**WARNING: LACTIC ACIDOSIS**

See full prescribing information for complete boxed warning.

- Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hyperthermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL (5.1)

- Risk factors include renal impairment, concomitant use of certain drugs, age >65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high-risk groups are provided in the Full Prescribing Information (5.1)

- If lactic acidosis is suspected, discontinue INVOKAMET/INVOKAMET XR and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.1)

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**INDICATIONS AND USAGE**

Canagliflozin is indicated to reduce the risk of end-stage kidney disease, heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy (1)

Canagliflozin is indicated to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease (1)

Canagliflozin is indicated to reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria (1).

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**ADVERSE REACTIONS**

- Most common adverse reactions associated with canagliflozin (5% or greater incidence) are diarrhea, nausea, vomiting, flatulence, asthenia, indigestion, increased urination (6.1)

- Common adverse reactions associated with metformin HCl (5% or greater incidence) are diarrhea, nausea, vomiting, flatulence, asthenia, indigestion, increased urination (6.1)

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**DRUG INTERACTIONS**

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

- Drugs that reduce metformin clearance (such as ranolazine, vandetanib, dolotegravic, and cimeticine) may increase the accumulation of metformin. Consider the benefits and risks of concomitant use (7.1)

- Alcohol: Warn patients against excessive intake (7.1)

- UGT inducers (e.g., rifampin): Canagliflozin exposure is reduced. Adjust canagliflozin dose (2.5, 7.2)

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**USE IN SPECIFIC POPULATIONS**

- Pregnancy: Advise females of the potential risk to a fetus especially during the second and third trimesters (8.1)

- Lactation: Not recommended when breastfeeding (8.2)

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

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See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/2020
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FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS
Post-marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradycardia. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (> 5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL [see Warnings and Precautions (5.1)].

Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment [see Warnings and Precautions (5.1)].

Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the full prescribing information [see Dosage and Administration (2.2, 2.3), Contraindications (4), Warnings and Precautions (5.1), Drug Interactions (7), and Use in Specific Populations (8.6, 8.7)].

If metformin-associated lactic acidosis is suspected, immediately discontinue INVOKAMET/INVOKAMET XR and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended [see Warnings and Precautions (5.1)].

1 INDICATIONS AND USAGE
INVOKAMET and INVOKAMET XR are a combination of canagliflozin and metformin hydrochloride (HCl) indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Canagliflozin is indicated to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD).

Canagliflozin is indicated to reduce the risk of end-stage kidney disease (ESKD) doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria greater than 300 mg/day.

Limitations of Use
INVOKAMET/INVOKAMET XR is not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients [see Warnings and Precautions (5.3)].

2 DOSAGE AND ADMINISTRATION
2.1 Prior to Initiation of INVOKAMET/INVOKAMET XR
• Assess renal function before initiating INVOKAMET/INVOKAMET XR and as clinically indicated [see Warnings and Precautions (5.1, 5.3), Contraindications (4)].
• In patients with volume depletion, correct this condition before initiating INVOKAMET/INVOKAMET XR [see Warnings and Precautions (5.3), Use in Specific Populations (8.5, 8.6)].

2.2 Dosage Overview
• INVOKAMET dosing is one tablet, twice daily with meals.
• INVOKAMET XR dosing is two tablets, once daily with the morning meal. Swallow each tablet whole and never crush, cut, or chew.
• The starting and maintenance dose of INVOKAMET/INVOKAMET XR is based on the patient’s current regimen and renal function [see Dosage and Administration (2.2, 2.3)].
• The maximum recommended daily dose is canagliflozin 300 mg and metformin HCl 2,000 mg in patients with an estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73 m² or greater. The recommended dosage for patients with renal impairment is shown in Table 1 [see Dosage and Administration (2.4)].

2.3 Starting Dose Based on Patient’s Current Regimen
Individualize the starting dose of INVOKAMET/INVOKAMET XR based on the patient’s current regimen and renal function [see Dosage and Administration (2.4)].

Patients Currently not Treated with Either Canagliflozin or Metformin HCl
• INVOKAMET: One tablet, twice daily, each tablet containing canagliflozin 50 mg and metformin HCl 500 mg; metformin HCl 500 mg.
• INVOKAMET XR: Two tablets, once daily, each tablet containing canagliflozin 50 mg and metformin HCl 500 mg.

Patients on Metformin HCl
• INVOKAMET: One tablet, twice daily, where the total daily dose contains canagliflozin 100 mg and the same, or nearest appropriate, daily dose of metformin HCl;
• INVOKAMET XR: Two tablets, once daily, where the total daily dose contains canagliflozin 100 mg and the patient’s same, or nearest appropriate, daily dose of metformin HCl.

Patients on Canagliflozin
• INVOKAMET: One tablet, twice daily, where the total daily dose contains the same daily dose of canagliflozin and metformin HCl 1,000 mg;
• INVOKAMET XR: Two tablets, once daily, where the total daily dose contains the patient’s same daily dose of canagliflozin and metformin HCl 1,000 mg.
INVOKAMET® (canagliflozin and metformin hydrochloride) tablets
INVOKAMET® XR (canagliflozin and metformin hydrochloride) extended-release tablets

Patients Already Treated with Canagliflozin and Metformin HCl

- INVOKAMET: One tablet, twice daily, where the total daily dose contains the same daily dose of canagliflozin and the same, or nearest appropriate, daily dose of metformin HCl;
- INVOKAMET XR: Two tablets, once daily, where the total daily dose contains the same daily dose of canagliflozin and the same, or nearest appropriate, daily dose of metformin HCl.

Patients with eGFR of 60 mL/min/1.73 m² or Greater and Require Additional Glycemic Control

- INVOKAMET: For patients tolerating canagliflozin 50 mg twice daily, increase the dose of canagliflozin to 100 mg twice daily, with gradual metformin HCl dose escalation based on tolerability [see Adverse Reactions (6.1)].
- INVOKAMET XR: For patients tolerating a daily dose of canagliflozin 100 mg, increase the dose to 200 mg once daily, with gradual metformin HCl dose escalation based on tolerability [see Adverse Reactions (6.1)].

Patients on Evening Dose of Metformin HCl Extended-Release Tablets

Patients taking an evening dose of metformin HCl extended-release tablets should skip their last dose before starting INVOKAMET/INVOKAMET XR the following morning.

2.4 Recommended Dosage for Patients with Renal Impairment

- Initiation of INVOKAMET or INVOKAMET XR is not recommended in patients with an eGFR less than 45 mL/min/1.73 m², due to the metformin component.
- Table 1 has dosage recommendations based on eGFR [see Use in Specific Populations (8.6), Clinical Studies (14.3)].

### Table 1: Recommended Dosage

<table>
<thead>
<tr>
<th>eGFR (mL/min/1.73 m²)</th>
<th>Recommended Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR 60 or greater</td>
<td>[See Dosage and Administration (2.3)].</td>
</tr>
<tr>
<td>eGFR 45 to less than 60</td>
<td>Limit the dose of canagliflozin component to 100 mg daily (two 50 mg tablets).</td>
</tr>
<tr>
<td>eGFR 30 to less than 45</td>
<td>Assess the benefit risk of continuing INVOKAMET or INVOKAMET XR; limit the dose of canagliflozin component to 100 mg daily (two 50 mg tablets).</td>
</tr>
<tr>
<td>eGFR less than 30</td>
<td>Contraindicated; discontinue INVOKAMET or INVOKAMET XR [see Contraindications (4)].</td>
</tr>
<tr>
<td>On dialysis</td>
<td>Contraindicated [see Contraindications (4)].</td>
</tr>
</tbody>
</table>

2.5 Concomitant Use with UDP-Glucuronosyltransferase Enzyme Inducers

If an inducer of UDP-Glucuronosyltransferase (UGT) (e.g., rifampin, phenytoin, phenobarbital, ritonavir) is co-administered with INVOKAMET/INVOKAMET XR, increase the total daily dose of canagliflozin to 200 mg in patients currently tolerating a total daily dose of canagliflozin 100 mg. The total daily dose of canagliflozin may be increased to a maximum of 300 mg in patients currently tolerating canagliflozin 200 mg and who require additional glycemic control [see Drug Interactions (7.2)].

Patients with eGFR less than 60 mL/min/1.73 m²

If an inducer of UG Ts (e.g., rifampin, phenytoin, phenobarbital, ritonavir) is co-administered with INVOKAMET/INVOKAMET XR, increase the total daily dose of canagliflozin to a maximum of 200 mg in patients currently tolerating canagliflozin 100 mg.

2.6 Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue INVOKAMET/INVOKAMET XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR of less than 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/INVOKAMET XR if renal function is stable [see Warnings and Precautions (5.1)].

3 DOSAGE FORMS AND STRENGTHS

INVOKAMET (canagliflozin and metformin HCl) tablets are available as follows:

<table>
<thead>
<tr>
<th>Canagliflozin Strength</th>
<th>Metformin HCl Strength</th>
<th>Color/Shape</th>
<th>Tablet Identifiers*</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg</td>
<td>500 mg</td>
<td>white/capsule-shaped</td>
<td>CM 155</td>
</tr>
<tr>
<td>50 mg</td>
<td>1,000 mg</td>
<td>beige/capsule-shaped</td>
<td>CM 551</td>
</tr>
<tr>
<td>150 mg</td>
<td>500 mg</td>
<td>yellow/capsule-shaped</td>
<td>CM 215</td>
</tr>
<tr>
<td>150 mg</td>
<td>1,000 mg</td>
<td>purple/capsule-shaped</td>
<td>CM 611</td>
</tr>
</tbody>
</table>

* Embossing appears on both sides of tablet.

INVOKAMET XR (canagliflozin and metformin hydrochloride) extended-release tablets are available as follows:

<table>
<thead>
<tr>
<th>Canagliflozin Strength</th>
<th>Metformin HCl Strength</th>
<th>Color/Shape</th>
<th>Tablet Identifiers*</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg</td>
<td>500 mg</td>
<td>almost white to light orange/oblong, biconvex</td>
<td>CM1</td>
</tr>
<tr>
<td>50 mg</td>
<td>1,000 mg</td>
<td>pink/oblong, biconvex</td>
<td>CM3</td>
</tr>
<tr>
<td>150 mg</td>
<td>500 mg</td>
<td>orange/oblong, biconvex</td>
<td>CM2</td>
</tr>
<tr>
<td>150 mg</td>
<td>1,000 mg</td>
<td>reddish brown/oblong, biconvex</td>
<td>CM4</td>
</tr>
</tbody>
</table>

* Embossing appears on one side only of tablet.

4 CONTRAINDICATIONS

INVOKAMET/INVOKAMET XR is contraindicated in patients:

- With severe renal impairment (eGFR less than 30 mL/min/1.73 m²) or on dialysis [see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)].
- With acute or chronic metabolic acidosis, including diabetic ketoacidosis [see Warnings and Precautions (5.4)].
- With serious hypersensitivity reaction to canagliflozin or metformin HCl, such as anaphylaxis or angioedema [see Warnings and Precautions (5.9) and Adverse Reactions (6)].

