CONTRAINDICATIONS

- Moderate to severe renal impairment (eGFR below 45 mL/min/1.73 m²), end stage renal disease or dialysis (4, 5.1, 5.5)

- Metabolic acidosis, including diabetic ketoacidosis (1, 4, 5.1)

- History of serious hypersensitivity reaction to canagliflozin or metformin (4, 5.10)

WARNINGS AND PRECAUTIONS

- Lactic acidosis: See boxed warning (5.1)

- Lower limb amputation: See boxed warning (5.2)

- 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 (5.3)

- Ketoacidosis: Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue INVOKAMET, evaluate and treat promptly. Before initiating INVOKAMET, consider risk factors for ketoacidosis. Patients on INVOKAMET may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis (5.4)

- Acute kidney injury and impairment in renal function: Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and prompt treat. Monitor renal function during therapy (5.5)

- Hyperkalemia: Monitor potassium levels in patients with impaired renal function and in patients predisposed to hyperkalemia (2.2, 5.6, 8.6)

- Urosepsis and pyelonephritis: Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated (5.7)

- Hypoglycemia: Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination with INVOKAMET (5.8)

- Genital mycotic infections: Monitor and treat if indicated (5.9)

- Hypersensitivity reactions: Discontinue INVOKAMET and monitor until signs and symptoms resolve (5.10)

- Bone fracture: Consider factors that contribute to fracture risk before initiating INVOKAMET (5.11)

- Vitamin B₁₂ deficiency: Metformin may lower vitamin B₁₂ levels. Monitor hematologic parameters annually (5.12)

- Increased LDL-C: Monitor LDL-C and treat if appropriate (5.13)

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

- Carbonic anhydrase inhibitors may increase risk of lactic acidosis. Consider more frequent monitoring (7.1)

- Drugs that are eliminated by renal tubular secretion (e.g. cationic drugs such as cimetidine), may increase the accumulation of metformin. Consider more frequent monitoring (7.1)

- Alcohol can potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake (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: Advise females of the potential risk to a fetus especially during the second and third trimesters (8.1)

- Lactation: INVOKAMET is not recommended when breastfeeding (8.2)

- Females and Males of Reproductive Potential: Advise premenopausal females of the potential for an unintended pregnancy (8.3)

- Geriatrics: Higher incidence of adverse reactions related to reduced intravascular volume. Assess renal function more frequently (5.3, 6.1, 8.5)

- Renal impairment: Higher incidence of adverse reactions related to reduced intravascular volume and renal function (2.2, 5.5, 8.6)

- Hepatic Impairment: Avoid use in patients with hepatic impairment (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.
INVOKAMET® (canagliflozin and metformin hydrochloride) tablets

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INVOKAMET® (canagliflozin and metformin hydrochloride) tablets

2.2 Recommended Dosage for Patients with Renal Impairment
- Assess renal function before initiating INVOKAMET and periodically thereafter.
- INVOKAMET is contraindicated in patients with an estimated glomerular filtration rate (eGFR) of 45 mL/min/1.73 m² [see Contraindications (4) and Warnings and Precautions (5.1, 5.5)].
- Limit the dose of the canagliflozin component to 50 mg twice daily in patients with moderate renal impairment with an eGFR of 45 to less than 60 mL/min/1.73 m².

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 canagliflozin 50 mg twice daily who have an eGFR of 60 mL/min/1.73 m² 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 m² receiving concurrent therapy with a UGT inducer.

2.4 Discontinuation for Iodinated Contrast Imaging Procedures
Discontinue INVOKAMET at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 45 and 60 mL/min/1.73 m²; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart INVOKAMET if renal function is stable [see Warnings and Precautions (5.1)].

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.
- 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 “811” on the other side.

4 CONTRAINDICATIONS
INVOKAMET is contraindicated in patients with:
- Moderate to severe renal impairment (eGFR below 45 mL/min/1.73 m²), end stage renal disease (ESRD) or patients on dialysis [see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)].
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis [see Warnings and Precautions (5.4)].
- History of a serious hypersensitivity reaction to canagliflozin or metformin, such as anaphylaxis or angioedema [see Warnings and Precautions (5.4)].

5 WARNINGS AND PRECAUTIONS
5.1 Lactic Acidosis
There have been post-marketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a sudden onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant bradycardia/rhythms have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate/pyruvate ratio; metformin plasma levels generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of INVOKAMET. In INVOKAMET-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin hydrochloride is dialyzable, with a clearance of up to 170 mL/minute under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery. Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue INVOKAMET and report these symptoms to their healthcare provider.

For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:

Renal Impairment: The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney [see Clinical Pharmacology (12.3)].
- Before initiating INVOKAMET, obtain an estimated glomerular filtration rate (eGFR).
- INVOKAMET is contraindicated in patients with an eGFR less than 45 mL/minute/1.73 m².
- Obtain an eGFR at least annually in all patients taking INVOKAMET. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

Drug Interactions: The concomitant use of INVOKAMET with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodilution, change, interfere with acid-base balance or increase metformin accumulation (e.g. certain drugs) [see Drug Interactions (7)]. Therefore, consider more frequent monitoring of patients.

5.2 Lower Limb Amputation
An approximately 2-fold increased risk of lower limb amputations associated with canagliflozin, a component of INVOKAMET, was observed in CANVAS and CANVAS-R, two large, randomized, placebo-controlled trials evaluating patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease. In CANVAS, canagliflozin-treated patients and placebo-treated patients had 5.9 and 2.8 amputations per 1000 patients per year, respectively. In CANVAS-R, canagliflozin-treated patients and placebo-treated patients had 7.5 and 4.2 amputations per 1000 patients per year, respectively. The risk of lower limb amputations was observed at both the 100 mg and 300 mg once daily dosage regimens. The amputation data for CANVAS and CANVAS-R are shown in Tables 2 and 3, respectively [see Adverse Reactions (6.1)].

Amputations of the toe and midfoot (99 out of 140 patients with amputations receiving canagliflozin in the two trials) were the most frequent; however, amputations involving the leg, below and above the knee, were also observed (41 out of 140 patients with amputations receiving canagliflozin in the two trials). Some patients had multiple amputations, some involving both lower limbs. Lower limb infections, gangrene, and diabetic foot ulcers were the most common precipitating medical events leading to the need for an amputation. The risk of amputation was highest in patients with a baseline history of prior amputation, peripheral vascular disease, and neuropathy.

Before initiating INVOKAMET, consider factors in the patient history that may predispose to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy and diabetic foot ulcers. Counsel patients about the importance of routine preventative foot care. Monitor patients receiving INVOKAMET for signs and symptoms of infection (including osteomyelitis), new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue INVOKAMET if these complications occur.

5.3 Hypoglycemia
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 m², elderly patients, patients on either...
INVOKE AMET® (canagliflozin and metformin hydrochloride) tablets

5.4 Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including canagliflozin. Fatal cases of ketoacidosis have been reported in patients taking canagliflozin. INVOKE AMET is not indicated for the treatment of patients with type 1 diabetes mellitus [see Indications and Usage (1)].

Patients treated with INVOKE AMET who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with INVOKE AMET may be present without elevated blood glucose levels below 250 mg/dL. If ketoacidosis is suspected, INVOKE AMET should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and institution of treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake due to illness or surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating INVOKE AMET consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficit from any cause, caloric restriction, and alcohol abuse. In patients treated with INVOKE AMET consider monitoring for ketoacidosis and temporarily discontinuing INVOKE AMET in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

5.5 Acute Kidney Injury and Impairment in Renal Function

Canagliflozin causes intravascular volume contraction [see Warnings and Precautions (5.3)] and can cause renal impairment [see Adverse Reactions (6.1)]. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving canagliflozin; some reports involved patients younger than 65 years of age.

Before initiating INVOKE AMET, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure, and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing INVOKE AMET in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue INVOKE AMET promptly and institute treatment.

