were not seen when canagliflozin was administered to pregnant rats or rabbits during the period of organogenesis or during a study in which maternal rats were dosed from gestation day (GD) 6 through PND 21 and pups were indirectly exposed *in utero* and throughout lactation.

In embryo-fetal development studies in rats and rabbits, canagliflozin was administered for intervals coinciding with the first trimester period of non-renal organogenesis in humans.

No developmental toxicities were observed at any dose tested other than a slight increase in the number of fetuses with reduced ossification at a dose that was associated with maternal toxicity and that is approximately 19 times the human exposure to canagliflozin at the 300 mg clinical dose.

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Canagliflozin and Metformin Combination

Co-administration of canagliflozin and metformin to pregnant rats during the period of organogenesis was neither embryolethal nor teratogenic when tested at doses yielding systemic exposures (AUC) up to 11 and 13 times the maximum recommended human dose (MRHD) (canagliflozin 300 mg and metformin 2000 mg), respectively. Minor skeletal abnormalities (delayed-ossification) in fetuses were observed that were related to the maternal body weight decreases. Maternal toxicity in rats for canagliflozin when co-administered with metformin was observed at 5.8 and 13 times the human exposure at the MRHD (canagliflozin 300 mg and metformin 2000 mg), respectively.

14 CLINICAL STUDIES

Canagliflozin has been studied in combination with metformin alone, metformin and sulfonylurea, metformin and a thiazolidinedione (i.e. pioglitazone), and metformin and insulin (with or without other anti-hyperglycemic agents). The efficacy of canagliflozin was compared to a dipeptidyl peptidase-4 (DPP-4) inhibitor (sitagliptin) and a sulfonylurea (glimepiride).

There have been no clinical efficacy studies conducted with INVOKAMET; however, bioequivalence of INVOKAMET to canagliflozin and metformin co-administered as individual tablets was demonstrated in healthy subjects.

In patients with type 2 diabetes, treatment with canagliflozin and metformin produced clinically and statistically significant improvements in HbA1C compared to placebo. Reductions in HbA1C were observed across subgroups including age, gender, race, and baseline body mass index (BMI).

14.1 Canagliflozin as Add-on Combination Therapy with Metformin

A total of 1284 patients with type 2 diabetes inadequately controlled on metformin monotherapy (greater than or equal to 2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated) participated in a 26-week, double-blind, placebo- and active-controlled study to evaluate the efficacy and safety of canagliflozin in combination with metformin. The mean age was 55 years, 47% of patients were men, and the mean baseline eGFR was 89 mL/min/1.73 m^2. Patients already on the required metformin dose (N=1009) were randomized after completing a 2-week, single-blind, placebo run-in period. Patients taking less than the required metformin dose or patients on metformin in combination with another antihyperglycemic agent (N=275) were switched to metformin monotherapy (at doses described above) for at least 8 weeks before entering the 2-week, single-blind, placebo run-in. After the placebo run-in period, patients were randomized to canagliflozin 100 mg, canagliflozin 300 mg, sitagliptin 100 mg, or placebo, administered once daily as add-on therapy to metformin.

At the end of treatment, canagliflozin 100 mg and 300 mg once daily resulted in a statistically significant improvement in HbA1C ($p<0.001$ for both doses) compared to placebo when added to metformin. Canagliflozin 100 mg and 300 mg once daily also resulted in a greater proportion of

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patients achieving an HbA1C less than 7%, in significant reduction in fasting plasma glucose (FPG), in improved postprandial glucose (PPG), and in percent body weight reduction compared to placebo when added to metformin (see Table 9). Statistically significant ($p<0.001$ for both doses) mean changes from baseline in systolic blood pressure relative to placebo were -5.4 mmHg and -6.6 mmHg with canagliflozin 100 mg and 300 mg, respectively.

Table 9: Results from 26-Week Placebo-Controlled Clinical Study of Canagliflozin in Combination with Metformin*

Efficacy Parameter	Placebo + Metformin (N=183)	Canagliflozin 100 mg + Metformin (N=368)	Canagliflozin 300 mg + Metformin (N=367)
HbA1C (%)			
Baseline (mean)	7.96	7.94	7.95
Change from baseline (adjusted mean)	-0.17	-0.79	-0.94
Difference from placebo (adjusted mean) (95% CI) †		-0.62‡ (-0.76, -0.48)	-0.77‡ (-0.91, -0.64)
Percent of patients achieving HbA1C < 7%	30	46‡	58‡
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	164	169	173
Change from baseline (adjusted mean)	2	-27	-38
Difference from placebo (adjusted mean) (95% CI) †		-30‡ (-36, -24)	-40‡ (-46, -34)
2-hour Postprandial Glucose (mg/dL)			
Baseline (mean)	249	258	262
Change from baseline (adjusted mean)	-10	-48	-57
Difference from placebo (adjusted mean) (95% CI) †		-38‡ (-49, -27)	-47‡ (-58, -36)
Body Weight			
Baseline (mean) in kg	86.7	88.7	85.4
% change from baseline (adjusted mean)	-1.2	-3.7	-4.2
Difference from placebo (adjusted mean) (95% CI) †		-2.5‡ (-3.1, -1.9)	-2.9‡ (-3.5, -2.3)