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, hypoglycemia and resistant bradycardias 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/INVOKAMET XR. In INVOKAMET/INVOKAMET XR-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin is dialyzable, with a clearance of up to 170 mL/min 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/INVOKAMET XR 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. Clinical recommendations based upon the patient’s renal function include [see Dosage and Administration (2.4), Clinical Pharmacology (12.3)].

- More initiating INVOKAMET/INVOKAMET XR, obtain an estimated glomerular filtration rate (eGFR).
- INVOKAMET/INVOKAMET XR is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m² [see Contraindications (4)].
- Obtain an eGFR at least annually in all patients taking INVOKAMET/INVOKAMET XR. 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/INVOKAMET XR with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation (e.g. cationic drugs) [see Drug Interactions (7)]. Therefore, consider more frequent monitoring of patients.

Age 65 or Greater: The risk of metformin-associated lactic acidosis increases with the patient’s age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients [see Use in Specific Populations (8.5)].

Radiological Studies with Contrast: Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop INVOKAMET/INVOKAMET XR at the time of, or prior to, an iodinated contrast imaging procedure in patients...
INVOKAMET® (canagliflozin and metformin hydrochloride) tablets

INVOKAMET® XR (canagliflozin and metformin hydrochloride) extended-release tablets

with an eGFR less than 60 mL/min/1.73 m²; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart INVOKAMET/INVOKAMET XR if renal function is stable. Surgery and Other Procedures: Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. INVOKAMET/INVOKAMET XR should be temporarily discontinued while patients have restricted food and fluid intake. Hypoxic States: Several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute respiratory failure, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause pre-reanatemia. When such events occur, discontinue INVOKAMET/INVOKAMET XR.

Excessive Alcohol Intake: Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving INVOKAMET/INVOKAMET XR.

Hepatic Impairment: Patients with hepatic impairment have developed metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of INVOKAMET/INVOKAMET XR in patients with clinical or laboratory evidence of hepatic disease.

5.2 Lower Limb Amputation

An increased risk of lower limb amputations associated with canagliflozin, a component of INVOKAMET/INVOKAMET XR, versus placebo was observed in CANVAS (5.5 vs 2.8 events per 1000 patient-years) and CANVAS-R (7.5 vs 4.2 events per 1000 patient-years), two randomized, placebo-controlled trials evaluating patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease. 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 3 and 4, 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/INVOKAMET XR, 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. Consider the importance of routine preventative foot care. Monitor patients receiving INVOKAMET/INVOKAMET XR for signs and symptoms of infection (including osteomyelitis), new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue INVOKAMET/INVOKAMET XR if these complications occur.

5.3 Volume Depletion

Canagliflozin can cause intravascular volume contraction which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine [see Adverse Reactions (6.1)]. There have been post-marketing reports of acute kidney injury which are likely related to volume depletion, some requiring hospitalizations and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including canagliflozin. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m²), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating INVOKAMET/INVOKAMET XR in patients with one or more of these characteristics, assess and correct volume status. Monitor for signs and symptoms of volume depletion after initiating therapy.

5.4 Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in clinical trials and postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including canagliflozin. In placebo-controlled trials of patients with type 1 diabetes, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. The risk of ketoacidosis may be greater with higher doses. Fatal cases of ketoacidosis have been reported in patients taking canagliflozin. INVOKAMET/INVOKAMET XR is not indicated for the treatment of patients with type 1 diabetes mellitus [see Indications and Usage (1)].

Patients treated with INVOKAMET/INVOKAMET XR 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 INVOKAMET/INVOKAMET XR may be present even if blood glucose is less than 250 mg/dL. Fatal cases of ketoacidosis have been reported in patients taking canagliflozin. INVOKAMET/INVOKAMET XR 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 the delay in 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 shivering. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake, surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating INVOKAMET/INVOKAMET XR consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.

For patients who undergo scheduled surgery, consider temporarily discontinuing INVOKAMET/INVOKAMET XR for at least 3 days prior to surgery [see Clinical Pharmacology (12.2, 12.3)]. Consider monitoring for ketoacidosis and temporarily discontinuing INVOKAMET/INVOKAMET XR in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting INVOKAMET/INVOKAMET XR.

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue INVOKAMET/INVOKAMET XR and seek medical attention immediately if signs and symptoms occur.

5.5 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 increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated [see Adverse Reactions (6.1)].

5.6 Hypoglycemia with Concomitant Use of Sulfonylurea or Insulin

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

5.7 Necrotizing Fasciitis of the Perineum (Fournier’s Gangrene)

Reports of necrotizing fasciitis of the perineum (Fournier’s gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in postmarketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including canagliflozin. Cases have been reported in both females and males. Some patients had multiple amputations, some involving both lower limbs. 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/INVOKAMET XR, 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. Consider the importance of routine preventative foot care. Monitor patients receiving INVOKAMET/INVOKAMET XR for signs and symptoms of infection (including osteomyelitis), new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue INVOKAMET/INVOKAMET XR if these complications occur.

5.8 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.

5.9 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 INVOKAMET/INVOKAMET XR; treat and monitor until signs and symptoms resolve [see Contraindications (4) and Adverse Reactions (6.1, 6.2)].

5.10 Bone Fracture

An increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed in patients using canagliflozin in the CANVAS trial [see Clinical Studies (14.2)]. Consider factors that contribute to fracture risk prior to initiating INVOKAMET/INVOKAMET XR.

5.11 Vitamin B12 Levels

In metformin HCl clinical trials of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, may be associated with anemia but appears to be gradually reversible with discontinuation of metformin HCl or vitamin B12 supplementation. Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. Measure hematologic parameters on an annual basis and vitamin B12 at
2- to 3-year intervals in patients on INVOKAMET/INVOKAMET XR and manage any abnormalities [see Adverse Reactions (6.1)].

6 ADVERSE REACTIONS

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

- Lactic Acidosis [see Boxed Warning and Warnings and Precautions (5.1, 5.3)]
- Lower Limb Amputation [see Warnings and Precautions (5.2)]
- Volume Depletion [see Warnings and Precautions (5.3)]
- Ketaocidosis [see Warnings and Precautions (5.4)]
- Urosepsis and Pyelonephritis [see Warnings and Precautions (5.5)]
- Hypoglycemia with Concomitant Use of Sulfonylurea or Insulin [see Warnings and Precautions (5.6)]
- Necrotizing Fasciitis of the Perineum (Fournier’s gangrene) [see Warnings and Precautions (5.7)]
- Genital Myotic Infections [see Warnings and Precautions (5.8)]
- Hypersensitivity Reactions [see Warnings and Precautions (5.9)]
- Bone Fracture [see Warnings and Precautions (5.10)]
- Vitamin B12 Deficiency [see Warnings and Precautions (5.11)]

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 for Glycemic Control

Canagliflozin

The data in Table 2 is derived from four 26-week placebo-controlled trials where canagliflozin was used as monotherapy in one trial and as add-on therapy in three trials. These data reflect exposure of 1,867 patients to canagliflozin and a mean duration of exposure to canagliflozin of 24 weeks with 1,275 patients exposed to a combination of canagliflozin and metformin HCl. Patients received canagliflozin 100 mg (N=833), canagliflozin 300 mg (N=834) or placebo (N=646) once daily. The mean daily dose of metformin HCl was 2,138 mg (SD 337.3) for the 1,275 patients in the three placebo-controlled metformin HCl add-on trials. The mean age of the population was 56 years and 2% were older than 75 years of age. Fifty percent 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 (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 (50%) of the population was male and 72% were Caucasian, 12% were Asian, and 5% were Black or African American.

Table 2 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 2 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</th>
<th>Canagliflozin 100 mg</th>
<th>Canagliflozin 300 mg</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>2.8%</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 myotic infections</td>
<td>2.6%</td>
<td>10.6%</td>
<td>11.6%</td>
</tr>
<tr>
<td>Vulvovaginal pruriitus</td>
<td>0.0%</td>
<td>1.6%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Male genital myotic 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 HCl, metformin HCl and sulfonylurea, or metformin HCl and pioglitazone.
* Female genital myotic infections include the following adverse reactions: Vulvovaginal candidiasis, Vulvovaginal myotic infection, Vulvovaginitis, Vaginal infection, Vulvitis, and Genital infection fungal.
* Urinary tract infections include the following adverse reactions: Urinary tract infection, Cystitis, Kidney infection, and Urosepsis.
* Increased urination includes the following adverse reactions: Polyuria, Polydipsia, Urosepsis, and Polydipsia.
* Male genital myotic infections include the following adverse reactions: Balanitis, Balanoposthitis, Balanitis candida, and Genital infection fungal.
* Thirst includes the following adverse reactions: Thirst, Dry mouth, and Polydipsia.

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

INVOKAMET® (canagliflozin and metformin hydrochloride) tablets
INVOKAMET® XR (canagliflozin and metformin hydrochloride) extended-release tablets

Table 3: CANVAS Amputations

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Canagliflozin 100 mg</th>
<th>Canagliflozin 300 mg</th>
<th>Canagliflozin (Pooled)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=1441</td>
<td>N=1445</td>
<td>N=1441</td>
<td>N=2886</td>
</tr>
<tr>
<td>Patients with an amputation, n (%)</td>
<td>22 (1.5)</td>
<td>50 (3.5)</td>
<td>45 (3.1)</td>
</tr>
<tr>
<td>Total amputations</td>
<td>33</td>
<td>83</td>
<td>79</td>
</tr>
<tr>
<td>Amputation incidence rate (per 1000 patient-years)</td>
<td>2.8</td>
<td>6.2</td>
<td>5.5</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>
</tr>
</tbody>
</table>

Hazard Ratio (95% CI) -- 2.24
INVOKAMET® (canagliflozin and metformin hydrochloride) tablets
INVOKAMET® XR (canagliflozin and metformin hydrochloride) extended-release tablets

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 4: CANVAS-R Amputations

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Canagliflozin 100 mg (with up-titration to 300 mg)</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.

Renal Cell Carcinoma
In the CANVAS trial (mean duration of follow-up of 5.7 years) [see Clinical Studies (14.2)], the incidence of renal cell carcinoma was 0.15% (2/1331) and 0.29% (8/2716) for placebo and canagliflozin, respectively, excluding patients with less than 6 months of follow-up, less than 90 days of treatment, or a history of renal cell carcinoma. A causal relationship to canagliflozin could not be established due to the limited number of cases.

Volume Depletion-Related Adverse Reactions
Canagliflozin results in an osmotic diuresis, which may lead to reductions in intravascular volume. In clinical trials for glycemic control, 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 in these trials 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 5) [see Use in Specific Populations (9.5 and 8.6)].

Table 5: Patients With at Least One Volume Depletion-Related Adverse Reaction (Pooled Results from 8 Clinical Trials for Glycemic Control)

<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
‡ 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
§ Includes patients with at least one hypoglycemic event

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.