Canagliflozin increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating INVOKE AMET [see Adverse Reactions (6.1)]. Renal function should be evaluated prior to initiation of INVOKE AMET and monitored periodically thereafter. Dosage adjustment and more frequent renal function monitoring are recommended in patients with an eGFR below 60 mL/ min/1.73 m². INVOKE AMET is contraindicated in patients with an eGFR below 45 mL/min/1.73 m² [see Dosage and Administration (2.2), Contraindications (4), Warnings and Precautions (5.1) and Use in Specific Populations (8.6)].

5.6 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 at an increased risk of developing hyperkalemia [see Dosage and Administration (2.2) and Adverse Reactions (6.1)].

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

5.7 Urosepsis and Pyelonephritis

There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including canagliflozin. Treatment with SGLT2 inhibitors has been associated with urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated [see Adverse Reactions (6)].

5.8 Hypoglycemia with Concomitant Use of Sulfonylurea or Insulin Canagliflozin

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 INVOKE AMET.

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 INVOKE AMET to minimize the risk of hypoglycemia in these patients.

5.9 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.

5.10 Hypersensitivity Reactions

Hypersensitivity reactions, including angioedema and anaphylaxis, have been reported with canagliflozin. These reactions generally occurred within hours to days after initiating canagliflozin. If hypersensitivity reactions occur, discontinue use of INVOKE AMET; treat and monitor until signs and symptoms resolve [see Contraindications (4) and Adverse Reactions (6.1, 6.2)].

5.11 Bone Fracture

An increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed in patients using canagliflozin. Consider factors that contribute to fracture risk prior to initiating INVOKE AMET [see Adverse Reactions (6.1)].

5.12 Vitamin B₁₂ Levels

In controlled, 28-week clinical trials of metformin, a decrease to subnormal levels of previously normal serum vitamin B₁₂ levels, without clinical manifestations, was observed in approximately 7% of metformin-treated patients. Such decreases, possibly due to interference with B₁₂ absorption from the B₁₂-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 B₁₂ levels appears to be rapidly reversible with discontinuation of metformin or vitamin B₁₂ supplementation. Measure hematologic parameters on an annual basis in patients on INVOKE AMET and investigate and treat if abnormalities occur. Patients with inadequate vitamin B₁₂ or calcium intake or absorption may be predisposed to developing subnormal vitamin B₁₂ levels, and routine serum vitamin B₁₂ measurement at 2- to 3-year intervals is recommended in these patients.

5.13 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 if appropriate after initiating INVOKE AMET [see Adverse Reactions (6.1)].

6 ADVERSE REACTIONS

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

- Lactic Acidosis [see Boxed Warning and Warnings and Precautions (5.3, 5.5)]
- Lower Limb Amputation [see Boxed Warning and Warnings and Precautions (5.2)]
- Hypertension [see Warnings and Precautions (5.3)]
- Ketoacidosis [see Warnings and Precautions (5.4)]
- Acute Kidney Injury and Impairment in Renal Function [see Warnings and Precautions (5.5)]
- Hyperkalemia [see Warnings and Precautions (5.6)]
- Urosepsis and Pyelonephritis [see Warnings and Precautions (5.7)]
- Hypoglycemia with Concomitant Use of Sulfonylurea or Insulin [see Warnings and Precautions (5.8)]
- Genital Mycotic Infections [see Warnings and Precautions (5.9)]
- Hypersensitivity Reactions [see Warnings and Precautions (5.10)]
- Bone Fracture [see Warnings and Precautions (5.11)]
- Vitamin B₁₂ Deficiency [see Warnings and Precautions (5.2)]
- Increases in Low-Density Lipoprotein (LDL-C) [see Warnings and Precautions (5.13)]
INVOKAMET® (canagliflozin and metformin hydrochloride) tablets

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 patients exposed to a combination of canagliflozin and metformin. Patients received canagliflozin 100 mg (N=833), canagliflozin 300 mg (N=634) or placebo (N=648) once daily. The mean daily dose of metformin was 2128 mg (SD 337.3) for the 1275 patients 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 m2).

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*

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo N=334</th>
<th>Canagliflozin 100 mg N=833</th>
<th>Canagliflozin 300 mg N=634</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infections</td>
<td>3.8%</td>
<td>5.9%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Increased urination</td>
<td>0.7%</td>
<td>5.1%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Thirst</td>
<td>0.1%</td>
<td>2.6%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Constipation</td>
<td>0.9%</td>
<td>1.8%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.6%</td>
<td>2.1%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Female genital mycotic infections</td>
<td>2.8%</td>
<td>10.6%</td>
<td>11.8%</td>
</tr>
<tr>
<td>Vulvovaginal pruritus</td>
<td>0.0%</td>
<td>1.6%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Male genital mycotic infections</td>
<td>0.7%</td>
<td>4.2%</td>
<td>3.8%</td>
</tr>
</tbody>
</table>

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

Lower Limb Amputation

An approximately 2-fold increased risk of lower limb amputations associated with canagliflozin, a component of INVOKAMET, was observed in CANVAS and CANVAS-R, two large, randomized, placebo-controlled trials evaluating patients with type 2 diabetes who had either established cardiovascular disease or were at high risk for cardiovascular disease. Patients in CANVAS and CANVAS-R were followed for an average of 5.7 and 2.1 years, respectively. The amputation data for CANVAS and CANVAS-R are shown in Tables 2 and 3, respectively [see Warnings and Precautions (5.2)].

Table 2: CANVAS Amputations

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=1441</th>
<th>Canagliflozin 100 mg N=1445</th>
<th>Canagliflozin 300 mg N=1441</th>
<th>Canagliflozin (Pooled) N=2886</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with an amputation, n (%)</td>
<td>22 (1.5)</td>
<td>50 (3.5)</td>
<td>45 (3.1)</td>
<td>95 (3.3)</td>
</tr>
<tr>
<td>Total amputations</td>
<td>33</td>
<td>83</td>
<td>79</td>
<td>162</td>
</tr>
<tr>
<td>Amputation incidence rate (per 1000 patient-years)</td>
<td>2.8</td>
<td>6.2</td>
<td>5.5</td>
<td>5.9</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>--</td>
<td>2.24 (1.36, 3.69)</td>
<td>2.01 (1.20, 3.34)</td>
<td>2.12 (1.34, 3.38)</td>
</tr>
</tbody>
</table>

Note: Incidence is based on the number of patients with at least one amputation, and not the total number of amputation events. A patient's follow-up is calculated from Day 1 to the first amputation event date. Some patients had more than one amputation.

Table 3: CANVAS-R Amputations

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=2903</th>
<th>Canagliflozin 100 mg (with up-titration to 300 mg) N=2904</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with an amputation, n (%)</td>
<td>25 (0.9)</td>
<td>45 (1.5)</td>
</tr>
<tr>
<td>Total amputations</td>
<td>36</td>
<td>59</td>
</tr>
<tr>
<td>Amputation incidence rate (per 1000 patient-years)</td>
<td>4.2</td>
<td>7.5</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>--</td>
<td>1.80 (1.10, 2.93)</td>
</tr>
</tbody>
</table>

Note: Incidence is based on the number of patients with at least one amputation, and not the total number of amputation events. A patient's follow-up is calculated from Day 1 to the first amputation event date. Some patients had more than one amputation.

INVOKAMET® (canagliflozin and metformin hydrochloride) tablets (N=2682) 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 75% 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 m2).

The types and frequency of common adverse reactions observed in the pool of eight clinical trials were consistent with those listed in Table 1. Percentages were weighted by studies. Study weights were proportional to the harmonic mean of the three treatment sample sizes. In this pool, canagliflozin was also associated with the adverse reactions of fatigue (1.8% 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 0.1%, 0.2%, and 0.1% receiving comparator, canagliflozin 100 mg, and canagliflozin 300 mg, respectively.