* Intent-to-treat population using last observation in study prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value and stratification factors
‡ $p<0.001$

14.2 Canagliflozin Compared to Glimepiride, Both as Add-on Combination Therapy with Metformin

A total of 1450 patients with type 2 diabetes inadequately controlled on metformin monotherapy (greater than or equal to 2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated) participated in a 52-week, double-blind, active-controlled study to evaluate the efficacy and safety of canagliflozin in combination with metformin.

The mean age was 56 years, 52% of patients were men, and the mean baseline eGFR was 90 mL/min/1.73 m^2. Patients tolerating maximally required metformin dose (N=928) were randomized after completing a 2-week, single-blind, placebo run-in period. Other patients

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(N=522) were switched to metformin monotherapy (at doses described above) for at least 10 weeks, then completed a 2-week single-blind run-in period. After the 2-week run-in period, patients were randomized to canagliflozin 100 mg, canagliflozin 300 mg, or glimepiride (titration allowed throughout the 52-week study to 6 or 8 mg), administered once daily as add-on therapy to metformin.

As shown in Table 10 and Figure 1, at the end of treatment, canagliflozin 100 mg provided similar reductions in HbA1C from baseline compared to glimepiride when added to metformin therapy. Canagliflozin 300 mg provided a greater reduction from baseline in HbA1C compared to glimepiride, and the relative treatment difference was -0.12% (95% CI: −0.22; −0.02). As shown in Table 10, treatment with canagliflozin 100 mg and 300 mg daily provided greater improvements in percent body weight change, relative to glimepiride.

Table 10: Results from 52−Week Clinical Study Comparing Canagliflozin to Glimepiride in Combination with Metformin*

Efficacy Parameter	Canagliflozin 100 mg + Metformin (N=483)	Canagliflozin 300 mg + Metformin (N=485)	Glimepiride (titrated) + Metformin (N=482)
HbA1C (%)			
Baseline (mean)	7.78	7.79	7.83
Change from baseline (adjusted mean)	-0.82	-0.93	-0.81
Difference from glimepiride (adjusted mean) (95% CI) †	-0.01‡ (-0.11, 0.09)	-0.12‡ (-0.22, -0.02)	
Percent of patients achieving HbA1C < 7%	54	60	56
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	165	164	166
Change from baseline (adjusted mean)	-24	-28	-18
Difference from glimepiride (adjusted mean) (95% CI) †	-6 (-10, -2)	-9 (-13, -5)	
Body Weight			
Baseline (mean) in kg	86.8	86.6	86.6
% change from baseline (adjusted mean)	-4.2	-4.7	1.0
Difference from glimepiride (adjusted mean) (95% CI) †	-5.2§ (-5.7, -4.7)	-5.7§ (-6.2, -5.1)	

* Intent-to-treat population using last observation in study prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value and stratification factors
‡ Canagliflozin + metformin is considered non-inferior to glimepiride + metformin because the upper limit of this confidence interval is less than the pre-specified non-inferiority margin of < 0.3%.
§ p<0.001

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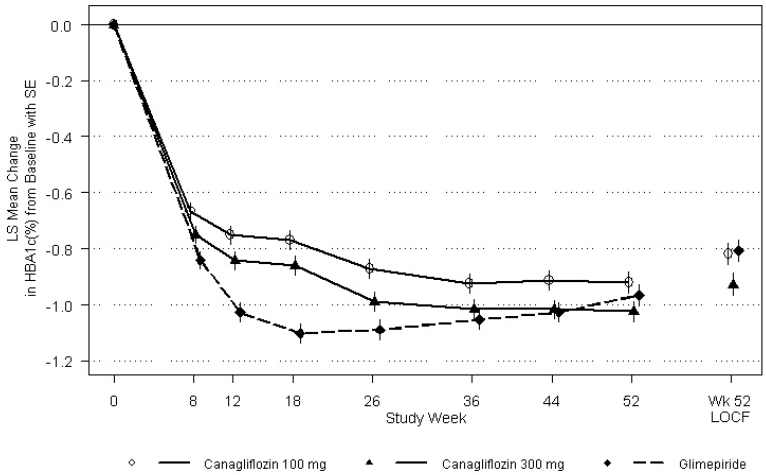
Figure 1: Mean HbA1C Change at Each Time Point (Completers) and at Week 52 Using Last Observation Carried Forward (mITT Population)