Genital Mycotic Infections
In the pool of four placebo-controlled clinical trials for glycemic control, female genital mycotic infections (e.g., vulvovaginal mycotic infection, vulvovaginitis, candidiasis, and vulvovaginitis) occurred in 2.8%, 10.6%, and 11.8% 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 (22% on canagliflozin versus none on placebo), and require treatment with oral or topical antifungal agents and anti-microbial agents than people 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 randomized trials evaluating glycemic control, phimosis was reported in 0.3% of uncircumcised male patients treated with canagliflozin and 0.2% required circumcision to treat the phimosis.

Hypoglycemia
In canagliflozin glycemic control 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 of glycemic control [see Clinical Studies (14.1)], episodes of hypoglycemia occurred at a higher rate when canagliflozin was co-administered with insulin or sulfonylureas (Table 6).

Table 6: Incidence of Hypoglycemia* in Randomized Clinical Studies of Glycemic Control

<table>
<thead>
<tr>
<th></th>
<th>Placebo (26 weeks)</th>
<th>Canagliflozin (N=192)</th>
<th>Canagliflozin (N=195)</th>
<th>Canagliflozin (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>
<td></td>
</tr>
<tr>
<td>In Combination with Metformin HCI (26 weeks)</td>
<td>Placebo + Metformin HCI (N=183)</td>
<td>Canagliflozin 100 mg + Metformin HCI (N=368)</td>
<td>Canagliflozin 300 mg + Metformin HCI (N=367)</td>
<td></td>
</tr>
<tr>
<td>Overall [N (%)]</td>
<td>3 (1.6)</td>
<td>16 (4.3)</td>
<td>17 (4.6)</td>
<td></td>
</tr>
<tr>
<td>Severe [N (%)]†</td>
<td>0 (0.0)</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td></td>
</tr>
<tr>
<td>In Combination with Metformin HCI 18 weeks§</td>
<td>Placebo (N=93)</td>
<td>Canagliflozin 100 mg (N=93)</td>
<td>Canagliflozin 300 mg (N=93)</td>
<td></td>
</tr>
<tr>
<td>Overall [N (%)]</td>
<td>3 (3.2)</td>
<td>4 (4.3)</td>
<td>3 (3.2)</td>
<td></td>
</tr>
<tr>
<td>In Combination with Metformin HCI + Sulfonylurea (26 weeks)</td>
<td>Placebo + Metformin HCI + Sulfonylurea (N=156)</td>
<td>Canagliflozin 100 mg + Metformin HCI + Sulfonylurea (N=157)</td>
<td>Canagliflozin 300 mg + Metformin HCI + Sulfonylurea (N=156)</td>
<td></td>
</tr>
<tr>
<td>Overall [N (%)]</td>
<td>24 (15.4)</td>
<td>43 (27.4)</td>
<td>47 (30.1)</td>
<td></td>
</tr>
<tr>
<td>Severe [N (%)]†</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>In Combination with Metformin HCI + Pioglitazone (26 weeks)</td>
<td>Placebo + Metformin HCI + Pioglitazone (N=115)</td>
<td>Canagliflozin 100 mg + Metformin HCI + Pioglitazone (N=113)</td>
<td>Canagliflozin 300 mg + Metformin HCI + Pioglitazone (N=114)</td>
<td></td>
</tr>
<tr>
<td>Overall [N (%)]</td>
<td>3 (2.6)</td>
<td>3 (2.7)</td>
<td>6 (5.3)</td>
<td></td>
</tr>
<tr>
<td>In Combination with Insulin 18 weeks§</td>
<td>Placebo (N=565)</td>
<td>Canagliflozin 100 mg (N=566)</td>
<td>Canagliflozin 300 mg (N=587)</td>
<td></td>
</tr>
<tr>
<td>Overall [N (%)]</td>
<td>208 (38.6)</td>
<td>279 (49.3)</td>
<td>285 (48.6)</td>
<td></td>
</tr>
<tr>
<td>Severe [N (%)]†</td>
<td>14 (2.5)</td>
<td>10 (1.8)</td>
<td>16 (2.7)</td>
<td></td>
</tr>
<tr>
<td>In Combination with Insulin and Metformin HCI (18 weeks)§</td>
<td>Placebo (N=145)</td>
<td>Canagliflozin 100 mg (N=139)</td>
<td>Canagliflozin 300 mg (N=140)</td>
<td></td>
</tr>
<tr>
<td>Overall [N (%)]</td>
<td>66 (45.5)</td>
<td>58 (41.7)</td>
<td>57 (40.7)</td>
<td></td>
</tr>
<tr>
<td>Severe [N (%)]†</td>
<td>4 (2.8)</td>
<td>1 (0.7)</td>
<td>3 (2.0)</td>
<td></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 HCI)
§ Subgroup of patients (N=287) from insulin substudy on canagliflozin in combination with metformin HCI and insulin (with or without other antglycemic agents)

Bone Fracture
In the CANVAS trial [see Clinical Studies (14.2)], the incidence rates of all adjudicated bone fracture were 1.09, 1.59, and 1.79 events per 100 patient-years of follow-up to placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. The fracture imbalance was observed within the first 26 weeks of therapy and remained through the end of the trial. Fractures were more likely to be low trauma (e.g., fall from no more than standing height), and affect the distal portion of upper and lower extremities.
Long-term treatment with metformin HCl has been associated with a decrease in abdominal discomfort, and headache.

Diabetes Control and Complications Trial (12.1)
The acute effect on eGFR reverses after treatment discontinuation suggesting acute hemodynamic changes may play a role in the renal function changes observed with canagliflozin.

Clinical Pharmacology (12.3)
Necrotizing Fasciitis of the Perineum (Fournier’s gangrene)
Anaphylaxis, Angioedema

Additional adverse reactions have been identified during post-approval use of INVOKAMET® (canagliflozin and metformin hydrochloride) tablets.

7 DRUG INTERACTIONS
7.1 Drug Interactions with Metformin

Table 7: Clinically Significant Drug Interactions with Metformin

<table>
<thead>
<tr>
<th>Carbonic Anhydride Inhibitors</th>
<th>Clinical Impact:</th>
<th>Intervention:</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbonic anhydrase inhibitors frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with INVOKAMET® XR may increase the risk for lactic acidosis.</td>
<td>Consider more frequent monitoring of these patients.</td>
<td>Topiramate or other carbonic anhydride inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide)</td>
<td></td>
</tr>
</tbody>
</table>

Alcohol

Clinical Impact:

Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 (OCT2) / multidrug and toxin extrusion [MATE] inhibitors) could increase systemic exposure to metformin and may increase the risk for lactic acidosis [see Clinical Pharmacology (12.3)].

Intervention:

Consider the benefits and risks of concomitant use.

Examples:

Ranolazine, vandetanib, dolasetravin, and cimetidine

Insulin Secretagogues or Insulin

Clinical Impact:

Coadministration of INVOKAMET® with an insulin secretagogue (e.g., sulfonylurea) or insulin may increase the risk of hypoglycemia. These patients may experience a faster onset of hypoglycemia.

Intervention:

Patients receiving an insulin secretagogue or insulin may require lower doses of the insulin secretagogue or insulin.

Table 8: Clinically Significant Drug Interactions with Canagliflozin

<table>
<thead>
<tr>
<th>UGT Enzyme Inducers</th>
<th>Clinical Impact:</th>
<th>Intervention:</th>
<th>Examples</th>
</tr>
</thead>
</table>
| May reduce the efficacy of INVOKAMET® XR. | For patients with eGFR 60 mL/min/1.73 m² or greater, if an inducer of UGTs is co-administered with INVOKAMET® XR, increase the total daily dose of canagliflozin to 200 mg in patients currently tolerating INVOKAMET® XR with a total daily dose of canagliflozin 100 mg. The total daily dose of canagliflozin may be increased to 300 mg in patients currently tolerating canagliflozin 200 mg and who require additional glycemic control.

Examples:

Rifampin, phenytoin, phenobarbital, ritonavir

Digoxin

Clinical Impact:

Canagliflozin increased digoxin exposure [see Clinical Pharmacology (12.3)].

Intervention:

Monitor patients taking INVOKAMET® XR with concomitant digoxin for a need to adjust dose of digoxin.

7.2 Drug Interactions with Canagliflozin
Table 8: Clinically Significant Drug Interactions with Canagliflozin (continued)

<table>
<thead>
<tr>
<th>Drug/Laboratory Test Interference</th>
<th>Positive Urine Glucose Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Interference with 1,5-anhydroglucitol (1,5-AG) Assay</td>
</tr>
<tr>
<td>Intervention:</td>
<td>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.</td>
</tr>
</tbody>
</table>

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data showing adverse renal effects from canagliflozin, INVOKEMET/INVOKAMET XR is not recommended during the second and third trimesters of pregnancy.

Limited data with INVOKEMET/INVOKAMET XR or canagliflozin in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. Published studies with metformin HCl use during pregnancy have not reported a clear association with metformin HCl and major birth defect or miscarriage risk (see Data). There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy (see Clinical Considerations). In 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 HCl was administered to pregnant Sprague Dawley rats and rabbits during the period of organogenesis at doses up to 2- and 6-times, respectively, a 2000 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 a 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, 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 HCl and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin HCl 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.

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 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.

8.2 Lactation

Risk Summary

There is no information regarding the presence of INVOKEMET/INVOKAMET XR 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 HCl on the breastfed infant and no available information on the effects of metformin HCl 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 lactational 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 INVOKEMET/INVOKAMET XR is not recommended while breastfeeding.

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, the studies were not designed to definitely establish the risk of use of metformin HCl during lactation because of small sample size and limited adverse event data collected in infants. 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 HCl may result in ovulation in some anovulatory women.

8.4 Pediatric Use

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

8.5 Geriatric Use

INVOKEMET and INVOKEMET XR

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 INVOKEMET/INVOKAMET XR in the elderly and then adjust dose based on renal function [see Dosage and Administration (2.4) and Warnings and Precautions (5.1, 5.3)].

Canagliflozin

In 13 clinical trials of canagliflozin, 2,294 patients 65 years and older, and 351 patients 75 years and older were exposed to canagliflozin. Of these patients, 1,534 patients 65 years and older and 196 patients 75 years and older were exposed to the combination of canagliflozin and metformin HCl (see Clinical Studies (14)). Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with canagliflozin (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300 mg daily dose, compared to younger patients; a more prominent 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 (0.7% 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 HCl

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

INVOKAMET® (canagliflozin and metformin hydrochloride) tablets
INVOKAMET® XR (canagliflozin and metformin hydrochloride) extended-release tablets

Metformin HCl

Metformin HCl 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 HCl

No adverse developmental effects were observed when canagliflozin and metformin HCl 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 HCl based on AUC.
The efficacy and safety of canagliflozin for glycemic control were evaluated in a trial that included patients with moderate renal impairment (eGFR 30 to less than 50 mL/min/1.73 m²). These patients had less overall glycemic efficacy, and patients treated with canagliflozin 300 mg per day had increases in serum potassium, which were transient and similar by the end of study. Patients with renal impairment using canagliflozin for glycemic control may also be more likely to experience hypotension and may be at higher risk for acute kidney injury [see Warnings and Precautions (5.3)].