In the pool of eight clinical trials, hypersensitivity-related adverse reactions (including erythema, rash, pruritis, 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:

- Constipation
- Abdominal pain
- Diarrhea
- Urinary tract infections
- Headache
- Pharyngitis
- Cough
- Flatulence
- Nausea
- Vomiting
- Rash
- Pruritus
- Itch
- Urticaria
- Angioedema
- Photosensitivity-related adverse reactions
INVOKAMET® (canagliflozin and metformin hydrochloride) tablets

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 renal impairment (eGFR 30 to less than 60 mL/min/1.73 m²), and age 75 years and older (Table 4) [see Dosage and Administration (2.2), Warnings and Precautions (5.3), and Use in Specific Populations (8.5, 8.6)].

Table 4: Proportion of Patients With at Least One Volume Depletion-Related Adverse Reaction (Pooled Results from 8 Clinical Trials)

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Comparator Group* %</th>
<th>Canagliflozin 100 mg %</th>
<th>Canagliflozin 300 mg %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall population</td>
<td>1.5%</td>
<td>2.3%</td>
<td>3.4%</td>
</tr>
<tr>
<td>75 years of age and older†</td>
<td>2.6%</td>
<td>4.9%</td>
<td>8.7%</td>
</tr>
<tr>
<td>eGFR less than 60 mL/min/1.73 m²</td>
<td>2.5%</td>
<td>4.7%</td>
<td>8.1%</td>
</tr>
<tr>
<td>Use of loop diuretic†</td>
<td>4.7%</td>
<td>3.2%</td>
<td>8.8%</td>
</tr>
</tbody>
</table>

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

Falls

In a pool of nine clinical trials with mean duration of exposure to canagliflozin of 85 weeks, the proportion of patients who experienced falls was 1.3%, 1.5%, and 2.1% with comparator, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. The higher risk of falls for patients treated with canagliflozin was observed within the first few weeks of treatment.

Impairment in Renal Function

Canagliflozin is associated with a dose-dependent increase in serum creatinine and a concomitant fall in estimated GFR (Table 5). Patients with moderate renal impairment at baseline had larger mean changes.

Table 5: Changes in Serum Creatinine and eGFR Associated with Canagliflozin in the Pool of Four Placebo-Controlled Trials and Moderate Renal Impairment Trial

<table>
<thead>
<tr>
<th>Pool of Four Placebo-Controlled Trials</th>
<th>Placebo N=646</th>
<th>Canagliflozin 100 mg N=833</th>
<th>Canagliflozin 300 mg N=834</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Creatinine (mg/dL)</td>
<td>0.84</td>
<td>0.82</td>
<td>0.82</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>87.0</td>
<td>88.3</td>
<td>88.8</td>
</tr>
<tr>
<td>Week 6 Change Creatinine (mg/dL)</td>
<td>0.01</td>
<td>0.03</td>
<td>0.05</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>-1.6</td>
<td>-3.8</td>
<td>-5.0</td>
</tr>
<tr>
<td>End of Treatment Change* Creatinine (mg/dL)</td>
<td>0.01</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>-1.6</td>
<td>-2.3</td>
<td>-3.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate Renal Impairment Trial</th>
<th>Placebo N=90</th>
<th>Canagliflozin 100 mg N=90</th>
<th>Canagliflozin 300 mg N=99</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Creatinine (mg/dL)</td>
<td>1.61</td>
<td>1.62</td>
<td>1.63</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>40.1</td>
<td>39.7</td>
<td>38.5</td>
</tr>
<tr>
<td>Week 3 Change Creatinine (mg/dL)</td>
<td>0.03</td>
<td>0.18</td>
<td>0.28</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>-0.7</td>
<td>-4.6</td>
<td>-6.2</td>
</tr>
<tr>
<td>End of Treatment Change* Creatinine (mg/dL)</td>
<td>0.07</td>
<td>0.16</td>
<td>0.18</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>-1.5</td>
<td>-3.6</td>
<td>-4.0</td>
</tr>
</tbody>
</table>

* Week 26 in mITT LOCF population

Table 6: Incidence of Hypoglycemia* in Controlled Clinical Studies

<table>
<thead>
<tr>
<th>Monotherapy (26 weeks)</th>
<th>Placebo (N=192)</th>
<th>Canagliflozin 100 mg (N=195)</th>
<th>Canagliflozin 300 mg (N=197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall [N (%)]</td>
<td>5 (2.6)</td>
<td>7 (3.6)</td>
<td>6 (3.0)</td>
</tr>
</tbody>
</table>

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 m² (mean baseline eGFR 39 mL/min/1.73 m²), 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 m² (mean baseline eGFR 48 mL/min/1.73 m²), 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 1.8% with canagliflozin 300 mg [see Warnings and Precautions (5.5)].

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 2.8%, 10.6%, and 11.6% 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 (5.9)].

In the pool of four placebo-controlled clinical trials, male genital mycotic infections (e.g., candidal balanitis, balanoposthitis) occurred in 0.7%, 4.2%, and 3.8% 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 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 (5.9)].

Hypoglycemia

In 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 (14.8)], episodes of hypoglycemia occurred at a higher rate when canagliflozin was co-administered with insulin or sulfonylureas (Table 6) [see Warnings and Precautions (5.8)].

Table 6: Incidence of Hypoglycemia* in Controlled Clinical Studies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Placebo (N=93)</th>
<th>Canagliflozin 100 mg + Metformin (N=183)</th>
<th>Canagliflozin 300 mg + Metformin (N=368)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall [N (%)]</td>
<td>3 (3.2)</td>
<td>16 (4.3)</td>
<td>17 (4.6)</td>
</tr>
<tr>
<td>Severe [N (%)]</td>
<td>0 (0)</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

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 m² and 30% lower than baseline, was 2.1% with placebo, 2.0% with canagliflozin 100 mg, and 4.1% with 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.
INVOKAMET® (canagliflozin and metformin hydrochloride) tablets

### Table 6: Incidence of Hypoglycemia* in Controlled Clinical Studies (continued)

<table>
<thead>
<tr>
<th>In Combination with Metformin + Sulfonylurea (26 weeks)</th>
<th>Placebo + Metformin + Sulfonylurea (N=156)</th>
<th>Canagliflozin 100 mg + Metformin + Sulfonylurea (N=157)</th>
<th>Canagliflozin 300 mg + Metformin + Sulfonylurea (N=156)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall [N (%)]</td>
<td>24 (15.4)</td>
<td>43 (27.2)</td>
<td>47 (30.1)</td>
</tr>
<tr>
<td>Severe [N (%)]</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>In Combination with Metformin + Pioglitazone (26 weeks)</th>
<th>Placebo + Metformin + Pioglitazone (N=115)</th>
<th>Canagliflozin 100 mg + Metformin + Pioglitazone (N=113)</th>
<th>Canagliflozin 300 mg + Metformin + Pioglitazone (N=114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall [N (%)]</td>
<td>2 (2.6)</td>
<td>3 (2.7)</td>
<td>6 (5.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>In Combination with Insulin (18 weeks)</th>
<th>Placebo (N=565)</th>
<th>Canagliflozin 100 mg (N=566)</th>
<th>Canagliflozin 300 mg (N=587)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall [N (%)]</td>
<td>208 (36.8)</td>
<td>279 (49.3)</td>
<td>285 (48.6)</td>
</tr>
<tr>
<td>Severe [N (%)]</td>
<td>14 (2.5)</td>
<td>10 (1.8)</td>
<td>16 (2.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>In Combination with Insulin and Metformin (18 weeks)‡</th>
<th>Placebo (N=145)</th>
<th>Canagliflozin 100 mg (N=139)</th>
<th>Canagliflozin 300 mg (N=148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall [N (%)]</td>
<td>66 (45.5)</td>
<td>58 (41.7)</td>
<td>70 (47.3)</td>
</tr>
<tr>
<td>Severe [N (%)]</td>
<td>4 (2.8)</td>
<td>1 (0.7)</td>
<td>3 (2.0)</td>
</tr>
</tbody>
</table>

* 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 antilglycemic agents)

Bone Fracture

The occurrence of bone fractures was evaluated in a pool of nine clinical trials with a mean duration of exposure to canagliflozin of 85 weeks. The incidence rates of adjudicated bone fractures were 1.1, 1.4, and 1.5 per 100 patient-years of exposure in the comparator, canagliflozin 100 mg, and canagliflozin 300 mg groups, respectively. Fractures were observed as early as 12 weeks after treatment initiation and were more likely to be low trauma (e.g., fall from no more than standing height), and affect the upper extremities [see Warnings and Precautions (5.11)].

