HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use INVOKAMET or INVOKAMET XR safely and effectively. See full prescribing information for INVOKAMET or INVOKAMET XR.

INVOKAMET® (canagliflozin and metformin hydrochloride) tablets, for oral use
INVOKAMET® XR (canagliflozin and metformin hydrochloride) extended-release tablets, for oral use
Initial U.S. Approval: 2014

WARNING: LACTIC ACIDOSIS
See full prescribing information for complete boxed warning.

- **Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, 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, hepatic impairment, and mitochondrial diseases. 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 or INVOKAMET XR and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.1)**

----------RECENT MAJOR CHANGES----------

Boxed Warning	08/2026
Dosage and Administration	
Recommendations Regarding Missed Dose (2.7)	08/2026
Warnings and Precautions	
Lactic Acidosis (5.1)	
Genitourinary Infections, including Urosepsis, Pyelonephritis, Necrotizing Fasciitis of the Perineum (Fournier's Gangrene), and Genital Mycotic Infections (5.5)	08/2026

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

INVOKAMET and INVOKAMET XR are a combination of canagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, and metformin hydrochloride (HCl), a biguanide, indicated as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus (1).

Canagliflozin
Canagliflozin, when used as a component of INVOKAMET or INVOKAMET XR is indicated in adults with type 2 diabetes mellitus to reduce the risk of:

- Major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease (1).
- 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).

Limitations of Use:
Not recommended for use to improve glycemic control in patients with type 1 diabetes mellitus (1).

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

- Assess renal function before initiating and as clinically indicated. Assess volume status and correct volume depletion before initiating (2.1).
- Individualize starting dose based on the patient's current regimen and renal function. See Table 1 in the full prescribing information for recommended starting dosages based on the current regimen (2.2, 2.3).
- The maximum recommended total daily dosage is 300 mg of canagliflozin and 2,000 mg of metformin HCl (2.2).
- Initiation of INVOKAMET or INVOKAMET XR is not recommended in patients with an eGFR less than 45 mL/min/1.73 m^2, due to the metformin HCl component (2.3).
- INVOKAMET: take one tablet orally twice daily with meals (2.2).
- INVOKAMET XR: take two tablets orally once daily with the morning meal. Swallow whole. Never crush, cut, or chew (2.2).
- Gradually escalate the dosage of metformin HCl in INVOKAMET or INVOKAMET XR to reduce the risk of gastrointestinal adverse reactions with metformin HCl (2.2).
- Dose adjustment for patients with renal impairment may be required (2.3).
- See full prescribing information for INVOKAMET and INVOKAMET XR dosage modifications due to drug interactions (2.4).
- May need to be discontinued at time of, or prior to, iodinated contrast imaging procedures (2.5).
- Withhold INVOKAMET or INVOKAMET XR at least 3 days, if possible, prior to surgery or procedures associated with prolonged fasting (2.6).

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

INVOKAMET tablets:

- Canagliflozin 50 mg and metformin HCl 500 mg (3)
- Canagliflozin 50 mg and metformin HCl 1,000 mg (3)
- Canagliflozin 150 mg and metformin HCl 500 mg (3)
- Canagliflozin 150 mg and metformin HCl 1,000 mg (3)

INVOKAMET XR extended-release tablets:

- Canagliflozin 50 mg and metformin HCl 500 mg (3)
- Canagliflozin 50 mg and metformin HCl 1,000 mg (3)
- Canagliflozin 150 mg and metformin HCl 500 mg (3)
- Canagliflozin 150 mg and metformin HCl 1,000 mg (3)

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

- Severe renal impairment (eGFR less than 30 mL/min/1.73 m^2) (4)
- Metabolic acidosis, including diabetic ketoacidosis (4)
- Serious hypersensitivity reaction to canagliflozin or metformin HCl (4)

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

- Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis: Consider ketone monitoring in patients at risk for ketoacidosis, as indicated. Assess for ketoacidosis regardless of presenting blood glucose levels and discontinue INVOKAMET or INVOKAMET XR if ketoacidosis is suspected. Monitor patients for resolution of ketoacidosis before restarting (5.2).
- Lower Limb Amputation: Monitor patients for infection or ulcers of lower limb and institute appropriate treatment (5.3).
- Volume Depletion: May result in acute kidney injury. Before initiating, assess and correct volume status in patients with renal impairment, elderly patients, or patients on loop diuretics. Monitor for signs and symptoms during therapy (5.4).
- Genitourinary Infections, including Urosepsis, Pyelonephritis, Necrotizing Fasciitis of the Perineum (Fournier's Gangrene), and Genital Mycotic Infections: Monitor patients for signs and symptoms of genitourinary infections and treat promptly, if indicated. Immediately evaluate patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, for necrotizing fasciitis and if suspected, discontinue INVOKAMET or INVOKAMET XR, and promptly institute appropriate medical and/or surgical intervention (5.5).
- Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues: Consider a lower dose of insulin or insulin secretagogue to reduce the risk of hypoglycemia when used in combination (5.6).
- Hypersensitivity Reactions: Discontinue and monitor until signs and symptoms resolve (5.7).
- Bone Fracture: Consider factors that contribute to fracture risk before initiating INVOKAMET or INVOKAMET XR (5.8).
- Vitamin B_{12} Deficiency: Metformin HCl may lower vitamin B_{12} levels. Measure hematological parameters annually and vitamin B_{12} at 2- to 3-year intervals and manage any abnormalities (5.9).