Efficacy and safety studies with canagliflozin did not enroll patients with ESKD on dialysis or patients with an eGFR less than 30 mL/min/1.73 m². Canagliflozin is contraindicated in patients with ESKD on dialysis [see Contraindications (4) and Clinical Pharmacology (12.1)].

Metformin HCl
Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. INVOKAMET INVOKAMET XR is contraindicated in severe renal impairment (eGFR less than 30 mL/min/1.73 m²) or in patients on dialysis [see Dosage and Administration (2.4), Contraindications (4), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)].

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

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

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

11 DESCRIPTION
INVOKAMET INVOKAMET XR contain canagliflozin and metformin HCl.

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 (1R)-1-[[1S]-(2-phenylacetyl)-2-thienyl]-2-thienyl[4]-methylbenzene-1-carboxamide and its molecular formula and weight are C$_{25}$H$_{25}$F$_{3}$O$_{5}$S+1/2 H$_{2}$O and 452.53, respectively. The structural formula for canagliflozin is:

![Structural formula of canagliflozin](image)

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

Metformin HCl
Metformin HCl is a biguanide chemically known as 1,1-Dimethylbiguanide hydrochloride and its molecular formula and weight are C$_{6}$H$_{11}$N$_{5}$• HCl and 165.62, respectively. The structural formula for metformin HCl is:

![Structural formula of metformin HCl](image)
INVOKAMET® (canagliflozin and metformin hydrochloride) tablets
INVOKAMET® XR (canagliflozin and metformin hydrochloride) extended-release tablets

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

12.3 Pharmacokinetics

INVOKAMET 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.

INVOKAMET XR After administration of INVOKAMET XR tablets with a high-fat breakfast, the peak (C_max) and total (AUC) exposure of canagliflozin were not altered relative to dosing in the fasted state. However, the AUC of metformin increased by approximately 61% and C_max increased by approximately 13%.

Canagliflozin The pharmacokinetics of canagliflozin is essentially similar in healthy subjects and patients with type 2 diabetes. Following single-dose oral administration of 100 mg and 300 mg of canagliflozin, peak plasma concentrations (median T_max) of canagliflozin occurs within 1 to 2 hours post-dose. Plasma C_max and AUC of canagliflozin increased in a dose-proportional manner from 50 mg to 300 mg. The apparent terminal half-life (t_{1/2}) was 10.8 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 HCl 500 mg tablet given under fasting conditions is approximately 50% to 60%. Trials using single oral doses of metformin HCl 500 mg 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.

Following a single oral dose of 1,000 mg metformin HCl extended-release tablets (two 500 mg tablets) after a meal, the time to reach maximum plasma metformin concentration (T_max) is achieved at approximately 7-8 hours. In both single and multiple-dose trials in healthy subjects, once daily 1,000 mg (two 500 mg tablets) dosing results in up to 35% higher C_max, of metformin relative to the immediate-release given as 500 mg twice daily without any change in overall systemic exposure, as measured by AUC.

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 HCl 850 mg immediate-release tablets averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonfonylures, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time.

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

Metformin Intravenous single-dose trials 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 [14C] canagliflozin dose to healthy subjects, 41.5%, 7.0%, and 3.2% of the administered radioactive dose was recovered in feces as canagliflozin, a hydroxylated metabolite, and an O-glucuronide metabolite, respectively. Enterohepatic circulation of canagliflozin was negligible.

Approximately 33% of the administered radioactive dose was excreted in urine, mainly as O-glucuronide metabolites (30.5%). Less than 1% of the dose was excreted as unchanged canagliflozin in urine. Renal clearance of canagliflozin 100 mg and 300 mg doses ranged from 1.30 to 1.95 mL/min.

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

Metformin Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination.

Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Specific Populations
Trials characterizing the pharmacokinetics of canagliflozin and metformin after administration of INVOKAMET/INVOKAMET XR 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 trial evaluated the pharmacokinetics of canagliflozin 200 mg in subjects with varying degrees of renal impairment (classified using the MDRD-eGFR formula) compared to healthy subjects.

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

Canagliflozin was negligibly removed by hemodialysis.

Metformin In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased [see Contraindications (4) and Warnings and Precautions (5.1)].

Following a single-dose administration of metformin HCl extended-release tablets 500 mg in patients with mild and moderate renal failure (based on measured creatinine clearance), the oral and renal clearance of metformin were decreased by 33% and 50% and 16% and 53%, respectively [see Warnings and Precautions (5.3)]. Metformin peak and systemic exposure was 27% and 61% greater, respectively, in mild renal impaired and 74% and 2.36-fold greater in moderate renal impaired patients as compared to healthy subjects [see Contraindications (4) and Warnings and Precautions (5.1)].

Hepatic Impairment
Canagliflozin Relative to subjects with normal hepatic function, the geometric mean ratios for C_max and AUC of canagliflozin were 107% and 110%, respectively, in subjects (N=3; eGFR greater than or equal to 90 mL/min/1.73 m^2), plasma 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 trials of metformin HCl tablets have been conducted in patients with hepatic insufficiency [see Warnings and Precautions (5.1)].
INVOKAMET® (canagliflozin and metformin hydrochloride) tablets
INVOKAMET® XR (canagliflozin and metformin hydrochloride) extended-release tablets

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

Metformin

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analyzed according to gender. No trials of metformin pharmacokinetic parameters according to race have been performed.

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 trials of metformin HCl tablets in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and Cmax 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 [see Warnings and Precautions (5.1, 5.3) and Use in Specific Populations (8.5)].

Drug-Drug Interactions

INVOKAMET® and INVOKAMET® XR

Pharmacokinetic drug interaction trials with INVOKAMET/INVOKAMET XR have not been performed; however, such trials have been conducted with the individual components canagliflozin and metformin HCl.

Co-administration of multiple doses of canagliflozin (300 mg) and metformin HCl (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, CYP2C9, and CYP3A4 based on in vitro studies with human hepatic microsomes. Canagliflozin is a weak inhibitor of P-gp.

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

In Vivo Assessment of Drug Interactions

Table 9: 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)</th>
<th>No Effect = 1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AUC† (90% CI)</td>
<td>Cmax (90% CI)</td>
<td></td>
</tr>
<tr>
<td>See Drug Interactions (7.2) for the clinical relevance of the following:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>600 mg QD for 8 days</td>
<td>300 mg</td>
<td>0.49 (0.44, 0.54)</td>
<td>0.72 (0.61, 0.84)</td>
</tr>
<tr>
<td>No dose adjustments of canagliflozin required for the following:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>400 mg</td>
<td>300 mg QD for 8 days</td>
<td>1.23 (1.18, 1.27)</td>
<td>1.01 (0.91, 1.11)</td>
</tr>
<tr>
<td>Ethinyl estradiol and levonorgestrel</td>
<td>0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel</td>
<td>200 mg QD for 6 days</td>
<td>0.91 (0.88, 0.94)</td>
<td>0.92 (0.84, 0.99)</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>25 mg QD for 35 days</td>
<td>300 mg QD for 7 days</td>
<td>1.12 (1.08, 1.17)</td>
<td>1.15 (1.06, 1.25)</td>
</tr>
<tr>
<td>Metformin HCl</td>
<td>2,000 mg</td>
<td>300 mg QD for 8 days</td>
<td>1.10 (1.05, 1.15)</td>
<td>1.05 (0.96, 1.16)</td>
</tr>
<tr>
<td>Probenecid</td>
<td>500 mg BID for 3 days</td>
<td>300 mg QD for 17 days</td>
<td>1.21 (1.16, 1.25)</td>
<td>1.13 (1.00, 1.28)</td>
</tr>
</tbody>
</table>

Table 10: 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)</th>
<th>No Effect = 1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AUC† (90% CI)</td>
<td>Cmax (90% CI)</td>
<td></td>
</tr>
<tr>
<td>See Drug Interactions (7.2) for the clinical relevance of the following:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>Digoxin</td>
<td></td>
</tr>
<tr>
<td>No dose adjustments of co-administered drug required for the following:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>1,000 mg</td>
<td>300 mg BID for 25 days</td>
<td>Acetaminophen</td>
<td></td>
</tr>
<tr>
<td>Ethinyl estradiol and levonorgestrel</td>
<td>0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel</td>
<td>200 mg QD for 6 days</td>
<td>Ethinyl estradiol</td>
<td>1.07 (0.99, 1.15)</td>
</tr>
<tr>
<td>Glyburide</td>
<td>1.25 mg</td>
<td>200 mg QD for 6 days</td>
<td>Glyburide</td>
<td>1.02 (0.98, 1.07)</td>
</tr>
<tr>
<td>Metformin HCl</td>
<td>2,000 mg</td>
<td>300 mg QD for 8 days</td>
<td>Metformin</td>
<td>1.20 (1.08, 1.34)</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>40 mg</td>
<td>300 mg QD for 7 days</td>
<td>Simvastatin</td>
<td>1.12 (0.94, 1.33)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>30 mg</td>
<td>300 mg QD for 12 days</td>
<td>(R)-warfarin</td>
<td>1.01 (0.96, 1.06)</td>
</tr>
<tr>
<td>INR</td>
<td></td>
<td></td>
<td>(S)-warfarin</td>
<td>1.09 (0.90, 1.33)</td>
</tr>
</tbody>
</table>

* Single dose unless otherwise noted
† AUCmean for drugs given as a single dose and AUC500m for drugs given as multiple doses QD = once daily; BID = twice daily
‡ AUCmean for drugs given as a single dose and AUCmean for drugs given as multiple doses QD = once daily; BID = twice daily
§ AUCmean for drugs given as a single dose and AUCmean for drugs given as multiple doses QD = once daily; BID = twice daily
¶ AUCmean for drugs given as a single dose and AUCmean for drugs given as multiple doses QD = once daily; BID = twice daily
# Steady state AUC0-12h.