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 B₁₂, which may very rarely result in clinically significant vitamin B₁₂ deficiency (e.g., megaloblastic anemia) [see Warnings and Precautions (5.12)].

Laboratory and Imaging Tests

**Increases in Serum Potassium**

In a pooled population of patients (N=723) with moderate renal impairment (eGFR 45 to less than 60 mL/min/1.73 m²), increases in serum potassium to greater than 5.4 mEq/L and 15% above baseline occurred in 5.3%, 5.0%, and 8.8% of patients treated with placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. Severe elevations (greater than or equal to 6.5 mEq/L) occurred in 0.4% of patients treated with placebo, no patients treated with canagliflozin 100 mg, and 1.3% of patients treated with canagliflozin 300 mg.

In these patients, increases in potassium were more commonly seen in those with elevated potassium at baseline. Among patients with moderate renal impairment, approximately 84% were taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, and angiotensin-receptor blockers [see Warnings and Precautions (5.3, 5.6) and Use in Specific Populations (8.6)].

**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.

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.

### Drug Interactions with Metformin

**Carbonic Anhydrase Inhibitors**

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently causes a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with INVOKAMET may increase the risk for lactic acidoses. Consider more frequent monitoring of these patients.

**Drugs That Reduce Metformin Clearance**

Drugs that are eliminated by renal tubular secretion (e.g. cationic drugs such as cimetidine) have the potential for interaction with metformin by competing for common renal tubular transport systems, and may increase the accumulation of metformin and the risk for lactic acidosis [see Clinical Pharmacology (12.3)]. Consider more frequent monitoring of these patients.

**Alcohol**

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving INVOKAMET.

**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, pheochromocytomas, 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.

## 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 (5.13)].

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.

### 6.2 Postmarketing Experience

Additional adverse reactions have been identified during postapproval use of canagliflozin. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Ketoacidosis** [see Warnings and Precautions (5.4)]

**Acute Kidney Injury and Impairment in Renal Function** [see Warnings and Precautions (5.5)]

**Anaphylaxis, Angioedema** [see Warnings and Precautions (5.10)]

**Urosepsis and Pyelonephritis** [see Warnings and Precautions (5.7)]

### 7. Drug Interactions

**Apixaban**

Apixaban is contraindicated with canagliflozin [see Warnings and Precautions (5.11)].

**Lipid Affecting Agents**

Drugs that affect lipid levels should be used with caution with canagliflozin [see Warnings and Precautions (5.12)].

**Anticoagulants**

The use of concomitant anticoagulants is not recommended with canagliflozin [see Warnings and Precautions (5.13)].
INVOKAMET® (canagliflozin and metformin hydrochloride) tablets

7.2 Drug Interactions with Canagliflozin

1. 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 m², and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m² receiving concurrent therapy with a UGT inducer and require additional glycemic control [see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)].

2. 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

Risk Summary

Based on animal data showing adverse renal effects, INVOKAMET is not recommended for use in women with renal disease.

Limited data with INVOKAMET or canagliflozin in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk [see Data]. There is a risk to the mother and fetus associated with poorly controlled diabetes during pregnancy [see Clinical Considerations].

Animal studies, adverse renal pelvic and tubule dilatations that were not reversible were observed in rats when canagliflozin was administered at an exposure 0.5-times the 300 mg clinical dose, based on AUC during a period of renal development corresponding to the late second and third trimesters of human pregnancy. No adverse developmental effects were observed when metformin was administered to pregnant Sprague Dawley rats and rabbits during the period of organogenesis at doses up to 1-5 times the 300 mg clinical dose, based on body surface area [see Data]. The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with an HbA1c >7 and has been reported to be as high as 20-25% in women with an HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2.4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data Human Data

Published data from post-marketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was used during pregnancy. However, these studies cannot definitively establish the absence of any metformin-associated risk because of methodological limitations, including small sample size and inconsistent comparator groups.

Animal Data

Canagliflozin

Canagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 4, 20, 65, or 100 mg/kg increased kidney weights and dose dependently increased the incidence and severity of renal pelvic and tubular dilatation at all doses tested. Exposure at the lowest dose was greater than or equal to 0.5-times the 300 mg clinical dose, based on AUC. These outcomes occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development. The renal pelvic dilatations observed in juvenile animals did not fully reverse within a 1 month recovery period.

8.2 Lactation

Risk Summary

There is no information regarding the presence of INVOKAMET or canagliflozin in human milk, the effects on the breastfed infant, or the effects on milk production. Limited published studies report that metformin is present in human milk [see Data]. However, there is insufficient information on the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. Canagliflozin is present in the milk of lactating rats [see Data]. Since human kidney maturation occurs in utero and during the first 2 years of life when lactation exposure may occur, there may be risk to the developing human kidney.

Because of the potential for serious adverse reactions in a breastfed infant, advise women that use of INVOKAMET is not recommended while breastfeeding.

Data Human Data

Published clinical lactation studies report that metformin is present in human milk which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1. However, these studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants.

Animal Data

Radiolabeled canagliflozin administered to lactating rats on day 13 post-partum was present at a milk/plasma ratio of 1.40, indicating that canagliflozin and its metabolites are transferred into milk at a concentration comparable to that in plasma. Juvenile rats directly exposed to canagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

8.3 Females and Males of Reproductive Potential

Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women.

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, 5.5)].

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 prominent 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

INVOKAMET® (canagliflozin and metformin hydrochloride) tablets

In embryo-fetal development studies in rats and rabbits, canagliflozin was administered for intervals coinciding with the first trimester period of organogenesis in humans. No developmental toxicities independent of maternal toxicity were observed when canagliflozin was administered at doses up to 100 mg/kg in pregnant rats and 160 mg/kg in pregnant rabbits during embryonic organogenesis or during a study in which maternal rats were dosed from gestation day (GD) 6 through PND 21, yielding exposures up to approximately 19-times the 300 mg clinical dose, based on AUC.

Metformin Hydrochloride

Metformin hydrochloride did not cause adverse developmental effects when administered to pregnant Sprague Dawley rats and rabbits up to 600 mg/kg/day during the period of organogenesis. This represents an exposure of about 2- and 6-times a 2000 mg clinical dose based on body surface area (mg/m²) for rats and rabbits, respectively.

Canagliflozin and Metformin

No adverse developmental effects were observed when canagliflozin and metformin were co-administered to pregnant rats during the period of organogenesis at exposures up to 11 and 13 times, respectively, the 300 mg and 2000 mg clinical doses of canagliflozin and metformin based on AUC.
INVOKAMET® (canagliflozin and metformin hydrochloride) tablets

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 (5.5), 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 60 mL/min/1.73 m2). These patients had less overall glyemic 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 80 mL/min/1.73 m2). Dose-related, transient mean increases in serum potassium were observed early after initiation of canagliflozin (i.e., within 3 weeks) in this trial. Increases in serum potassium of greater than 5 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. Severe elevations (greater than or equal to 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 [see Dosage and Administration (2.2), Contraindications (4), Warnings and Precautions (5.1, 5.4, 5.5), 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 m2), with ESRD, or patients with normal renal function (eGFR greater than or equal to 60 mL/min/1.73 m2). Dose-related, transient mean increases in serum potassium were observed early after initiation of canagliflozin (i.e., within 3 weeks) in this trial. Increases in serum potassium of greater than 5 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. Severe elevations (greater than or equal to 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. Severe elevations (greater than or equal to 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. Severe elevations (greater than or equal to 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. Severe elevations (greater than or equal to 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.