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

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

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

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

- Carbonic Anhydrase Inhibitors: May increase risk of lactic acidosis. Consider more frequent monitoring (7).
- Drugs that Reduce Metformin Clearance: May increase risk of lactic acidosis. Consider benefits and risks of concomitant use (7).
- See full prescribing information for additional drug interactions and information on interference of INVOKAMET and INVOKAMET XR with laboratory tests. (7).

----------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).
- Geriatrics: Higher incidence of adverse reactions related to reduced intravascular volume. Assess renal function more frequently (8.5).
- Renal Impairment: Higher incidence of adverse reactions related to hypotension and renal function (8.6).
- Hepatic Impairment: Avoid use in patients with hepatic impairment (8.7).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: LACTIC ACIDOSIS
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Prior to Initiation of INVOKAMET or INVOKAMET XR
2.2 Recommended Dosage and Administration
2.3 Recommended Dosage in Adults and Pediatric Patients Aged 10 Years and Older with Renal Impairment
2.4 Concomitant Use with UDP-Glucuronosyltransferase (UGT) Enzyme Inducers
2.5 Discontinuation for Iodinated Contrast Imaging Procedures
2.6 Temporary Interruption for Surgery
2.7 Recommendations Regarding Missed Dose
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Lactic Acidosis
5.2 Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis
5.3 Lower Limb Amputation
5.4 Volume Depletion
5.5 Genitourinary Infections, including Urosepsis, Pyelonephritis, Necrotizing Fasciitis of the Perineum (Fournier's Gangrene), and Genital Mycotic Infections
5.6 Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues
5.7 Hypersensitivity Reactions
5.8 Bone Fracture
5.9 Vitamin B_{12} Deficiency
6 ADVERSE REACTIONS
6.1 Clinical Studies Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Glycemic Control Trials in Adults with Type 2 Diabetes Mellitus
14.2 Glycemic Control Trial in Pediatric Patients Aged 10 Years and Older with Type 2 Diabetes Mellitus
14.3 Canagliflozin Cardiovascular Outcomes in Adults with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease
14.4 Canagliflozin Renal and Cardiovascular Outcomes in Adults with Diabetic Nephropathy and Albuminuria
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS

- **Post-marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. 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, hepatic impairment, and mitochondrial diseases *[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 or 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

INVOKAMET is a combination of canagliflozin and metformin HCl immediate-release indicated as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus.

INVOKAMET XR

INVOKAMET XR is a combination of canagliflozin and metformin HCl extended-release indicated as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus.

Canagliflozin

Canagliflozin, when used as a component of INVOKAMET or INVOKAMET XR, is indicated in adults with type 2 diabetes mellitus 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).
- 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 or INVOKAMET XR are not recommended for use to improve glycemic control in patients with type 1 diabetes mellitus *[see Warnings and Precautions (5.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Prior to Initiation of INVOKAMET or INVOKAMET XR

Assess renal function before initiating INVOKAMET or INVOKAMET XR and as clinically indicated *[see Dosage and Administration (2.3), Contraindications (4), and Warnings and Precautions (5.1, 5.4)]*.

In patients with volume depletion, correct this condition before initiating INVOKAMET or INVOKAMET XR *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.5, 8.6)]*.

2.2 Recommended Dosage and Administration

INVOKAMET and INVOKAMET XR

- INVOKAMET and INVOKAMET XR contain canagliflozin and metformin HCl. For the available strengths of the canagliflozin and metformin HCl components in INVOKAMET and INVOKAMET XR, *[*see *Dosage Forms and Strengths (3)]*.
- Individualize the starting dosage of INVOKAMET or INVOKAMET XR based on the patient's current regimen as presented in Table 1 and based on renal function as presented in Table 2 *[see Dosage and Administration (2.3)]*.

INVOKAMET

Take one tablet of INVOKAMET orally twice daily with meals.