14.3 Canagliflozin as Add-on Combination Therapy with Metformin and Sulfonylurea

A total of 469 patients with type 2 diabetes inadequately controlled on the combination of metformin (greater than or equal to 2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated) and sulfonylurea (maximal or near-maximal effective dose) participated in a 26-week, double-blind, placebo-controlled study to evaluate the efficacy and safety of canagliflozin in combination with metformin and sulfonylurea. The mean age was 57 years, 51% of patients were men, and the mean baseline eGFR was 89 mL/min/1.73 m^2. Patients already on the protocol-specified doses of metformin and sulfonylurea (N=372) entered a 2-week, single-blind, placebo run-in period. Other patients (N=97) were required to be on a stable protocol-specified dose of metformin and sulfonylurea for at least 8 weeks before entering the 2-week run-in period. Following the run-in period, patients were randomized to canagliflozin 100 mg, canagliflozin 300 mg, or placebo administered once daily as add-on to metformin and sulfonylurea.

At the end of treatment, canagliflozin 100 mg and 300 mg once daily resulted in a statistically significant improvement in HbA1C ($p<0.001$ for both doses) compared to placebo when added to metformin and sulfonylurea. Canagliflozin 100 mg and 300 mg once daily also resulted in a greater proportion of patients achieving an HbA1C less than 7.0%, in a significant reduction in fasting plasma glucose (FPG), and in percent body weight reduction compared to placebo when added to metformin and sulfonylurea (see Table 11).

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Table 11: Results from 26−Week Placebo-Controlled Clinical Study of Canagliflozin in Combination with Metformin and Sulfonylurea*

Efficacy Parameter	Placebo + Metformin and Sulfonylurea (N=156)	Canagliflozin 100 mg + Metformin and Sulfonylurea (N=157)	Canagliflozin 300 mg + Metformin and Sulfonylurea (N=156)
HbA1C (%)			
Baseline (mean)	8.12	8.13	8.13
Change from baseline (adjusted mean)	-0.13	-0.85	-1.06
Difference from placebo (adjusted mean) (95% CI) †		-0.71‡ (-0.90, -0.52)	-0.92‡ (-1.11, -0.73)
Percent of patients achieving HbA1C < 7%	18	43‡	57‡
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	170	173	168
Change from baseline (adjusted mean)	4	-18	-31
Difference from placebo (adjusted mean) (95% CI) †		-22‡ (-31, -13)	-35‡ (-44, -25)
Body Weight			
Baseline (mean) in kg	90.8	93.5	93.5
% change from baseline (adjusted mean)	-0.7	-2.1	-2.6
Difference from placebo (adjusted mean) (95% CI) †		-1.4‡ (-2.1, -0.7)	-2.0‡ (-2.7, -1.3)

* Intent-to-treat population using last observation in study prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value and stratification factors
‡ $p<0.001$

14.4 Canagliflozin Compared to Sitagliptin, Both as Add-on Combination Therapy with Metformin and Sulfonylurea

A total of 755 patients with type 2 diabetes inadequately controlled on the combination of metformin (greater than or equal to 2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated) and sulfonylurea (near-maximal or maximal effective dose) participated in a 52 week, double-blind, active-controlled study to compare the efficacy and safety of canagliflozin 300 mg versus sitagliptin 100 mg in combination with metformin and sulfonylurea. The mean age was 57 years, 56% of patients were men, and the mean baseline eGFR was 88 mL/min/1.73 m^2. Patients already on protocol-specified doses of metformin and sulfonylurea (N=716) entered a 2-week single-blind, placebo run-in period. Other patients (N=39) were required to be on a stable protocol-specified dose of metformin and sulfonylurea for at least 8 weeks before entering the 2-week run-in period. Following the run-in period, patients were randomized to canagliflozin 300 mg or sitagliptin 100 mg as add-on to metformin and sulfonylurea.

As shown in Table 12 and Figure 2, at the end of treatment, canagliflozin 300 mg provided greater HbA1C reduction compared to sitagliptin 100 mg when added to metformin and sulfonylurea ($p<0.05$). Canagliflozin 300 mg resulted in a mean percent change in body weight from baseline of -2.5% compared to +0.3% with sitagliptin 100 mg. A mean change in systolic

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blood pressure from baseline of -5.06 mmHg was observed with canagliflozin 300 mg compared to +0.85 mmHg with sitagliptin 100 mg.