8.7 Hepatic Impairment

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. INVOKAMET is not recommended in patients with hepatic impairment. [see Warnings and Precautions (5.1)].

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 only for removal of accumulated metformin from patients in whom INVOKAMET overdosage is suspected.

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 (1S,5R)-1-[(5S)-2-thienyl(methyl)-4-methylphenyl]-D-glucitol hemihydrate and its molecular formula and weight are C24H25FO5S•1/2 H2O and 453.53, respectively. The structural formula for canagliflozin is:

![Chemical Structure of Canagliflozin](image)

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

Metformin Hydrochloride

Metformin hydrochloride is a salt of metformin. 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 C9H14N2•HCl and 165.62, respectively. The structural formula for metformin hydrochloride is:

![Chemical Structure of Metformin Hydrochloride](image)
INVOKAMET® (canagliflozin and metformin hydrochloride) tablets

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 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 \( t_{\text{max}} \)) of canagliflozin occurs within 1 to 2 hours post-dose. Plasma \( C_{\text{max}} \) and AUC of canagliflozin increased in a dose-proportional manner from 50 mg to 300 mg. The apparent terminal half-life (\( t_{\text{1/2}} \)) 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 83.5 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 ± 356 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonlureas, 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 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
\( D,\text{-}glucuronidation is the major metabolic elimination pathway for canagliflozin, which is catalyzed by UGT1A9 and UGT2B4 to two inactive \( D,\text{-}glucuronide metabolites. CYP2A4-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 \( D,\text{-}glucuronide metabolite, respectively. Enteroglomerular circulation of canagliflozin was negligible. Approximately 23% of the administered radioactive dose was excreted in urine, mainly as \( D,\text{-}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 2.5 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 8.2 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.

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 \( C_{\text{max}} \) of canagliflozin. Compared to healthy subjects (\( N=3 \), eGFR greater than or equal to 50 mL/min/1.73 m\(^2\)), plasma AUC of canagliflozin was increased by approximately 15%, 29%, and 55% 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. Levels of 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 (5.5)].

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 (5.5)].

Hepatic Impairment
Canagliflozin
Relative to subjects with normal hepatic function, the geometric mean ratios for \( C_{\text{max}} \) 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 (5.1)].

Metformin
No pharmacokinetic studies of metformin have been conducted in patients with hepatic insufficiency [see Warnings and Precautions (5.1)].

Pharmacokinetic Effects of Age, Body Mass Index (BMI)/Weight, Gender and Race
Canagliflozin
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, 5.5) 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 \( C_{\text{max}} \) 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.

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,
Table 7: Effect of Co-Administered Drugs on Systemic Exposures of Canagliflozin

<table>
<thead>
<tr>
<th>Co-Administered Drug</th>
<th>Dose of Co-Administered Drug</th>
<th>Dose of Canagliflozin</th>
<th>Geometric Mean Ratio (Ratio With/Without Co-Administered Drug) No Effect = 1.0</th>
<th>AUC† (90% CI)</th>
<th>Cmax† (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>600 mg QD for 8 days</td>
<td>300 mg</td>
<td>No Effect = 1.0</td>
<td>1.23 (1.19, 1.27)</td>
<td>1.01 (0.91, 1.11)</td>
</tr>
</tbody>
</table>

See Drug Interactions (7.2) for the clinical relevance of the following:

- Cyclosporine
- Ethinyl estradiol and levonorgestrel
- Hydrochlorothiazide
- Metformin
- Probenecid

No dose adjustments of co-administered drug required for the following:

- Acetaminophen 1,000 mg
- Ethinyl estradiol and levonorgestrel 0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel
- Metformin 2,000 mg
- Probenecid 500 mg BID

Table 8: Effect of Canagliflozin on Systemic Exposure of Co-Administered Drugs

<table>
<thead>
<tr>
<th>Co-Administered Drug</th>
<th>Dose of Co-Administered Drug</th>
<th>Dose of Canagliflozin</th>
<th>Geometric Mean Ratio (Ratio With/Without Co-Administered Drug) No Effect = 1.0</th>
<th>AUC† (90% CI)</th>
<th>Cmax† (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>0.5 mg QD first day followed by 0.25 mg QD for 6 days</td>
<td>300 mg QD for 7 days</td>
<td>No Effect = 1.0</td>
<td>1.20 (1.12, 1.28)</td>
<td>1.36 (1.21, 1.53)</td>
</tr>
</tbody>
</table>

See Drug Interactions (7.2) for the clinical relevance of the following:

- Acetaminophen
- Ethinyl estradiol and levonorgestrel
- Glyburide
- Hydrochlorothiazide
- Metformin
- Simvastatin
- Warfarin

No dose adjustments of co-administered drug required for the following:

- Acetaminophen 1,000 mg
- Ethinyl estradiol and levonorgestrel 0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel
- Glyburide 1.25 mg
- Hydrochlorothiazide 25 mg QD for 35 days
- Metformin 2,000 mg
- Simvastatin 40 mg
- Warfarin 30 mg

Table 9: Effect of Co-Administered Drugs on Plasma Metformin Systemic Exposures

<table>
<thead>
<tr>
<th>Co-Administered Drug</th>
<th>Dose of Co-Administered Drug</th>
<th>Dose of Metformin</th>
<th>Geometric Mean Ratio (Ratio With/Without Co-Administered Drug) No Effect = 1.0</th>
<th>AUC† (90% CI)</th>
<th>Cmax† (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyburide</td>
<td>5 mg</td>
<td>500 mg</td>
<td>No Effect = 1.0</td>
<td>0.98 (0.91, 1.03)</td>
<td>0.99 (0.92, 1.03)</td>
</tr>
<tr>
<td>Furosemide</td>
<td>40 mg</td>
<td>850 mg</td>
<td>No Effect = 1.0</td>
<td>1.09 (1.02, 1.16)</td>
<td>1.22 (1.14, 1.30)</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>10 mg</td>
<td>850 mg</td>
<td>No Effect = 1.0</td>
<td>0.90 (0.84, 0.96)</td>
<td>0.94 (0.88, 1.02)</td>
</tr>
<tr>
<td>Propranolol</td>
<td>40 mg</td>
<td>850 mg</td>
<td>No Effect = 1.0</td>
<td>0.87 (0.80, 0.95)</td>
<td>0.94 (0.87, 1.02)</td>
</tr>
</tbody>
</table>

Drugs that are eliminated by renal tubular secretion increase the accumulation of metformin [see Warnings and Precautions (5) and Drug Interactions (7)].

Table 10: Effect of Metformin on Co-Administered Drug Systemic Exposures

<table>
<thead>
<tr>
<th>Co-Administered Drug</th>
<th>Dose of Co-Administered Drug</th>
<th>Dose of Metformin</th>
<th>Geometric Mean Ratio (Ratio With/Without Co-Administered Drug) No Effect = 1.0</th>
<th>AUC† (90% CI)</th>
<th>Cmax† (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyburide</td>
<td>5 mg</td>
<td>500 mg</td>
<td>No Effect = 1.0</td>
<td>0.78 (0.70, 0.86)</td>
<td>0.63 (0.55, 0.71)</td>
</tr>
<tr>
<td>Furosemide</td>
<td>40 mg</td>
<td>850 mg</td>
<td>No Effect = 1.0</td>
<td>0.87 (0.79, 0.96)</td>
<td>0.69 (0.61, 0.78)</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>10 mg</td>
<td>850 mg</td>
<td>No Effect = 1.0</td>
<td>1.09 (1.00, 1.19)</td>
<td>1.08 (1.00, 1.17)</td>
</tr>
<tr>
<td>Propranolol</td>
<td>40 mg</td>
<td>850 mg</td>
<td>No Effect = 1.0</td>
<td>0.97 (0.89, 1.05)</td>
<td>0.94 (0.86, 1.03)</td>
</tr>
</tbody>
</table>

No dose adjustments required for the following:

- Steady state AUC0-T.