INVOKAMET XR

Take two tablets of INVOKAMET XR orally once daily with the morning meal. Swallow each tablet whole and never crush, cut, or chew.

Table 1 presents the recommended starting dosage of INVOKAMET and INVOKAMET XR based on the patient's current regimen.

Table 1: Recommended Starting Dosage Based on the Current Regimen

Current Regimen	INVOKAMET Recommended Dosage	INVOKAMET XR Recommended Dosage
Not treated with either canagliflozin or metformin HCl	Total daily dosage is canagliflozin 100 mg and metformin HCl 1,000 mg	
Metformin HCl*	Total daily dosage is canagliflozin 100 mg and the nearest appropriate total daily dosage of metformin HCl	
Canagliflozin	The same total daily dosage of canagliflozin and a total daily dosage of metformin HCl 1,000 mg	
Canagliflozin and metformin HCl*	The same total daily dosage of canagliflozin and the nearest appropriate total daily dosage of metformin HCl	

* For patients taking an evening dosage of metformin HCl extended-release tablets, skip the last dose before starting INVOKAMET or INVOKAMET XR the following morning.

Recommended Dosage for Additional Glycemic Control in Adults and Pediatric Patients Aged 10 Years and Older

INVOKAMET

The dosage of canagliflozin in INVOKAMET may be increased to the maximum total daily dosage of 300 mg (150 mg orally twice daily) in patients tolerating a dosage of 100 mg (50 mg twice daily) of canagliflozin.

The dosage of metformin HCl in INVOKAMET may be increased to the maximum total daily dosage of 2,000 mg (1,000 mg orally twice daily), with gradual escalation to reduce the risk of gastrointestinal adverse reactions with metformin HCl *[see Adverse Reactions (6.1)]*.

INVOKAMET XR

The dosage of canagliflozin in INVOKAMET XR may be increased to the maximum total daily dosage of 300 mg orally once daily in patients tolerating a 100 mg once daily dosage of canagliflozin.

The dosage of metformin HCl in INVOKAMET XR may be increased to the maximum total daily dosage of 2,000 mg once daily, with gradual escalation to reduce the risk of gastrointestinal adverse reactions with metformin HCl *[see Adverse Reactions (6.1)]*.

2.3 Recommended Dosage in Adults and Pediatric Patients Aged 10 Years and Older with Renal Impairment

- Initiation of INVOKAMET or INVOKAMET XR is not recommended in adults or pediatric patients aged 10 years and older with an eGFR less than 45 mL/min/1.73 m^2, due to the metformin component.

- Table 2 provides dosage recommendations for adults and pediatric patients aged 10 years and older with renal impairment, based on eGFR *[see Use in Specific Populations (8.6) and Clinical Studies (14.4)]*.

Table 2: Recommended Dosage in Adults and Pediatric Patients Aged 10 Years and Older with Renal Impairment

Estimated Glomerular Filtration Rate [eGFR (mL/min/1.73 m^2)]	**Recommended Dosage of INVOKAMET or INVOKAMET XR***
eGFR 45 to less than 60	The maximum total daily dosage of canagliflozin is 100 mg.
eGFR 30 to less than 45	Assess the benefit risk of continuing INVOKAMET or INVOKAMET XR. The maximum total daily dosage of canagliflozin is 100 mg.
eGFR less than 30	Contraindicated. If eGFR falls below 30 during treatment; discontinue INVOKAMET or INVOKAMET XR *[see Contraindications (4)]*.

* For the dosing frequency of INVOKAMET and INVOKAMET XR, see *Dosage and Administration (2.2).*

2.4 Concomitant Use with UDP-Glucuronosyltransferase (UGT) Enzyme Inducers

When co-administering INVOKAMET or INVOKAMET XR with an inducer of UGT (e.g., rifampin, phenytoin, phenobarbital, ritonavir), increase the total daily dosage of canagliflozin based on renal function *[see Drug Interactions (7)]*:

- In patients with eGFR 60 mL/min/1.73 m^2 or greater, increase the total daily dosage of canagliflozin to 200 mg in patients currently tolerating a total daily dosage of canagliflozin 100 mg. The maximum total daily dosage of canagliflozin is 300 mg.
- In patients with eGFR less than 60 mL/min/1.73 m^2, increase the total daily dosage of canagliflozin to a maximum of 200 mg in patients currently tolerating a total daily dosage of canagliflozin 100 mg.

2.5 Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue INVOKAMET or 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 m^2; 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 or INVOKAMET XR if renal function is stable *[see Warnings and Precautions (5.1)]*.