Table 12: Results from 52−Week Clinical Study Comparing Canagliflozin to Sitagliptin in Combination with Metformin and Sulfonylurea*

Efficacy Parameter	Canagliflozin 300 mg + Metformin and Sulfonylurea (N=377)	Sitagliptin 100 mg + Metformin and Sulfonylurea (N=378)
HbA1C (%)		
Baseline (mean)	8.12	8.13
Change from baseline (adjusted mean)	-1.03	-0.66
Difference from sitagliptin (adjusted mean) (95% CI) [†]	-0.37[‡] (-0.50, -0.25)	
Percent of patients achieving HbA1C < 7%	48	35
Fasting Plasma Glucose (mg/dL)		
Baseline (mean)	170	164
Change from baseline (adjusted mean)	-30	-6
Difference from sitagliptin (adjusted mean) (95% CI) [†]	-24 (-30, -18)	
Body Weight		
Baseline (mean) in kg	87.6	89.6
% change from baseline (adjusted mean)	-2.5	0.3
Difference from sitagliptin (adjusted mean) (95% CI) [†]	-2.8[§] (-3.3, -2.2)	

* Intent-to-treat population using last observation in study prior to glycemic rescue therapy

[†] Least squares mean adjusted for baseline value and stratification factors

[‡] Canagliflozin + metformin+ sulfonylurea is considered non-inferior to sitagliptin + metformin+ sulfonylurea because the upper limit of this confidence interval is less than the pre-specified non-inferiority margin of < 0.3%.

[§] p<0.001

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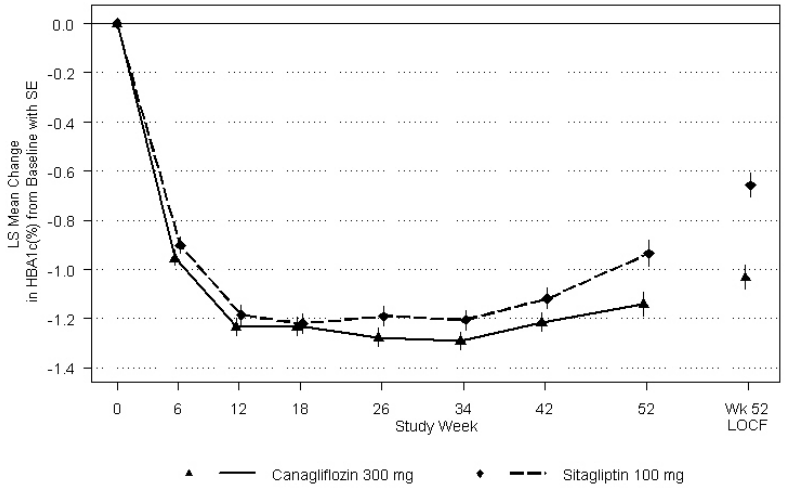
Figure 2: Mean HbA1C Change at Each Time Point (Completers) and at Week 52 Using Last Observation Carried Forward (mITT Population)



14.5 Canagliflozin as Add-on Combination Therapy with Metformin and Pioglitazone

A total of 342 patients with type 2 diabetes inadequately controlled on the combination of metformin (greater than or equal to 2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated) and pioglitazone (30 or 45 mg/day) participated in a 26-week, double-blind, placebo-controlled study to evaluate the efficacy and safety of canagliflozin in combination with metformin and pioglitazone. The mean age was 57 years, 63% of patients were men, and the mean baseline eGFR was 86 mL/min/1.73 m^2. Patients already on protocol-specified doses of metformin and pioglitazone (N=163) entered a 2-week, single-blind, placebo run-in period. Other patients (N=181) were required to be on stable protocol-specified doses of metformin and pioglitazone for at least 8 weeks before entering the 2-week run-in period. Following the run-in period, patients were randomized to canagliflozin 100 mg, canagliflozin 300 mg, or placebo, administered once daily as add-on to metformin and pioglitazone.

At the of end of treatment, canagliflozin 100 mg and 300 mg once daily resulted in a statistically significant improvement in HbA1C ($p<0.001$ for both doses) compared to placebo when added to metformin and pioglitazone. Canagliflozin 100 mg and 300 mg once daily also resulted in a greater proportion of patients achieving an HbA1C less than 7%, in significant reduction in fasting plasma glucose (FPG), and in percent body weight reduction compared to placebo when added to metformin and pioglitazone (see Table 13). Statistically significant ($p<0.05$ for both doses) mean changes from baseline in systolic blood pressure relative to placebo were -4.1 mmHg and -3.5 mmHg with canagliflozin 100 mg and 300 mg, respectively.