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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies have been conducted with the combined products in INVKAMET 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.

INVOKAMET® (canagliflozin and metformin hydrochloride) tablets

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.
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, onychogryphosis, onychophagia, and adnexal hyperplasia 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.

### 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

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.

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.

### 14 CLINICAL STUDIES

Canagliflozin has been studied in combination with metformin alone, metformin and sulfonylurea, metformin and 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), both as add-on combination therapy with metformin and sulfonylurea, and a sulfonylurea (glimepiride), both as add-on combination therapy with metformin.

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 Initial Combination Therapy with Metformin

A total of 1186 patients with type 2 diabetes inadequately controlled with diet and exercise participated in a 26-week double-blind, active-controlled, parallel-group, 5-arm, multicenter study to evaluate the efficacy and safety of initial therapy with canagliflozin in combination with metformin XR. The median age was 55 years, 47% of patients were men, and the mean baseline eGFR was 89 mL/min/1.73 m². 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 anti-hyperglycemic 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 canagliflozin 300 mg in combination with metformin XR resulted in a statistically significant greater improvement in HbA1C compared to their respective canagliflozin doses (100 mg and 300 mg) alone or metformin XR alone.

### Table 11: Results from 26-Week Active-Controlled Clinical Study of Canagliflozin Alone or Canagliflozin as Initial Combination Therapy with Metformin*

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Metformin XR (N=237)</th>
<th>Canagliflozin 100 mg (N=237)</th>
<th>Canagliflozin 300 mg (N=238)</th>
<th>Canagliflozin 100 mg + Metformin XR (N=237)</th>
<th>Canagliflozin 300 mg + Metformin XR (N=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1C (%)</td>
<td>Baseline (mean)</td>
<td>8.81</td>
<td>8.78</td>
<td>8.77</td>
<td>8.83</td>
</tr>
<tr>
<td></td>
<td>Change from baseline</td>
<td>-1.30</td>
<td>-1.37</td>
<td>-1.42</td>
<td>-1.77</td>
</tr>
<tr>
<td></td>
<td>(adjusted mean)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference from</td>
<td>canagliflozin 100</td>
<td>-0.40†</td>
<td>-0.40†</td>
<td>-0.36†</td>
<td>-0.46†</td>
</tr>
<tr>
<td></td>
<td>mg (adjusted mean)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference from</td>
<td>canagliflozin 300</td>
<td>-0.36†</td>
<td>-0.36†</td>
<td>-0.46†</td>
<td>-0.48†</td>
</tr>
<tr>
<td></td>
<td>mg (adjusted mean)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference from</td>
<td>metformin XR (adjusted</td>
<td>-0.46†</td>
<td>-0.46†</td>
<td>-0.48†</td>
<td>-0.48†</td>
</tr>
<tr>
<td></td>
<td>mean)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent of patients achieving HbA1C &lt; 7%</td>
<td>38</td>
<td>34</td>
<td>39</td>
<td>47§</td>
<td>51§</td>
</tr>
</tbody>
</table>

* Intent-to-treat population
† Least squares mean adjusted for covariates including baseline value and stratification factor
‡ Adjusted p<0.001
§ Adjusted p<0.05
¶ There were 121 patients without week 26 efficacy data. Analyses addressing missing data gave consistent results with the results provided in this table.

14.2 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 m². 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 anti-hyperglycemic agent (N=275) were switched to metformin monotherapy (at doses described above) for at least 8 weeks prior to 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 canagliflozin 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 patients achieving an HbA1C less than 7%, in significant reduction in fasting plasma glucose (PPG), in improved postprandial glucose (PPG), and in percent body weight reduction compared to placebo when added to metformin (see Table 12). 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.
A total of 1450 patients with type 2 diabetes inadequately controlled on metformin participated in a 52-week, double-blind, active-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-monotherapy (greater than or equal to 2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated) to metformin. Canagliflozin in combination with metformin and sitagliptin. The mean age was 57 years, 58% of patients were men, 73% of patients were Caucasian, 15% were Asian, and 12% were Black or African-American. The mean baseline eGFR was 90 mL/min/1.73 m<sup>2</sup>. Patients tolerating maximally required metformin combination with metformin.

### Efficacy Parameter

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Placebo + Metformin (N=183)</th>
<th>Canagliflozin 100 mg + Metformin (N=368)</th>
<th>Canagliflozin 300 mg + Metformin (N=367)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA&lt;sub&gt;1C&lt;/sub&gt; (%)</td>
<td>7.96</td>
<td>7.94</td>
<td>7.95</td>
</tr>
<tr>
<td>Percentage of patients achieving HbA&lt;sub&gt;1C&lt;/sub&gt; &lt; 7%</td>
<td>30</td>
<td>46†</td>
<td>58‡</td>
</tr>
<tr>
<td>Fasting Plasma Glucose (mg/dL)</td>
<td>164</td>
<td>169</td>
<td>173</td>
</tr>
<tr>
<td>2-hour Postprandial Glucose (mg/dL)</td>
<td>249</td>
<td>258</td>
<td>262</td>
</tr>
<tr>
<td>Body Weight (mean) in kg</td>
<td>86.7</td>
<td>88.7</td>
<td>85.4</td>
</tr>
</tbody>
</table>

### Table 12: Results from 26-Week Placebo-Controlled Clinical Study of Canagliflozin in Combination with Metformin<sup>*</sup>

### Table 13: Results from 52-Week Clinical Study Comparing Canagliflozin to Glimepiride in Combination with Metformin<sup>†</sup>

### 14.3 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.

### 14.4 Canagliflozin as Add-on Combination Therapy with Metformin and Sitagliptin

A total of 217 patients with type 2 diabetes inadequately controlled on the combination of metformin (greater than or equal to 1,500 mg/day) and sitagliptin 100 mg/day (or equivalent fixed-dose combination) participated in a 26-week, double-blind, placebo-controlled study to evaluate the efficacy and safety of canagliflozin in combination with metformin and sitagliptin. The mean age was 57 years, 58% of patients were men, 73% of patients were Caucasian, 15% were Asian, and 12% were Black or African-American. The mean baseline eGFR was...


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90 mL/min/1.73 m² and the mean baseline BMI was 32 kg/m². The mean duration of diabetes was 10 years. Eligible patients entered a 2-week, single-blind, placebo-run in period and were subsequently randomized to canagliflozin 100 mg or placebo, administered once daily as add-on to metformin and sitagliptin. Patients with a baseline eGFR of 70 mL/min/1.73 m² or greater who were tolerating canagliflozin 100 mg and who required additional glyemic control (fasting finger stick 100 mg/dL or greater at least twice within 2 weeks) were up-titrated to canagliflozin 300 mg. While up-titration occurred as early as week 4, most (90%) patients randomized to canagliflozin were up-titrated to canagliflozin 300 mg by 6 to 8 weeks.

At the end of 26 weeks, canagliflozin once daily resulted in a statistically significant improvement in HbA1C (p<0.001) compared to placebo when added to metformin and sitagliptin.

**Table 14: Results from 26-Week Placebo-Controlled Clinical Study of Canagliflozin in Combination with Metformin and Sitagliptin**

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Placebo + Metformin and Sitagliptin (N=108*)</th>
<th>Canagliflozin + Metformin and Sitagliptin (N=109*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1C (%)</td>
<td>8.40</td>
<td>8.50</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean) (95% CI)</td>
<td>-0.03 (-0.83)</td>
<td>-0.81 (-1.11; -0.51)</td>
</tr>
<tr>
<td>Percent of patients achieving HbA1C &lt; 7%‡</td>
<td>9</td>
<td>28</td>
</tr>
</tbody>
</table>

*To preserve the integrity of randomization, all randomized patients were included in the analysis. The patient who was randomized once to each arm was analyzed on canagliflozin.