Table 11: 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 HCl</th>
<th>Geometric Mean Ratio (Ratio With/Without Co-Administered Drug)</th>
<th>No Effect = 1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AUC† (90% CI)</td>
<td>Cmax (90% CI)</td>
<td></td>
</tr>
<tr>
<td>No dose adjustments of co-administered drug required for the following:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glyburide</td>
<td>5 mg</td>
<td>500 mg</td>
<td>Glyburide</td>
<td>0.98 (0.95, 1.01)</td>
</tr>
<tr>
<td>Furosemide</td>
<td>40 mg</td>
<td>850 mg</td>
<td>Furosemide</td>
<td>1.09 (1.06, 1.13)</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>10 mg</td>
<td>850 mg</td>
<td>Nifedipine</td>
<td>1.16 (1.13, 1.20)</td>
</tr>
<tr>
<td>Prasugrenol</td>
<td>40 mg</td>
<td>850 mg</td>
<td>Prasugrenol</td>
<td>0.99 (0.95, 1.03)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>400 mg</td>
<td>850 mg</td>
<td>Ibuprofen</td>
<td>1.05 (1.02, 1.08)</td>
</tr>
<tr>
<td>Drugs that are eliminated by renal tubular secretion increase the accumulation of metformin [see Warnings and Precautions (5) and Drug Interactions (7)]:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cimicidine</td>
<td>400 mg</td>
<td>850 mg</td>
<td>Cimicidine</td>
<td>1.10 (1.08, 1.13)</td>
</tr>
<tr>
<td>Carbonyl anhydrase inhibitors may cause metabolic acidosis [see Warnings and Precautions (5) and Drug Interactions (7)]:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>100 mg</td>
<td>500 mg</td>
<td>Topiramate</td>
<td>1.25 (1.22, 1.29)</td>
</tr>
</tbody>
</table>

* Single dose unless otherwise noted
† AUCmean for drugs given as a single dose and AUCmean for drugs given as multiple doses
‡ AUCmean for drugs given as a single dose and AUCmean for drugs given as multiple doses
§ AUCmean for drugs given as a single dose and AUCmean for drugs given as multiple doses
¶ AUCmean for drugs given as a single dose and AUCmean for drugs given as multiple doses
# Steady state AUC0-12h.
Table 12: Effect of Metformin HCl 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 HCl</th>
<th>Geometric Mean Ratio (Ratio With/Without Co-Administered Drug)</th>
<th>No Effect = 1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>AUC†</td>
<td>Cmax†</td>
</tr>
<tr>
<td>Glyburide</td>
<td>5 mg</td>
<td>500 mg</td>
<td>0.78†</td>
<td>0.63†</td>
</tr>
<tr>
<td>Furosemide</td>
<td>40 mg</td>
<td>850 mg</td>
<td>0.87†</td>
<td>0.89†</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>10 mg</td>
<td>850 mg</td>
<td>1.10†</td>
<td>1.08</td>
</tr>
<tr>
<td>Propranolol</td>
<td>40 mg</td>
<td>850 mg</td>
<td>1.01†</td>
<td>0.94</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>400 mg</td>
<td>850 mg</td>
<td>0.97†</td>
<td>1.01†</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>400 mg</td>
<td>850 mg</td>
<td>0.95†</td>
<td>1.01†</td>
</tr>
</tbody>
</table>

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

CVIKAMET and CVIKAMET XR

No animal studies have been conducted with the combined products in CVIKAMET/CVKAMET XR to evaluate carcinogenesis, mutagenesis, or impairment of fertility. The following data are based on findings in studies with canagliflozin and metformin HCl 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 trial, LH did not increase in males treated with canagliflozin.

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

Mutagenesis

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

Metformin HCl

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 HCl was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin HCl in male rats. There was, however, an increased incidence of benign uterine polyps in female rats treated with 900 mg/kg/day.

Mutagenesis

There was no evidence of a mutagenic potential of metformin HCl in the following in vitro tests: Ames test (Salmonella 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 HCl 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

14.1 Glycemic Control Trials in Adults with Type 2 Diabetes Mellitus

Canagliflozin has been studied in combination with metformin HCl alone, metformin HCl and sulfonylurea, metformin HCl and sitagliptin, metformin HCl and a thiazolidinedione (i.e., pioglitazone), and metformin HCl 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 HCl and sulfonylurea, and a sulfonylurea (gliptiude), both as add-on combination therapy with metformin HCl.

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

Canagliflozin as Initial Combination Therapy with Metformin HCl

A total of 1,188 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 trial to evaluate the efficacy and safety of initial therapy with canagliflozin in combination with metformin HCl XR. The median age was 56 years, 48% of patients were men, and the mean baseline eGFR was 87.6 mL/min/1.73 m². The median duration of diabetes was 1.6 years, and 72% of patients were treatment naive. After completing a 2-week single-blind placebo run-in period, patients were randomly assigned for a double-blind treatment period of 26 weeks to 1 of 5 treatment groups (Table 13). The metformin HCl XR dose was initiated at 500 mg/day for the first week of treatment and then increased to 1,000 mg/day. Metformin HCl XR or matching placebo was up-titrated every 2-3 weeks during the next 8 weeks of treatment to a maximum daily dose of 1,500 to 2,000 mg/day, as tolerated; about 90% of patients reached 2,000 mg/day.

At the end of treatment, canagliflozin 100 mg and canagliflozin 300 mg in combination with metformin HCl XR resulted in a statistically significant greater improvement in HbA1C compared to their respective canagliflozin doses (100 mg and 300 mg) alone or metformin HCl XR alone.

Table 13: Results from 26-Week Active-Controlled Clinical Study of Canagliflozin Alone or Canagliflozin as Initial Combination Therapy with Metformin HCl XR*

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Metformin HCl XR (N=237)</th>
<th>Canagliflozin 100 mg + Metformin HCl XR (N=237)</th>
<th>Canagliflozin 300 mg + Metformin HCl XR (N=237)</th>
<th>Canagliflozin 100 mg (N=237)</th>
<th>Canagliflozin 300 mg (N=238)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1C (%)</td>
<td>8.81</td>
<td>8.78</td>
<td>8.77</td>
<td>8.83</td>
<td>8.90</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-1.30</td>
<td>-1.37</td>
<td>-1.42</td>
<td>-1.77</td>
<td>-1.78</td>
</tr>
<tr>
<td>Difference from canagliflozin 100 mg (adjusted mean) (95% CI)</td>
<td>-0.49† (-0.59, -0.21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference from canagliflozin 300 mg (adjusted mean) (95% CI)</td>
<td>-0.36† (-0.56, -0.17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference from metformin HCl XR (adjusted mean) (95% CI)</td>
<td>-0.48† (-0.67, -0.28)</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
¶¶ Adjusted p<0.01
§§§ Adjusted p<0.05
¶¶¶ Adjusted p<0.01
The mean age was 56 years, 52% of patients were men, and the mean baseline eGFR was 80 mL/min/1.73 m². Patients tolerating maximally required metformin HCl dose (N=920) were randomized after completing a 2-week, single-blind, placebo run-in period. The 2-week run-in period, patients were randomized to canagliflozin 100 mg, canagliflozin 300 mg, or glimepiride (titration allowed throughout the 52-week trial to 6 or 8 mg). Administered once daily as add-on therapy to metformin HCl.

As shown in Table 15 and Figure 1, at the end of treatment, canagliflozin 100 mg provided similar reductions in HbA1C from baseline compared to glimepiride when added to metformin HCl therapy. Canagliflozin 300 mg provided a greater reduction from baseline in HbA1C compared to glimepiride, and the relative treatment difference was -0.12% (95% CI: -0.22, -0.02). As shown in Table 15, treatment with canagliflozin 100 mg and 300 mg daily provided greater improvements in percent body weight change, relative to glimepiride.

Table 15: Results from 52-Week Clinical Study Comparing Canagliflozin to Glimepiride in Combination with Metformin HCl*

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

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

Figure 1: Mean HbA1C Change at Each Time Point (Completers) and at Week 52 Using Last Observation Carried Forward (mITT Population)
Canagliflozin as Add-on Combination Therapy with Metformin HCl and Sitagliptin

A total of 217 patients with type 2 diabetes inadequately controlled on the combination of metformin HCl (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 trial to evaluate the efficacy and safety of canagliflozin in combination with metformin HCl 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 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 HCl 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 glycemic control (fasting finger stick 100 mg/dL or greater at least twice within 2 weeks) were up-titrated to canagliflozin 300 mg. While up-titratin 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 HCl and sitagliptin (see Table 16).

Table 16: Results from 26-Week Placebo-Controlled Clinical Study of Canagliflozin in Combination with Metformin HCl and Sitagliptin

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Placebo + Metformin HCl and Sitagliptin (N=108*)</th>
<th>Canagliflozin + Metformin HCl and Sitagliptin (N=109*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1C (%)</td>
<td>Baseline (mean) 8.40</td>
<td>8.50</td>
</tr>
<tr>
<td></td>
<td>Change from baseline (adjusted mean) -0.03</td>
<td>-0.83</td>
</tr>
<tr>
<td></td>
<td>Difference from placebo (adjusted mean) (95% CI)</td>
<td>(-0.81, -0.51)</td>
</tr>
<tr>
<td>Percent of patients achieving HbA1C &lt; 7%</td>
<td>9</td>
<td>28</td>
</tr>
<tr>
<td>Fasting Plasma Glucose (mg/dL)</td>
<td>Baseline (mean) 180</td>
<td>185</td>
</tr>
<tr>
<td></td>
<td>Change from baseline (adjusted mean) -3</td>
<td>-28</td>
</tr>
<tr>
<td></td>
<td>Difference from placebo (adjusted mean) (95% CI)</td>
<td>(-25, -11)</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%.

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 HCl and sitagliptin. 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 HCl and sitagliptin (see Table 17).

Table 17: Results from 26-Week Placebo-Controlled Clinical Study of Canagliflozin in Combination with Metformin HCl and Sitagliptin

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Placebo + Metformin HCl and Sitagliptin (N=156)</th>
<th>Canagliflozin 100 mg + Metformin HCl and Sitagliptin (N=157)</th>
<th>Canagliflozin 300 mg + Metformin HCl and Sitagliptin (N=156)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1C (%)</td>
<td>Baseline (mean) 8.12</td>
<td>8.13</td>
<td>8.13</td>
</tr>
<tr>
<td></td>
<td>Change from baseline (adjusted mean) -0.13</td>
<td>-0.85</td>
<td>-1.06</td>
</tr>
<tr>
<td></td>
<td>Difference from placebo (adjusted mean) (95% CI)</td>
<td>-0.71† (-0.90, -0.52)</td>
<td>-0.92‡ (-1.11, -0.73)</td>
</tr>
<tr>
<td>Percent of patients achieving HbA1C &lt; 7%</td>
<td>18</td>
<td>433†</td>
<td>57†</td>
</tr>
<tr>
<td>Fasting Plasma Glucose (mg/dL)</td>
<td>Baseline (mean) 170</td>
<td>173</td>
<td>168</td>
</tr>
<tr>
<td></td>
<td>Change from baseline (adjusted mean) 4</td>
<td>-18</td>
<td>-31</td>
</tr>
<tr>
<td></td>
<td>Difference from placebo (adjusted mean) (95% CI)</td>
<td>-22‡ (-31, -13)</td>
<td>-35† (-44, -25)</td>
</tr>
<tr>
<td>Body Weight</td>
<td>Baseline (mean) in kg 90.8</td>
<td>93.5</td>
<td>93.5</td>
</tr>
<tr>
<td></td>
<td>% change from baseline (adjusted mean) -0.7</td>
<td>-2.1</td>
<td>-2.6</td>
</tr>
<tr>
<td></td>
<td>Difference from placebo (adjusted mean) (95% CI)</td>
<td>-1.4‡ (-2.1, -0.7)</td>
<td>-2.0‡ (-2.7, -1.3)</td>
</tr>
</tbody>
</table>

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

Canagliflozin Compared to Sitagliptin, Both as Add-on Combination Therapy with Metformin HCl and sitagliptin

A total of 755 patients with type 2 diabetes inadequately controlled on the combination of metformin HCl (greater than or equal to 2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated) and sitagliptin (near-maximal or maximal effective dose) participated in a 52-week, double-blind, active-controlled trial to compare the efficacy and safety of canagliflozin 300 mg versus sitagliptin 100 mg in combination with metformin HCl and sitagliptin. The mean age was 57 years, 56% of patients were men, and the mean baseline eGFR was 86 mL/min/1.73 m². Patients already on protocol-specified doses of metformin HCl and sitagliptin (N=716) entered a 2-week single-blind, placebo run-in period. Other patients (N=39) were required to be on a stable protocol-specified dose of metformin HCl and sitagliptin for at least 8 weeks before entering the 2-week run-in period. Following the run-in period, patients were randomized to canagliflozin 300 mg or sitagliptin 100 mg as add-on to metformin HCl and sitagliptin.