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Table 13: Results from 26−Week Placebo-Controlled Clinical Study of Canagliflozin in Combination with Metformin and Pioglitazone*

Efficacy Parameter	Placebo + Metformin and Pioglitazone (N=115)	Canagliflozin 100 mg + Metformin and Pioglitazone (N=113)	Canagliflozin 300 mg + Metformin and Pioglitazone (N=114)
HbA1C (%)			
Baseline (mean)	8.00	7.99	7.84
Change from baseline (adjusted mean)	-0.26	-0.89	-1.03
Difference from placebo (adjusted mean) (95% CI)†		-0.62‡ (-0.81, -0.44)	-0.76‡ (-0.95, -0.58)
Percent of patients achieving HbA1C < 7%	33	47‡	64‡
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	164	169	164
Change from baseline (adjusted mean)	3	-27	-33
Difference from placebo (adjusted mean) (95% CI)†		-29‡ (-37, -22)	-36‡ (-43, -28)
Body Weight			
Baseline (mean) in kg	94.0	94.2	94.4
% change from baseline (adjusted mean)	-0.1	-2.8	-3.8
Difference from placebo (adjusted mean) (95% CI)†		-2.7‡ (-3.6, -1.8)	-3.7‡ (-4.6, -2.8)

* Intent-to-treat population using last observation in study prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value and stratification factors
‡ $p<0.001$

14.6 Canagliflozin as Add-on Combination Therapy with Insulin (With or Without Other Anti-Hyperglycemic Agents, Including Metformin)

A total of 1718 patients with type 2 diabetes inadequately controlled on insulin greater than or equal to 30 units/day or insulin in combination with other antihyperglycemic agents participated in an 18-week, double-blind, placebo-controlled substudy of a cardiovascular study to evaluate the efficacy and safety of canagliflozin in combination with insulin. Of these patients, a subgroup of 432 patients with inadequate glycemic control received canagliflozin or placebo plus metformin and ≥ 30 units/day of insulin over 18 weeks.

In this subgroup, the mean age was 61 years, 67% of patients were men, and the mean baseline eGFR was 81 mL/min/1.73 m^2. Patients on metformin in combination with basal, bolus, or basal/bolus insulin for at least 10 weeks entered a 2-week, single-blind, placebo run-in period. Approximately 74% of these patients were on a background of metformin and basal/bolus insulin regimen. After the run-in period, patients were randomized to canagliflozin 100 mg, canagliflozin 300 mg, or placebo, administered once daily as add-on to metformin and insulin. The mean daily insulin dose at baseline was 93 units, which was similar across treatment groups.

At the of end of treatment, canagliflozin 100 mg and 300 mg once daily resulted in a statistically significant improvement in HbA1C ($p<0.001$ for both doses) compared to placebo when added to metformin and insulin. Canagliflozin 100 mg and 300 mg once daily also resulted in a greater

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proportion of patients achieving an HbA1C less than 7%, in significant reductions in fasting plasma glucose (FPG), and in percent body weight reductions compared to placebo (see Table 14). Statistically significant (p=0.023 for the 100 mg and p<0.001 for the 300 mg dose) mean change from baseline in systolic blood pressure relative to placebo was –3.5 mmHg and –6 mmHg with canagliflozin 100 mg and 300 mg, respectively. Fewer patients on canagliflozin in combination with metformin and insulin required glycemic rescue therapy: 3.6% of patients receiving canagliflozin 100 mg, 2.7% of patients receiving canagliflozin 300 mg, and 6.2% of patients receiving placebo. An increased incidence of hypoglycemia was observed in this study, which is consistent with the expected increase of hypoglycemia when an agent not associated with hypoglycemia is added to insulin *[see Warnings and Precautions (5.6); Adverse Reactions (6.1)]*.

Table 14: Results from 18−Week Placebo-Controlled Clinical Study of Canagliflozin in Combination with Metformin and Insulin ≥ 30 Units/Day*

Efficacy Parameter	**Placebo + Metformin + Insulin (N=145)**	**Canagliflozin 100 mg + Metformin + Insulin (N=139)**	**Canagliflozin 300 mg + Metformin + Insulin (N=148)**
HbA1C (%)			
Baseline (mean)	8.15	8.20	8.22
Change from baseline (adjusted mean)	0.03	-0.64	-0.79
Difference from placebo (adjusted mean) (95% CI) †		-0.66‡ (-0.81, -0.51)	-0.82‡ (-0.96, -0.67)
Percent of patients achieving HbA1C < 7%	9	19§	29‡
Fasting Plasma Glucose (mg/dL)			
Baseline	163	168	167
Change from baseline (adjusted mean)	1	-16	-24
Difference from placebo (adjusted mean) (97.5% CI) †		-16‡ (-28, -5)	-25‡ (-36, -14)
Body Weight			
Baseline (mean) in kg	102.3	99.7	101.1
% change from baseline (adjusted mean)	0.0	-1.7	-2.7
Difference from placebo (adjusted mean) (97.5% CI) †		-1.7‡ (-2.4, -1.0)	-2.7‡ (-3.4, -2.0)

* Intent-to-treat population using last observation in study prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value and stratification factors
‡ p≤0.001
§ p≤0.01

16 HOW SUPPLIED/STORAGE AND HANDLING

INVOKAMET (canagliflozin and metformin hydrochloride) tablets are available in the strengths and packages listed below:

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Canagliflozin 50 mg and metformin hydrochloride 500 mg tablets are immediate-release, capsule-shaped, white film-coated tablets with “CM” on one side and “155” on the other side.