† Early treatment discontinuation before week 26 occurred in 11.0% and 24.1% of canagliflozin and placebo patients, respectively.

‡ Patients without week 26 efficacy data were considered as non-responders when estimating the proportion achieving HbA1C < 7%.

§ Estimated using a multiple imputation method modeling a “wash-out” of the treatment effect for patients having missing data who discontinued treatment. Missing data was imputed only at week 26 and analyzed using ANCOVA.

¶ Estimated using a multiple imputation method modeling a “wash-out” of the treatment effect for patients having missing data who discontinued treatment. A mixed model for repeated measures was used to analyze the imputed data.

$p<0.001$

**14.5 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 m². 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 or canagliflozin 300 mg 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 15).

**Table 15: Results from 26-Week Placebo-Controlled Clinical Study of Canagliflozin in Combination with Metformin and Sulfonylurea**

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Placebo + Metformin and Sulfonylurea (N=156)</th>
<th>Canagliflozin 100 mg + Metformin and Sulfonylurea (N=157)</th>
<th>Canagliflozin 300 mg + Metformin and Sulfonylurea (N=156)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1C (%)</td>
<td>8.12</td>
<td>8.13</td>
<td>8.13</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-0.13</td>
<td>-0.85</td>
<td>-1.06</td>
</tr>
<tr>
<td>Difference from placebo (95% CI)†</td>
<td>-0.71 (-0.90, -0.52)</td>
<td>-0.92 (-1.11, -0.73)</td>
<td></td>
</tr>
<tr>
<td>Percent of patients achieving HbA1C &lt; 7%</td>
<td>18</td>
<td>43‡</td>
<td>57‡</td>
</tr>
</tbody>
</table>

Fasting Plasma Glucose (mg/dL)†

<table>
<thead>
<tr>
<th>Baseline (mean)</th>
<th>170</th>
<th>173</th>
<th>168</th>
</tr>
</thead>
</table>

% change from baseline (adjusted mean) | -0.7 | -2.1 | -2.6 |

Difference from placebo (95% CI)† | -1.4 (-2.1, -0.7) | -2.0 (-2.7, -1.3) |                                                                 |

† Least squares mean adjusted for baseline value and stratification factors

‡ p<0.001

**Table 16: Results from 52-Week Clinical Study Comparing Canagliflozin to Sitagliptin in Combination with Metformin and Sulfonylurea**

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Canagliflozin 300 mg + Metformin and Sulfonylurea (N=377)</th>
<th>Sitagliptin 100 mg + Metformin and Sulfonylurea (N=378)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1C (%)</td>
<td>8.12</td>
<td>8.13</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-1.03</td>
<td>-0.66</td>
</tr>
<tr>
<td>Difference from sitagliptin (adjusted mean) (95% CI)†</td>
<td>-0.37 (-0.50, -0.25)</td>
<td></td>
</tr>
<tr>
<td>Percent of patients achieving HbA1C &lt; 7%</td>
<td>48</td>
<td>35</td>
</tr>
</tbody>
</table>
**INVOKAMET® (canagliflozin and metformin hydrochloride) tablets**

### Table 16: Results from 52-Week Clinical Study Comparing Canagliflozin to Sitagliptin in Combination with Metformin and Pioglitazone* (continued)

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Canagliflozin 300 mg + Metformin and Pioglitazone (N=377)</th>
<th>Sitagliptin 100 mg + Metformin and Pioglitazone (N=378)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-30</td>
<td>-18</td>
</tr>
<tr>
<td>Difference in fasting plasma glucose (mg/dL) (95% CI)*</td>
<td>-24</td>
<td>-18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Baseline (mean) in kg</th>
<th>% change from baseline (adjusted mean)</th>
<th>Difference from placebo (adjusted mean) (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (mean) in kg</td>
<td>87.5</td>
<td>89.6</td>
<td>-2.8</td>
</tr>
</tbody>
</table>

* 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

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

**INVOKAMET® (canagliflozin and metformin hydrochloride) tablets**

### Table 17: Results from 26-Week Placebo-Controlled Clinical Study of Canagliflozin in Combination with Metformin and Pioglitazone*

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Placebo + Metformin and Pioglitazone (N=115)</th>
<th>Canagliflozin 100 mg + Metformin and Pioglitazone (N=113)</th>
<th>Canagliflozin 300 mg + Metformin and Pioglitazone (N=114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (mean) in kg</td>
<td>87.5</td>
<td>89.6</td>
<td>94.0</td>
</tr>
<tr>
<td>% change from baseline (adjusted mean)</td>
<td>-2.5</td>
<td>0.3</td>
<td>-3.8</td>
</tr>
<tr>
<td>Difference from placebo (adjusted mean) (95% CI)*</td>
<td>-2.6</td>
<td>-0.8</td>
<td>-1.0</td>
</tr>
</tbody>
</table>

* 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

### 14.8 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 in combination with other antihyperglycemic agents participated in an 18-week, double-blind, placebo-controlled study 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 85 mL/min/1.73 m². 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 92 units, which was similar across treatment groups.

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 insulin. Canagliflozin 100 mg and 300 mg once daily also resulted in a greater 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 18). 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 -8 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 (6.8) and Adverse Reactions (6.1)).
### Table 18: Results from 18-Week Placebo-Controlled Clinical Study of Canagliflozin in Combination with Metformin and Insulin ≥ 30 Units/Day*  

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Placebo + Metformin (N=145)</th>
<th>Canagliflozin 100 mg + Metformin (N=139)</th>
<th>Canagliflozin 300 mg + Metformin (N=148)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HbA1c (%)</td>
<td>Change from baseline (adjusted mean)</td>
<td>Change from baseline (adjusted mean)</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.15</td>
<td>0.03</td>
<td>-0.66</td>
</tr>
<tr>
<td>Percent of patients achieving HbA1c &lt;7%</td>
<td>9</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>Fasting Plasma Glucose (mg/dL)</td>
<td>163</td>
<td>166</td>
<td>167</td>
</tr>
<tr>
<td>Body Weight (mean)</td>
<td>102.3</td>
<td>-1.7</td>
<td>-2.7</td>
</tr>
</tbody>
</table>

* Least squares mean adjusted for baseline value and stratification factors

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

**INVOCA-L® (canagliflozin and metformin hydrochloride) tablets** are available in the strengths and packages listed below:

- 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.
- Canagliflozin 50 mg and metformin hydrochloride 1,000 mg tablets are immediate-release, capsule-shaped, white 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.

**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 and dispense in the original container. Storage in a pill box or pill organizer is allowed for up to 30 days.

### 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 INVOCA-L® 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 INVOCA-L®, gastrointestinal symptoms, which are common during initiation of metformin, are unlikely to recur. Later occurrences of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.
- **Instruct patients to keep INVOCA-L® in the original bottle to protect from moisture. Advise patients that storage in a pill box or pill organizer is allowed for up to 30 days.**
- **Counsel patients against excessive alcohol intake while receiving INVOCA-L®.**
- **Inform patients about importance of regular testing of renal function and hematological parameters while receiving INVOCA-L®.**