As shown in Table 18 and Figure 2, at the end of treatment, canagliflozin 300 mg provided greater HbA1C reduction compared to sitagliptin 100 mg when added to metformin HCl and sitagliptin (p<0.05). Canagliflozin 300 mg resulted in a mean percent change in body weight from baseline of -2.5% compared to -0.3% with sitagliptin 100 mg. A mean change in systolic blood pressure from baseline of -5.06 mmHg was observed with canagliflozin 300 mg compared to +0.85 mmHg with sitagliptin 100 mg.
Table 18: Results from 52−Week Clinical Study Comparing Canagliflozin to Sitagliptin in Combination with Metformin HCl and Sulfonylurea*

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Canagliflozin 300 mg + Metformin HCl and Sulfonylurea (N=377)</th>
<th>Sitagliptin 100 mg + Metformin HCl and Sulfonylurea (N=378)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1C (%)</td>
<td>Baseline (mean) 8.12</td>
<td>Baseline (mean) 8.13</td>
</tr>
<tr>
<td></td>
<td>Change from baseline (adjusted mean) -1.03</td>
<td>Change from baseline (adjusted mean) -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>
<tr>
<td>Fasting Plasma Glucose (mg/dL)</td>
<td>Baseline (mean) 170</td>
<td>Baseline (mean) 164</td>
</tr>
<tr>
<td></td>
<td>Change from baseline (adjusted mean) -30</td>
<td>Change from baseline (adjusted mean) -6</td>
</tr>
<tr>
<td>Difference from sitagliptin (adjusted mean) (95% CI)</td>
<td>-24 (-30, -18)</td>
<td></td>
</tr>
<tr>
<td>Body Weight</td>
<td>Baseline (mean) in kg 87.6</td>
<td>Baseline (mean) in kg 89.6</td>
</tr>
<tr>
<td></td>
<td>% change from baseline (adjusted mean) -2.5</td>
<td>% change from baseline (adjusted mean) 0.3</td>
</tr>
<tr>
<td>Difference from sitagliptin (adjusted mean) (95% CI)</td>
<td>-2.8‡ (-3.3, -2.2)</td>
<td></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 HCl + sulfonylurea is considered non-inferior to sitagliptin + metformin HCl + 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)

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

A total of 342 patients with type 2 diabetes inadequately controlled on the combination of metformin HCl (greater than or equal to 2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated) and pioglitazone (30 or 45 mg/day) participated in a 26-week, double-blind, placebo-controlled trial to evaluate the efficacy and safety of canagliflozin in combination with metformin HCl and pioglitazone. The mean age was 57 years, 63% of patients were men, and the mean baseline eGFR was 86 mL/min/1.73 m². Patients already on protocol-specified doses of metformin HCl and pioglitazone (N=163) entered a 2-week, single-blind, placebo run-in period. Other patients (N=181) were required to be on stable protocol-specified doses of metformin HCl and pioglitazone for at least 8 weeks before entering the 2-week run-in period. Following the run-in period, patients were randomized to canagliflozin 100 mg, canagliflozin 300 mg, or placebo, administered once daily as add-on to metformin HCl and pioglitazone.

Table 19: Results from 26−Week Placebo-Controlled Clinical Study of Canagliflozin in Combination with Metformin HCl and Pioglitazone*

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

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

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 HCl and pioglitazone. Canagliflozin 100 mg and 300 mg once daily also resulted in a greater proportion of patients achieving an HbA1C less than 7%, in significant reduction in fasting plasma glucose (FPG), and in percent body weight reduction compared to placebo when added to metformin HCl and pioglitazone (see Table 19). Statistically significant (p<0.05 for both doses) mean changes from baseline in systolic blood pressure relative to placebo were +4.1 mmHg and -3.5 mmHg with canagliflozin 100 mg and 300 mg, respectively.

A total of 1,718 patients with type 2 diabetes inadequately controlled on insulin greater than or equal to 30 units/day or insulin in combination with other antihyperglycemic agents participated in an 18-week, double-blind, placebo-controlled substudy of a cardiovascular trial 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 HCl and ≥ 30 units/day of insulin over 18 weeks.

In this subgroup, the mean age was 61 years, 67% of patients were men, and the mean baseline eGFR was 81 mL/min/1.73 m². Patients on metformin HCl 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 HCl 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 HCl and insulin. The mean daily insulin dose at baseline was 93 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 HCl 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 20). Statistically significant (p=0.023 for the 100 mg and p<0.001 for the 300 mg dose)
mean change from baseline in systolic blood pressure relative to placebo was –3.5 mmHg and –6 mmHg with canagliflozin 100 mg and 300 mg, respectively. Fewer patients on canagliflozin in combination with metformin HCl 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 trial, which is consistent with the expected increase of hypoglycemia when an agent not associated with hypoglycemia is added to insulin [see Warnings and Precautions (6.6) and Adverse Reactions (6.1)].

Table 20: Results from 18-Week Placebo-Controlled Clinical Study of Canagliflozin in Combination with Metformin HCl and Insulin ≥ 30 Units/Day

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Placebo + Metformin HCl + Insulin (N=145)</th>
<th>Canagliflozin 100 mg + Metformin HCl + Insulin (N=139)</th>
<th>Canagliflozin 300 mg + Metformin HCl + Insulin (N=148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1C (%)</td>
<td>8.15</td>
<td>8.20</td>
<td>8.22</td>
</tr>
<tr>
<td>Difference from placebo (adjusted mean)</td>
<td>-0.66‡ (-0.81, -0.51)</td>
<td>-0.82‡ (-0.96, -0.67)</td>
<td></td>
</tr>
<tr>
<td>Percent of patients achieving HbA1C &lt; 7%</td>
<td>9%</td>
<td>19%</td>
<td>29%</td>
</tr>
<tr>
<td>Fasting Plasma Glucose (mg/dL)</td>
<td>Baseline 163</td>
<td>168</td>
<td>167</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-16† (-28, -5)</td>
<td>-25† (-36, -14)</td>
<td></td>
</tr>
<tr>
<td>Body Weight</td>
<td>Baseline (mean) in kg 102.3</td>
<td>99.7</td>
<td>101.1</td>
</tr>
<tr>
<td>% change from baseline (adjusted mean)</td>
<td>-1.7</td>
<td>-2.7</td>
<td></td>
</tr>
<tr>
<td>Difference from placebo (adjusted mean)</td>
<td>-1.7† (-2.4, -1.0)</td>
<td>-2.7† (-3.4, -2.0)</td>
<td></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
§ p≤0.01

14.2 Canagliflozin Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease

Canagliflozin is indicated to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD). The CANVAS and CANVAS-R trials were multicenter, multi-national, randomized, double-blind parallel group, with similar inclusion and exclusion criteria. Patients eligible for enrollment in both CANVAS and CANVAS-R trials were: 30 years of age or older and had established, stable, cardiovascular, cerebrovascular, peripheral artery disease (68% of the enrolled population) or were 50 years of age or older and had two or more other specified risk factors for cardiovascular disease (34% of the enrolled population).

The integrated analysis of the CANVAS and CANVAS-R trials compared the risk of Major Adverse Cardiovascular Event (MACE) between canagliflozin and placebo when these were added to and used concomitantly with standard of care treatments for diabetes and atherosclerotic cardiovascular disease. The primary endpoint, MACE, was the time to first occurrence of a three-part composite outcome which included cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.

In CANVAS, patients were randomly assigned 1:1:1 to canagliflozin 100 mg, canagliflozin 300 mg, or matching placebo. In CANVAS-R, patients were randomly assigned 1:1 to canagliflozin 100 mg or matching placebo, and titration to 300 mg was permitted at the investigator’s discretion (based on tolerability and glycemic needs) after Week 13. Concomitant antidiabetic and atherosclerotic therapies could be adjusted, at the discretion of investigators, to ensure participants were treated according to the standard care for these diseases.

A total of 10,134 patients were treated (4,327 in CANVAS and 5,807 in CANVAS-R; total of 4,344 randomly assigned to placebo and 5,790 to canagliflozin) for a mean exposure duration of 149 weeks (223 weeks [4.3 years] in CANVAS and 94 weeks [1.8 years] in CANVAS-R). Approximately 78% of the trial population was Caucasian, 13% was Asian, and 3% was Black. The mean age was 63 years and approximately 64% were male.

The mean HbA1c at baseline was 8.2% and mean duration of diabetes was 13.5 years with 70% of patients having had diabetes for 10 years or more. Approximately 31%, 21% and 17% reported a past history of neuropathy, retinopathy and nephropathy, respectively, and the mean eGFR 76 mL/min/1.73 m². At baseline, patients were treated with one (19%) or more (80%) antidiabetic medications including metformin (77%), insulin (50%), and sulfonylurea (43%). At baseline, the mean systolic blood pressure was 137 mmHg, the mean diastolic blood pressure was 78 mmHg, the mean LDL was 89 mg/dL, the mean HDL was 46 mg/dL, and the mean urinary albumin to creatinine ratio (UACR) was 115 mg/g. At baseline, approximately 80% of patients were treated with renin angiotensin system inhibitors, 53% with beta-blockers, 13% with loop diuretics, 38% with non-loop diuretics, 75% with statins, and 74% with antiplatelet agents (mostly aspirin). During the trial, investigators could modify anti-diabetic and cardiovascular therapies to achieve local standard of care treatment targets with respect to blood glucose, lipid, and blood pressure. More patients receiving canagliflozin compared to placebo initiated anti-thromboprophylaxis (52% vs 41%) and statins (65% vs 48%) during the trial.

For the primary analysis, a stratified Cox proportional hazards model was used to test for non-inferiority against a pre-specified risk margin of 1.3 for the hazard ratio of MACE.