- NDC 50458-540-60 Bottle of 60

Canagliflozin 50 mg and metformin hydrochloride 1,000 mg tablets are immediate-release, capsule-shaped, beige film-coated tablets with “CM” on one side and “551” on the other side.

- NDC 50458-541-60 Bottle of 60

Canagliflozin 150 mg and metformin hydrochloride 500 mg tablets are immediate-release, capsule-shaped, yellow film-coated tablets with “CM” on one side and “215” on the other side.

- NDC 50458-542-60 Bottle of 60

Canagliflozin 150 mg and metformin hydrochloride 1,000 mg tablets are immediate-release, capsule-shaped, purple film-coated tablets with “CM” on one side and “611” on the other side.

- NDC 50458-543-60 Bottle of 60

Storage and Handling

Keep out of reach of children.

Store at 68-77°F (20-25°C); excursions permitted between 59°F and 86°F (15°C and 30°C) [see USP Controlled Room Temperature]. Store in the original container.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-Approved Patient Labeling (Medication Guide).

- Lactic Acidosis: Explain the risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in *Warnings and Precautions (5.1)*. Advise patients to discontinue INVOKAMET immediately and to promptly notify their healthcare provider if unexplained hyperventilation, myalgias, malaise, unusual somnolence or other nonspecific symptoms occur. Once a patient is stabilized on INVOKAMET, gastrointestinal symptoms, which are common during initiation of metformin, are unlikely to recur. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

- Instruct patients to keep INVOKAMET in the original bottle to protect from moisture. Do not put INVOKAMET in pill boxes or pill organizers.

- Counsel patients against excessive alcohol intake while receiving INVOKAMET.

- Inform patients about importance of regular testing of renal function and hematological parameters while receiving INVOKAMET.

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- Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

- Instruct patients to take INVOKAMET only as prescribed twice daily with food. If a dose is missed, advise patients not to take two doses of INVOKAMET at the same time.

- Hypotension: Inform patients that symptomatic hypotension may occur with INVOKAMET and advise them to contact their doctor if they experience such symptoms *[see Warnings and Precautions (5.2)]*. Inform patients that dehydration may increase the risk for hypotension and to have adequate fluid intake.

- Genital Mycotic Infections in Females: Inform female patients that vaginal yeast infection (e.g., vulvovaginitis) may occur and provide them with information on the signs and symptoms of a vaginal yeast infection. Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions (5.7)]*.

- Genital Mycotic Infections in Males: Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with prior history. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions (5.7)]*.

- Hypersensitivity Reactions: Inform patients that serious hypersensitivity reactions, such as urticaria and rash, have been reported with canagliflozin. Advise patients to report immediately any signs or symptoms suggesting allergic reaction or angioedema and to take no more drug until they have consulted prescribing physicians *[see Warnings and Precautions (5.8)]*.

- Urinary Tract Infections: Inform patients of the potential for urinary tract infections. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur.

- Laboratory Tests: Inform patients that they will test positive for glucose in their urine while on INVOKAMET *[see Drug Interactions (7.2)]*.

- Pregnancy: Inform female patients of child bearing age that the use of INVOKAMET during pregnancy has not been studied in humans, and to use INVOKAMET during pregnancy only if the potential benefit justifies the potential risk to the fetus. Instruct patients to report pregnancies to their physicians as soon as possible *[see Use in Specific Populations (8.1)]*.

- Nursing Mothers: Inform nursing mothers to discontinue INVOKAMET or nursing, taking into account the importance of drug to the mother *[see Use in Specific Populations (8.3)]*.

- Inform patients that the most common adverse reactions associated with canagliflozin are genital mycotic infection, urinary tract infection, and increased urination. Most common

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adverse reactions associated with metformin are diarrhea, nausea, vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache.

Manufactured for:

Janssen Pharmaceuticals, Inc.

Titusville, NJ 08560

Finished product manufactured by:

Janssen Ortho, LLC

Gurabo, PR 00778

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MEDICATION GUIDE

INVOKAMET® (IN VOK' A MET)

(canagliflozin and metformin hydrochloride)

Tablets

What is the most important information I should know about INVOKAMET?

INVOKAMET can cause serious side effects, including:

- **Lactic Acidosis.** Metformin, 1 of the medicines in INVOKAMET, can cause a rare but serious condition called lactic acidosis (a build-up of lactic acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in the hospital.