### INVOCA-L® (canagliflozin and metformin hydrochloride) tablets

- **Advises 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 INVOCA-L® only as prescribed twice daily, with food. If a dose is missed, advise patients not to take two doses of INVOCA-L® at the same time.**
- **Lower Limb Amputation:** Inform patients that INVOCA-L® is associated with an increased risk of amputations. Counsel patients about the importance of routine preventative foot care. Instruct patients to contact their doctor if they experience such symptoms [see Warnings and Precautions (5.3)].
- **Hypotension:** Inform patients that symptomatic hypotension may occur with INVOCA-L® and advise them to contact their doctor if they experience symptoms [see Warnings and Precautions (5.4)].
- **Acute Kidney Injury:** Inform patients that acute kidney injury has been reported during use of canagliflozin. Advise patients to seek medical advice immediately if they have reduced oral intake (such as due to acute illness or fasting), or increased fluid losses (such as due to vomiting, diarrhea, or excessive heat exposure), as it may be appropriate to temporarily discontinue INVOCA-L® use in those settings [see Warnings and Precautions (5.5)].
- **Serious Urinary Tract Infections:** Inform patients of the potential for urinary tract infections, which may be serious. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if symptoms occur [see Warnings and Precautions (5.6)].
- **Genital Mycotic Infections in Males:** Inform male patients that yeast infection of the 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 (redness or rash in 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, rash, anaphylaxis, and angioedema, have been reported with canagliflozin. Advise patients to report immediately any signs or symptoms suggesting allergic reaction and to discontinue drug until they have consulted prescribing physicians [see Warnings and Precautions (5.10)].
- **Bone Fracture:** Inform patients that bone fractures have been reported in patients taking canagliflozin. Provide them with information on factors that may contribute to fracture risk.
- **Laboratory Tests:** Inform patients that they will test positive for glucose in their urine when on INVOCA-L® [see Drug Interactions (7.2)].
- **Pregnancy:** Advise pregnant women, and females of reproductive potential of the potential risk to a fetus with treatment with INVOCA-L® [see Use in Specific Populations (8.1)]. Instruct females of reproductive potential to report pregnancies to their physicians as soon as possible.
- **Lactation:** Advise women that breastfeeding is not recommended during treatment with INVOCA-L® [see Use in Specific Populations (8.2)].
- **Inform females that treatment with INVOCA-L® may result in ovulation in some premenopausal anovulatory women which may lead to unintended pregnancy [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 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

Licensed from Mitsubishi Tanabe Pharma Corporation

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076294-170714
What is the most important information I should know about INVOKAMET?

INVOKAMET can cause serious side effects, including:

- **Lactic Acidosis.** Metformin, one 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.

  Call your doctor right away if you have any of the following symptoms, which could be signs of lactic acidosis:
  - you feel cold in your hands or feet
  - you have a slow or irregular heartbeat
  - you feel very weak or tired
  - you have unusual (not normal) muscle pain
  - you have stomach pains, nausea, or vomiting
  - you feel dizzy or lightheaded
  - you have unusual sleepiness or sleep longer than usual
  - you have trouble breathing
  - you have unusual (not normal) muscle pain
  - you have stomach pains, nausea, or vomiting
  - you feel dizzy or lightheaded

  Most people who have had lactic acidosis had other conditions that, in combination with metformin use, led to the lactic acidosis. Tell your doctor if you have any of the following, because you have a higher chance for getting lactic acidosis with INVOKAMET if you:
  - have severe kidney problems or your kidneys are affected by certain x-ray tests that use injectable dye.
  - have liver problems.
  - drink alcohol very often, or drink a lot of alcohol in short-term “binge” drinking.
  - 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.

  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.

- **Amputations.** INVOKAMET may increase your risk of lower limb amputations. Amputations mainly involve removal of the toe or part of the foot, however, amputations involving the leg, below and above the knee, have also occurred. Some people had more than one amputation, some on both sides of the body.

  You may be at a higher risk of lower limb amputation if you:
  - have a history of amputation
  - have heart disease or are at risk for heart disease
  - have had blocked or narrowed blood vessels, usually in your leg
  - have damage to the nerves (neuropathy) in your leg
  - have had diabetic foot ulcers or sores

  Call your doctor right away if you have new pain or tenderness, any sores, ulcers, or infections in your leg or foot. Your doctor may decide to stop your INVOKAMET for a while if you have any of these signs or symptoms.

  Talk to your doctor about proper foot care.

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 both canagliflozin and metformin is appropriate.

- 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 moderate to 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:
  - rash
  - raised red patches on your skin (hives)
  - swelling of the face, lips, mouth, 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 a history of amputation.
- have heart disease or are at risk for heart disease.
- have had blocked or narrowed blood vessels, usually in your leg.
- have damage to the nerves (neuropathy) in your leg.
- have had diabetic foot ulcers or sores.
- have moderate to severe kidney problems.
- have liver problems.
- have a history of urinary tract infections or problems with urination.
- 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 may 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.
- are going to have surgery.
- are eating less due to illness, surgery, or a change in your diet.
- have or have had problems with your pancreas, including pancreatitis or surgery on your pancreas.
- drink alcohol very often, or drink a lot of alcohol in the short-term (“binge” drinking).
- have other medical conditions.
- are pregnant or plan to become pregnant. INVOKAMET may harm your unborn baby. If you become pregnant while taking INVOKAMET, tell your doctor as soon as possible. Talk with your doctor about the best way to control your blood sugar while you are pregnant.
- are a premenopausal woman (before the “change of life”), who does not have periods regularly or at all. INVOKAMET may increase your chance of becoming pregnant. Talk to your doctor about birth control choices while taking INVOKAMET, if you are not planning to become pregnant. Tell your doctor right away if you become pregnant while taking INVOKAMET.
- are breastfeeding or plan to breastfeed. INVOKAMET may pass into your breast milk and may harm your baby. Talk with your doctor about the best way to feed your baby if you are taking INVOKAMET. Do not breastfeed while 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:

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

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.
- 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 a 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 become dehydrated (the loss of too much body water). 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:

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

Talk to your doctor about what you can do to prevent dehydration including how much fluid you should drink on a daily basis.

- Ketoacidosis (increased ketones in your blood or urine). Ketoacidosis has happened in people who have type 1 diabetes or type 2 diabetes, during treatment with canagliflozin, one of the medicines in INVOKAMET. Ketoacidosis is a serious condition, which may need to be treated in a hospital. Ketoacidosis may lead to death. Ketoacidosis can happen with INVOKAMET, even if your blood sugar is less than 250 mg/dL. Stop taking INVOKAMET and call your doctor right away if you get any of the following symptoms:
  - nausea
  - vomiting
  - stomach area (abdominal) pain
What are the possible side effects of INVOKAMET? (continued)

If you get any of these symptoms during treatment with INVOKAMET, if possible, check for ketones in your urine, even if your blood sugar is less than 250 mg/dL.

- **kidney problems.** Sudden kidney injury has happened to people taking INVOKAMET. Talk to your doctor right away if you:
  - reduce the amount of food or liquid you drink for example, if you are sick or cannot eat or
  - you start to lose liquids from your body for example, from vomiting, diarrhea or being in the sun too long.

- **a high amount of potassium in your blood.**
  - reduce the amount of food or liquid you drink for example, if you are sick or cannot eat or
  - you start to lose liquids from your body for example, from vomiting, diarrhea or being in the sun too long.

- **serious urinary tract infections.** Serious urinary tract infections that may lead to hospitalization have happened in people who are taking canagliflozin, one of the medicines in INVOKAMET. Tell your doctor if you have any signs or symptoms of a urinary tract infection such as a burning feeling when passing urine, a need to urinate often, the need to urinate right away, pain in the lower part of your stomach (pelvis), or blood in the urine. Sometimes people may also have a fever, back pain, nausea, or vomiting.

- **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
  - confusion
  - dizziness
  - 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
  - foul smelling discharge from the penis
  - rash of 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.

- **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.

- **broken bones (fractures).** Bone fractures have been seen in patients taking canagliflozin. Talk to your doctor about factors that may increase your risk of bone fracture.

- **low vitamin B<sub>12</sub> (vitamin B<sub>12</sub> deficiency).** Using metformin for long periods of time may cause a decrease in the amount of vitamin B<sub>12</sub> in your blood, especially if you have had low vitamin B<sub>12</sub> blood levels before. Your doctor may do blood tests to check your vitamin B<sub>12</sub> levels.

Other common side effects of INVOKAMET include:

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

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).
- Store in the original container to protect from moisture. Storage in a pill box or pill organizer is allowed for up to 30 days.

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).

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This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised 07/2017

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