In the integrated analysis of CANVAS and CANVAS-R trials, canagliflozin reduced the risk of first occurrence of MACE. The estimated hazard ratio (95% CI) for time to first MACE was 0.86 (0.75, 0.97). Refer to Table 21. Vital status was obtained for 99.6% of patients across the trials. The Kaplan-Meier curve depicting time to first occurrence of MACE is shown in Figure 3.

Table 21: Treatment Effect for the Primary Composite Endpoint, MACE, and its Components in the Integrated Analysis of CANVAS and CANVAS-R studies

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Placebo N=4347 (%)</th>
<th>Canagliflozin N=5795 (%)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke (time to first occurrence)§ ¹, ²</td>
<td>426 (10.4)</td>
<td>585 (9.2)</td>
<td>0.86 (0.75, 0.97)</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction§ ¹</td>
<td>159 (3.9)</td>
<td>215 (3.4)</td>
<td>0.85 (0.69, 1.05)</td>
</tr>
<tr>
<td>Non-fatal Stroke§ ¹</td>
<td>116 (2.8)</td>
<td>158 (2.5)</td>
<td>0.90 (0.71, 1.15)</td>
</tr>
<tr>
<td>Cardiovascular Death§ ¹</td>
<td>185 (4.6)</td>
<td>268 (4.1)</td>
<td>0.87 (0.72, 1.06)</td>
</tr>
</tbody>
</table>

* Intent-To-Treat Analysis Set
† P-value for superiority (2-sided) = 0.0156
¹ Number and percentage of first events
¹ Due to pooling of unequal randomization ratios, Cochran-Mantel-Haenszel weights were applied to calculate percentages
² Stratified Cox-proportional hazards model with treatment as a factor and stratified by study and by prior CV disease

Figure 3: Time to First Occurrence of MACE
INVOKAMET® (canagliflozin and metformin hydrochloride) tablets
INVOKAMET® XR (canagliflozin and metformin hydrochloride) extended-release tablets

14.3 Canagliflozin Renal and Cardiovascular Outcomes in Patients with Diabetic Nephropathy and Albuminuria

Canagliflozin is indicated to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria ≥ 300 mg/day.

The Canagliflozin and Renal Events in Diabetes with Established Nephropathy and Albuminuria > 300 mg/day.

The Canagliflozin and Renal Outcomes (CREDENCE) was a multinational, randomized, double-blind, placebo-controlled trial comparing canagliflozin with placebo in patients with type 2 diabetes mellitus, an eGFR ≥ 30 to < 90 mL/min/1.73 m² and albuminuria > 300 mg/day.

The primary objective of CREDENCE was to assess the efficacy of canagliflozin relative to placebo in reducing the composite endpoint of end stage kidney disease (ESKD), doubling of serum creatinine, and renal or CV death.

Patients were randomized to receive canagliflozin 100 mg (N=2,202) or placebo (N=2,199) and treatment was continued until the initiation of dialysis or renal transplantation.

The median follow-up duration for the 4,401 randomized subjects was 137 weeks. Vital status was obtained for 99.9% of subjects. The population was 67% White, 20% Asian, and 5% Black; 32% were of Hispanic or Latino ethnicity. The mean age was 63 years and 66% were male.

At randomization, the mean HbA1C was 8.3%, the median urine albumin/creatinine was 927 mg/g, the mean eGFR was 56.2 mL/min/1.73 m², 50% had prior CV disease, and 15% reported a history of heart failure. The most frequent antihyperglycemic agents (AHA) medications used at baseline were insulin (66%), biguanides (58%), and sulfonylureas (29%). Nearly all subjects (99.9%) were on ACEi or ARB at randomization, approximately 60% were taking an anti-thrombotic agent (including aspirin), and 69% were on a statin.

The primary composite endpoint in the CREDENCE study was the time to first occurrence of ESKD (defined as an eGFR < 15 mL/min/1.73 m²), initiation of chronic dialysis or renal transplant, doubling of serum creatinine, and renal or CV death. Canagliflozin 100 mg significantly reduced the risk of the primary composite endpoint based on a time-to-event analysis [HR: 0.70; 95% CI: 0.59, 0.82; p<0.001] (see Figure 4). The treatment effect reflected a reduction in progression to ESKD, as the explanatory variable and stratified by screening eGFR (≥ 30 to < 45, ≥ 45 to < 60, ≥ 60 to < 90 mL/min/1.73 m²). HR is not presented for renal death due to the small number of events in each group.

The Kaplan-Meier curve (Figure 4) shows time to first occurrence of the primary composite endpoint of ESKD, doubling of serum creatinine, renal death, or CV death. The curves begin to separate by Week 52 and continue to diverge thereafter.

Figure 4: CREDENCE: Time to First Occurrence of the Primary Composite Endpoint

Table 22: Analysis of Primary Endpoint (including the Individual Components) and Secondary Endpoints from the CREDENCE Study

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo</th>
<th>canagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=2,199 (%)</td>
<td>N=2,202 (%)</td>
<td>HR</td>
</tr>
<tr>
<td>Primary Composite Endpoint (ESKD, doubling of serum creatinine, renal death, or CV death)</td>
<td>340 (15.5)</td>
<td>245 (11.1)</td>
</tr>
<tr>
<td>ESKD</td>
<td>165 (7.5)</td>
<td>116 (5.3)</td>
</tr>
<tr>
<td>Doubling of serum creatinine</td>
<td>188 (8.5)</td>
<td>118 (5.4)</td>
</tr>
<tr>
<td>Renal death</td>
<td>5 (0.2)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>CV death</td>
<td>140 (6.4)</td>
<td>110 (5.0)</td>
</tr>
<tr>
<td>CV death or hospitalization for heart failure</td>
<td>253 (11.5)</td>
<td>179 (8.1)</td>
</tr>
<tr>
<td>CV death, non-fatal myocardial infarction or non-fatal stroke</td>
<td>269 (12.2)</td>
<td>217 (9.9)</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>87 (4.0)</td>
<td>71 (3.2)</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>68 (3.0)</td>
<td>53 (2.4)</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>141 (6.4)</td>
<td>89 (4.0)</td>
</tr>
<tr>
<td>ESKD, doubling of serum creatinine or renal death</td>
<td>224 (10.2)</td>
<td>153 (6.9)</td>
</tr>
</tbody>
</table>

Table 22: Analysis of Primary Endpoint (including the Individual Components) and Secondary Endpoints from the CREDENCE Study

INVOKAMET® XR tablets are available in bottles of 60 in the strengths listed below:

<table>
<thead>
<tr>
<th>Invokamet XR Strength</th>
<th>Tablet Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg/500 mg</td>
<td>551</td>
</tr>
<tr>
<td>50 mg/1000 mg</td>
<td>215</td>
</tr>
<tr>
<td>150 mg/500 mg</td>
<td>155</td>
</tr>
<tr>
<td>150 mg/1000 mg</td>
<td>611</td>
</tr>
</tbody>
</table>

16 HOW SUPPLIED/STORAGE AND HANDLING
INVOKAMET® tablets are available in bottles of 60 in the strengths listed below:

<table>
<thead>
<tr>
<th>Invokamet Tablet Strength</th>
<th>Tablet Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg/500 mg</td>
<td>551</td>
</tr>
<tr>
<td>50 mg/1000 mg</td>
<td>215</td>
</tr>
<tr>
<td>150 mg/500 mg</td>
<td>611</td>
</tr>
<tr>
<td>150 mg/1000 mg</td>
<td>155</td>
</tr>
</tbody>
</table>

Storage and Handling
Keep out of reach of children.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [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

Advising 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. Advise patients to discontinue INVOKAMET/INVOKAMET XR immediately and to promptly notify their healthcare provider if unexplained hyperventilation, myalgias, malaise, unusual somnolence or other nonspecific symptoms occur. Once a patient is stabilized on INVOKAMET/INVOKAMET XR, gastrointestinal symptoms, which are common during initiation of metformin HCI, are unlikely to recur. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease. Counsel patients against excessive alcohol intake while receiving INVOKAMET/INVOKAMET XR.

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

Instruct patients to inform their doctor that they are taking INVOKAMET/INVOKAMET XR prior to any surgical or radiological procedure, as temporary discontinuation of INVOKAMET/INVOKAMET XR may be required until renal function has been confirmed to be normal [see Warnings and Precautions (5.11)].

Lower Limb Amputation:
Inform patients that INVOKAMET/INVOKAMET XR is associated with an increased risk of amputations. Counsel patients about the importance of routine preventative foot care. Instruct patients to monitor for new pain or tenderness, sores or ulcers, or infections involving the leg or foot and to seek medical advice immediately if such signs or symptoms develop [see Warnings and Precautions (5.2)].

Volume Depletion:
Inform patients that symptomatic hypotension may occur with INVOKAMET/INVOKAMET XR and advise them to contact their doctor if they experience such symptoms [see Warnings and Precautions (5.3)]. Inform patients that dehydration may increase the risk for hypotension and to have adequate fluid intake.

Ketoacidosis:
Inform patients that ketoacidosis is a serious life-threatening condition and that cases of ketoacidosis have been reported during use of canagliflozin, sometimes associated with illness or surgery among other risk factors. Instruct patients to check ketones (when possible) if symptoms consistent with ketoacidosis occur even if blood glucose is not elevated. If symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing) occur, instruct patients to discontinue INVOKAMET/INVOKAMET XR and seek medical attention immediately [see Warnings and Precautions (5.4)].

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 such symptoms occur [see Warnings and Precautions (5.5)].

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene):
Inform patients that necrotizing infections of the perineum (Fournier's gangrene) have occurred with INVOKAMET/INVOKAMET XR. Counsel patients to promptly seek medical attention if they develop pain or tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, along with a fever above 100.4°F or malaise [see Warnings and Precautions (5.7)].

Genital Mycotic Infections in Females (e.g., Vulvovaginitis):
Inform female patients that vaginal yeast infection (e.g., vulvovaginitis) may occur and provide them with information on the signs and symptoms of a vaginal yeast infection. Advise them of treatment options and when to seek medical advice [see Warnings and Precautions (5.8)].

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis):
Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with prior history. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice [see Warnings and Precautions (5.8)].

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 immediately until they have consulted prescribing physicians [see Warnings and Precautions (5.9)].

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 [see Warnings and Precautions (5.10)].

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

Females of Reproductive Age:
Advise pregnant women, and females of reproductive potential of the potential risk to a fetus with treatment with INVOKAMET/INVOKAMET XR [see Use in Specific Populations (8.1)]. Instruct females of reproductive potential to report pregnancies to their physicians as soon as possible.

Inform females that treatment with INVOKAMET/INVOKAMET XR may result in ovulation in some premenopausal anovulatory women which may lead to unintended pregnancy [see Use in Specific Populations (8.2)].

Lactation:
Advise women that breastfeeding is not recommended during treatment with INVOKAMET/INVOKAMET XR [see Use in Specific Populations (8.2)].