  Stop taking INVOKAMET and call your doctor right away if you have any of the following symptoms which could be signs of lactic acidosis:

  - you feel very weak or tired
  - you have unusual (not normal) muscle pain
  - you have trouble breathing
  - you have unusual sleepiness or sleep longer than usual
  - you have stomach pains, nausea, or vomiting
  - you feel dizzy or lightheaded
  - you have a slow or irregular heartbeat

You have a higher chance of getting lactic acidosis with INVOKAMET if you:

- have kidney problems or your kidneys are affected by certain x-ray tests that use injectable dye. People whose kidneys are not working properly should not take INVOKAMET.
- have liver problems.
- have congestive heart failure that requires treatment with medicines.
- drink alcohol very often, or drink a lot of alcohol in short-term "binge" drinking.

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- get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids.
- have surgery
- have a heart attack, severe infection, or stroke
- are 80 years of age or older and have not had your kidneys tested

The best way to keep from having a problem with lactic acidosis from metformin is to tell your doctor if you have any of the problems in the list above. Your doctor will decide to stop your INVOKAMET for a while if you have any of these things.

INVOKAMET can have other serious side effects. See "What are the possible side effects of INVOKAMET?"

What is INVOKAMET?

- INVOKAMET contains 2 prescription medicines called canagliflozin (INVOKANA) and metformin hydrochloride (GLUCOPHAGE). INVOKAMET can be used along with diet and exercise to improve blood sugar (glucose) control in adults with type 2 diabetes when treatment with either canagliflozin or metformin has not controlled your blood sugar.
- INVOKAMET is not for people with type 1 diabetes.
- INVOKAMET is not for people with diabetic ketoacidosis (increased ketones in blood or urine).
- It is not known if INVOKAMET is safe and effective in children under 18 years of age.

Who should not take INVOKAMET?

Do not take INVOKAMET if you:

- have severe kidney problems or are on dialysis.
- have a condition called metabolic acidosis or diabetic ketoacidosis (increased ketones in the blood or urine)
- are allergic to canagliflozin, metformin, or any of the ingredients in INVOKAMET. See the end of this Medication Guide for a list of ingredients in INVOKAMET. Symptoms of allergic reaction to INVOKAMET may include:

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- rash
- raised red patches on your skin (hives)
- swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing

What should I tell my doctor before taking INVOKAMET?

Before you take INVOKAMET, tell your doctor if you:

- have kidney problems.
- have liver problems.
- are on a low sodium (salt) diet. Your doctor may change your diet or your dose of INVOKAMET.
- have ever had an allergic reaction to INVOKAMET.
- are going to get an injection of dye or contrast agents for an x-ray procedure. INVOKAMET will need to be stopped for a short time. Talk to your doctor about when you should stop INVOKAMET and when you should start INVOKAMET again. See "What is the most important information I should know about INVOKAMET?"
- have heart problems, including congestive heart failure.
- drink alcohol very often, or drink a lot of alcohol in short term "binge" drinking.
- have other medical conditions.
- are pregnant or plan to become pregnant. It is not known if INVOKAMET will harm your unborn baby. If you are pregnant, talk with your doctor about the best way to control your blood sugar while you are pregnant.
- are breastfeeding or plan to breastfeed. It is not known if INVOKAMET passes into your breast milk. Talk with your doctor about the best way to feed your baby if you are taking INVOKAMET.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

INVOKAMET may affect the way other medicines work and other medicines may affect how INVOKAMET works. Especially tell your doctor if you take:

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- diuretics (water pills)
- rifampin (used to treat or prevent tuberculosis)
- phenytoin or phenobarbital (used to control seizures)
- ritonavir (Norvir®, Kaletra®)* (used to treat HIV infection)
- digoxin (Lanoxin®)* (used to treat heart problems)

Ask your doctor or pharmacist for a list of these medicines if you are not sure if your medicine is listed above.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How should I take INVOKAMET?

- Take INVOKAMET by mouth 2 times each day with meals exactly as your doctor tells you to take it. Taking INVOKAMET with meals may lower your chance of having an upset stomach.
- Your doctor will tell you how much INVOKAMET to take and when to take it. Your doctor may change your dose if needed.
- Your doctor may tell you to take INVOKAMET along with other diabetes medicines. Low blood sugar can happen more often when INVOKAMET is taken with certain other diabetes medicines. See "**What are the possible side effects of INVOKAMET?**"
- If you miss a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and take the medicine at the next regularly scheduled time. Do not take 2 doses of INVOKAMET at the same time. Talk to your doctor if you have questions about a missed dose.
- If you take too much INVOKAMET, call your doctor or go to the nearest hospital emergency room right away.
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection, or surgery, the amount of diabetes medicine you need may change. Tell your doctor right away if you have any of these conditions and follow your doctor's instructions.
- Stay on your prescribed diet and exercise program while taking INVOKAMET.

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- Check your blood sugar as your doctor tells you to.
- INVOKAMET will cause your urine to test positive for glucose.
- Your doctor may do certain blood tests before you start INVOKAMET and during treatment as needed. Your doctor may change your dose of INVOKAMET based on the results of your blood tests.
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1C.

What should I avoid while taking INVOKAMET?

- Avoid drinking alcohol very often, or drinking a lot of alcohol in short period of time ("binge" drinking). It can increase your chances of getting serious side effects.

What are the possible side effects of INVOKAMET?

INVOKAMET may cause serious side effects including:

See **"What is the most important information I should know about INVOKAMET?"**

- **dehydration. INVOKAMET can cause some people to have dehydration (the loss of body water and salt). Dehydration may cause you to feel dizzy, faint, lightheaded, or weak, especially when you stand up (orthostatic hypotension).**

You may be at higher risk of dehydration if you:

  - o have low blood pressure
  - o take medicines to lower your blood pressure, including diuretics (water pill)
  - o are on a low sodium (salt) diet
  - o have kidney problems
  - o are 65 years of age or older

- **kidney problems**
- **a high amount of potassium in your blood**

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- **low blood sugar (hypoglycemia).** If you take INVOKAMET with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take INVOKAMET.

  Signs and symptoms of low blood sugar may include:

  - headache
  - drowsiness
  - weakness
  - dizziness
  - confusion
  - irritability
  - hunger
  - fast heartbeat
  - sweating
  - shaking or feeling jittery

- **vaginal yeast infection.** Women who take INVOKAMET may get vaginal yeast infections. Symptoms of a vaginal yeast infection include:

  - vaginal odor
  - white or yellowish vaginal discharge (discharge may be lumpy or look like cottage cheese)
  - vaginal itching

- **yeast infection of the penis (balanitis or balanoposthitis).** Men who take INVOKAMET may get a yeast infection of the skin around the penis. Certain men who are not circumcised may have swelling of the penis that makes it difficult to pull back the skin around the tip of the penis. Other symptoms of yeast infection of the penis include:

  - redness, itching, or swelling of the penis
  - rash of the penis
  - foul smelling discharge from the penis
  - pain in the skin around the penis

Talk to your doctor about what to do if you get symptoms of a yeast infection of the vagina or penis. Your doctor may suggest you use an over-the-counter antifungal medicine. Talk to your doctor right away if you use an over-the-counter antifungal medication and your symptoms do not go away.

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- **serious allergic reaction.** If you have any symptoms of a serious allergic reaction, stop taking INVOKAMET and call your doctor right away or go to the nearest hospital emergency room. See **"Who should not take INVOKAMET?".** Your doctor may give you a medicine for your allergic reaction and prescribe a different medicine for your diabetes.
- **low vitamin B_{12} (vitamin B_{12} deficiency).** Using metformin for long periods of time may cause a decrease in the amount of vitamin B_{12} in your blood, especially if you have had low vitamin B_{12} blood levels before. Your doctor may do blood tests to check your vitamin B_{12} levels.

Other common side effects of INVOKAMET include:

- urinary tract infection
- changes in urination, including urgent need to urinate more often, in larger amounts, or at night
- diarrhea
- nausea and vomiting
- gas
- weakness
- indigestion
- upset stomach
- headache

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of INVOKAMET. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Janssen Pharmaceuticals, Inc. at 1-800-526-7736.

How should I store INVOKAMET?

- Store INVOKAMET at room temperature between 68°F to 77°F (20°C to 25°C).

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- Store in the original container to protect from moisture. **Do not** put INVOKAMET in pill boxes or pill organizers.

Keep INVOKAMET and all medicines out of the reach of children.

General information about the safe and effective use of INVOKAMET

Medicines are sometimes prescribed for purposes other than those listed in the Medication Guide. Do not use INVOKAMET for a condition for which it was not prescribed. Do not give INVOKAMET to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about INVOKAMET. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about INVOKAMET that is written for healthcare professionals.

For more information about INVOKAMET, call 1-800-526-7736 or visit our website at www.invokamet.com.

What are the ingredients of INVOKAMET?

Active ingredients: canagliflozin and metformin hydrochloride

Inactive ingredients: The tablet core contains croscarmellose sodium, hypromellose, magnesium stearate, and microcrystalline cellulose. The magnesium stearate is vegetable-sourced. In addition, the tablet coating contains Macrogol/PEG, polyvinyl alcohol (partially hydrolyzed), talc, titanium dioxide, iron oxide yellow (50 mg/1,000 mg and 150 mg/500 mg tablets only), iron oxide red (50 mg/1,000 mg, 150 mg/500 mg and 150 mg/1,000 mg tablets only), and iron oxide black (150 mg/1,000 mg tablets only).

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Manufactured by:
Janssen Ortho, LLC

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