Manufactured for:
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Titusville, NJ 08560
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INVOKAMET® (canagliflozin and metformin hydrochloride) tablets
INVOKAMET® XR (canagliflozin and metformin hydrochloride) extended-release tablets
What is the most important information I should know about INVOKAMET or INVOKAMET XR?

INVOKAMET and INVOKAMET XR can cause serious side effects, including:

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

  Stop taking INVOKAMET or INVOKAMET XR and call your doctor right away if you have any of the following symptoms of lactic acidosis:

  - feel cold in your hands or feet
  - feel very weak or tired
  - have trouble breathing
  - have stomach pains, nausea, or vomiting
  - have a slow or irregular heartbeat
  - have unusual (not normal) muscle pain
  - have unusual sleepiness or sleep longer than usual
  - 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 or INVOKAMET XR 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.
  - have surgery.
  - have heart attack, severe infection, or stroke.
  - are 65 years of age or older.

  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 or INVOKAMET XR for a while if you have any of these things.

- **Amputations.** INVOKAMET or INVOKAMET XR 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 or INVOKAMET XR for a while if you have any of these signs or symptoms.

  Talk to your doctor about proper foot care.

- **Dehydration.** INVOKAMET or INVOKAMET XR 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). There have been reports of sudden worsening of kidney function in people with type 2 diabetes who are taking canagliflozin, one of the medicines in INVOKAMET and INVOKAMET XR.

  You may be at a higher risk of dehydration if you:

  - 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. Call your healthcare provider right away if you reduce the amount of food or liquid you drink, for example if you cannot eat or you start to lose liquids from your body, for example from vomiting, diarrhea, or being in the sun too long.
What is the most important information I should know about INVOKAMET or INVOKAMET XR? (continued)

- **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 canagli flozin, one of the medicines in INVOKAMET and INVOKAMET XR. Ketoacidosis has also happened in people with diabetes who were sick or who had surgery during treatment with INVOKAMET or INVOKAMET XR. Ketoacidosis is a serious condition, which needs to be treated in a hospital. Ketoacidosis may lead to death. Ketoacidosis can happen with INVOKAMET or INVOKAMET XR, even if your blood sugar is less than 250 mg/dL. Stop taking INVOKAMET or INVOKAMET XR and call your doctor right away if you get any of the following symptoms:
  - nausea
  - vomiting
  - stomach area (abdominal) pain
If you get any of these symptoms during treatment with INVOKAMET or INVOKAMET XR, if possible, check for ketones in your urine, even if your blood sugar is less than 250 mg/dL.

- **Vaginal yeast infection.** 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 skin around the penis (balanitis or balanoposthitis).** Swelling of an uncircumcised penis may develop 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.

INVOKAMET or INVOKAMET XR can have other serious side effects. See “What are the possible side effects of INVOKAMET or INVOKAMET XR?”

What is INVOKAMET or INVOKAMET XR?

- INVOKAMET contains 2 prescription medicines called canagli flozin (INVOKANA) and metformin hydrochloride (GLUCOPHAGE). INVOKAMET XR contains 2 prescription medicines called canagli flozin (INVOKANA) and metformin hydrochloride extended-release (GLUMETZA). INVOKAMET or INVOKAMET XR can be used:
  - along with diet and exercise to lower blood sugar (glucose) in adults with type 2 diabetes.
  - in adults with type 2 diabetes who have known cardiovascular disease and canagli flozin is needed to reduce the risk of major cardiovascular events such as heart attack, stroke, or death.
  - in adults with type 2 diabetes and diabetic kidney disease (nephropathy) with a certain amount of protein in the urine, and canagli flozin is needed to reduce the risk of end stage kidney disease (ESKD), worsening of kidney function, cardiovascular death, and hospitalization for heart failure.
- INVOKAMET or INVOKAMET XR is not for people with type 1 diabetes. It may increase their risk of diabetic ketoacidosis (increased ketones in blood or urine).
- It is not known if INVOKAMET or INVOKAMET XR is safe and effective in children under 18 years of age.

Do not take INVOKAMET or INVOKAMET XR if you:

- have severe kidney problems
- are on kidney dialysis
- have a condition called metabolic acidosis.
- are allergic to canagli flozin, metformin, or any of the ingredients in INVOKAMET or INVOKAMET XR. See the end of this Medication Guide for a list of ingredients in INVOKAMET and INVOKAMET XR. Symptoms of an allergic reaction to INVOKAMET and INVOKAMET XR 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
Before taking INVOKAMET or INVOKAMET XR, tell your doctor about all of your medical conditions, including 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 or INVOKAMET XR.
- have ever had an allergic reaction to INVOKAMET or INVOKAMET XR.
- are going to get an injection of dye or contrast agents for an x-ray procedure. INVOKAMET or INVOKAMET XR may need to be stopped for a short time. Talk to your doctor about when you should stop INVOKAMET or INVOKAMET XR and when you should start INVOKAMET or INVOKAMET XR again. See “What is the most important information I should know about INVOKAMET or INVOKAMET XR?”
- have heart problems, including congestive heart failure.
- are going to have surgery. Your doctor may stop your INVOKAMET or INVOKAMET XR before you have surgery. Talk to your doctor if you are having surgery about when to stop taking INVOKAMET or INVOKAMET XR and when to start it again.
- are eating less or there is 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 low levels of vitamin B12 or calcium in your blood.
- are pregnant or plan to become pregnant. INVOKAMET or INVOKAMET XR may harm your unborn baby. If you become pregnant while taking INVOKAMET or INVOKAMET XR, 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 premenopausal (before the “change of life”), and do not have periods regularly or at all. INVOKAMET or INVOKAMET XR may increase your chance of becoming pregnant. Talk to your doctor about birth control choices while taking INVOKAMET or INVOKAMET XR, if you are not planning to become pregnant. Tell your doctor right away if you become pregnant while taking INVOKAMET or INVOKAMET XR.
- are breastfeeding or plan to breastfeed. INVOKAMET or INVOKAMET XR 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 or INVOKAMET XR. Do not breastfeed while taking INVOKAMET or INVOKAMET XR.

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

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

- diuretics (water pills)
- phenytoin or phenobarbital (used to control seizures)
- digoxin (used to treat heart problems)
- rifampin (used to treat or prevent tuberculosis)
- ritonavir (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 or INVOKAMET XR?

- If you are prescribed INVOKAMET, take 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.
- If you are prescribed INVOKAMET XR, take by mouth 1 time each day with the morning meal exactly as your doctor tells you to take it. Taking INVOKAMET XR with a meal may lower your chance of having an upset stomach.
- Swallow INVOKAMET XR whole. Do not crush, cut, or chew.
- You may sometimes pass a soft mass in your stools (bowel movement) that looks like INVOKAMET XR tablets. It is normal to see this in your stool.
- Your doctor may change your dose if needed.
- Your doctor may tell you to take INVOKAMET or INVOKAMET XR along with other diabetes medicines. Low blood sugar can happen more often when INVOKAMET or INVOKAMET XR is taken with certain other diabetes medicines. See “What are the possible side effects of INVOKAMET or INVOKAMET XR?”
- If you miss a dose of INVOKAMET, 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 tablets of INVOKAMET at the same time. Talk to your doctor if you have questions about a missed dose.
How should I take INVOKAMET or INVOKAMET XR? (continued)

- If you miss a dose of INVOKAMET XR, 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 more than 2 tablets of INVOKAMET XR at the same time. Talk to your doctor if you have questions about a missed dose.
- If you take too much INVOKAMET or INVOKAMET XR, 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 or INVOKAMET XR.
- Check your blood sugar as your doctor tells you to.
- INVOKAMET and INVOKAMET XR will cause your urine to test positive for glucose.
- Your doctor may do certain blood tests before you start INVOKAMET or INVOKAMET XR and during treatment as needed. Your doctor may change your dose of INVOKAMET or INVOKAMET XR 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 or INVOKAMET XR?

- 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 or INVOKAMET XR?

INVOKAMET or INVOKAMET XR may cause serious side effects including:

- **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 and INVOKAMET XR. 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 or INVOKAMET XR 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 or INVOKAMET XR. Signs and symptoms of low blood sugar may include:
  - headache
  - drowsiness
  - weakness
  - confusion
  - dizziness
  - irritability
  - hunger
  - fast heartbeat
  - sweating
  - shaking or feeling jittery

- **a rare but serious bacterial infection that causes damage to the tissue under the skin (necrotizing fasciitis) in the area between and around the anus and genitals (perineum).** Necrotizing fasciitis of the perineum has happened in people who take canagliflozin, one of the medicines in INVOKAMET and INVOKAMET XR. Necrotizing fasciitis of the perineum may lead to hospitalization, may require multiple surgeries, and may lead to death. Seek medical attention immediately if you have a fever or you are feeling very weak, tired or uncomfortable (malaise) and you develop any of the following symptoms in the area between and around your anus and genitals:
  - pain or tenderness
  - swelling
  - redness of the skin (erythema)

- **serious allergic reaction.** If you have any symptoms of a serious allergic reaction, stop taking INVOKAMET or INVOKAMET XR and call your doctor right away or go to the nearest hospital emergency room. See “Do not take INVOKAMET or INVOKAMET XR if you”.
  - 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 B₁₂ (vitamin B₁₂ deficiency).** Using metformin for long periods of time may cause a decrease in the amount of vitamin B₁₂ in your blood, especially if you have had low vitamin B₁₂ blood levels before. Your doctor may do blood tests to check your vitamin B₁₂ levels.

Other common side effects of INVOKAMET or INVOKAMET XR include:

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

These are not all the possible side effects of INVOKAMET or INVOKAMET XR.

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 or INVOKAMET XR?**
- Store INVOKAMET or INVOKAMET XR at room temperature between 68°F to 77°F (20°C to 25°C).
- Store INVOKAMET or INVOKAMET XR 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 INVOKAMET XR and all medicines out of the reach of children.**

**General information about the safe and effective use of INVOKAMET or INVOKAMET XR.**
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use INVOKAMET or INVOKAMET XR for a condition for which it was not prescribed. Do not give INVOKAMET or INVOKAMET XR to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or doctor for information about INVOKAMET or INVOKAMET XR that is written for health professionals.

**What are the ingredients in 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/PEG3350, 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).

**What are the ingredients of INVOKAMET XR?**
Active ingredients: canagliflozin and metformin hydrochloride
Inactive ingredients: The tablet core contains croscarmellose sodium, hydroxypropyl cellulose, hypromellose, lactose anhydrous, magnesium stearate (vegetable-sourced), microcrystalline cellulose, polyethylene oxide, and silicified microcrystalline cellulose (50 mg/500 mg and 50 mg/1,000 mg tablets only). In addition, the tablet coating contains macrogol/PEG3350, polyvinyl alcohol (partially hydrolyzed), talc, titanium dioxide, iron oxide red, iron oxide yellow, and iron oxide black (50 mg/1,000 mg and 150 mg/1,000 mg tablets only).


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