2.6 Temporary Interruption for Surgery

Withhold INVOKAMET or INVOKAMET XR at least 3 days, if possible, prior to surgery or procedures associated with prolonged fasting. Resume INVOKAMET or INVOKAMET XR when the patient is clinically stable and has resumed oral intake *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.2)]*.

2.7 Recommendations Regarding Missed Dose

- If a dose is missed, instruct patients to take the dose as soon as possible.
- Advise patients not to double up the next dose.

3 DOSAGE FORMS AND STRENGTHS

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

Canagliflozin Strength	Metformin HCl Strength	Color/Shape	Tablet Identifiers*
50 mg	500 mg	white/capsule-shaped	CM 155
50 mg	1,000 mg	beige/capsule-shaped	CM 551
150 mg	500 mg	yellow/capsule-shaped	CM 215
150 mg	1,000 mg	purple/capsule-shaped	CM 611

* Embossing appears on both sides of tablet.

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

Canagliflozin Strength	Metformin HCl Strength	Color/Shape	Tablet Identifiers*
50 mg	500 mg	almost white to light orange/oblong, biconvex	CM1
50 mg	1,000 mg	pink/oblong, biconvex	CM3
150 mg	500 mg	orange/oblong, biconvex	CM2
150 mg	1,000 mg	reddish brown/oblong, biconvex	CM4

* Embossing appears on one side only of tablet.

4 CONTRAINDICATIONS

INVOKAMET or INVOKAMET XR is contraindicated in patients with:

- Severe renal impairment (eGFR less than 30 mL/min/1.73 m^2) *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)]*.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis *[see Warnings and Precautions (5.2)]*.
- Serious hypersensitivity reaction to canagliflozin or metformin HCl, such as anaphylaxis or angioedema *[see Warnings and Precautions (5.7) 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 subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant bradyarrhythmias 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 or INVOKAMET XR. In INVOKAMET or 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 or 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 (2.3) and Clinical Pharmacology (12.3)]*.

- Before initiating INVOKAMET or INVOKAMET XR, obtain an estimated glomerular filtration rate (eGFR).
- INVOKAMET or INVOKAMET XR is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2 *[see Contraindications (4)]*.
- Obtain an eGFR at least annually in all patients taking INVOKAMET or 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 or 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 or INVOKAMET XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR less than 60 mL/min/1.73 m^2; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart INVOKAMET or 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 or 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 myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause pre-renal azotemia. When such events occur, discontinue INVOKAMET or 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 or 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 or INVOKAMET XR in patients with clinical or laboratory evidence of hepatic disease.

Mitochondrial Diseases: Metformin may increase the risk of lactic acidosis in patients with mitochondrial diseases such as mitochondrial encephalomyopathy with lactic acidosis, and stroke-like episodes (MELAS) syndrome and maternally inherited diabetes and deafness (MIDD).

INVOKAMET and INVOKAMET XR are not recommended in patients with mitochondrial diseases such as MELAS syndrome and MIDD.

If a patient taking INVOKAMET or INVOKAMET XR develops elevated lactic acid levels (with or without accompanying neurologic signs and symptoms), discontinue INVOKAMET or INVOKAMET XR. Depending on the clinical context, consider evaluating the patient for MELAS, MIDD, or other mitochondrial disease.

5.2 Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis

In patients with type 1 diabetes mellitus, INVOKAMET or INVOKAMET XR significantly increases the risk of diabetic ketoacidosis, a life-threatening event, beyond the background rate. In placebo-controlled trials of patients with type 1 diabetes mellitus, the risk of ketoacidosis was markedly increased in patients who received sodium glucose transporter 2 (SGLT2) inhibitors compared to patients who received placebo; this risk may be greater with higher doses of INVOKAMET or INVOKAMET XR. INVOKAMET or INVOKAMET XR is not indicated for glycemic control in patients with type 1 diabetes mellitus.

Type 2 diabetes mellitus and pancreatic disorders (e.g., history of pancreatitis or pancreatic surgery) are also risk factors for ketoacidosis. There have been postmarketing reports of fatal events of ketoacidosis in patients with type 2 diabetes mellitus using SGLT2 inhibitors, including INVOKAMET or INVOKAMET XR.

Precipitating conditions for diabetic ketoacidosis or other ketoacidosis include under-insulinization due to insulin dose reduction or missed insulin doses, acute febrile illness, reduced caloric intake, ketogenic diet, surgery, volume depletion, and alcohol abuse.

Signs and symptoms are consistent with dehydration and severe metabolic acidosis and include nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. Blood glucose levels at presentation may be below those typically expected for diabetic ketoacidosis (e.g., less than 250 mg/dL). Ketoacidosis and glucosuria may persist longer than typically expected. Urinary glucose excretion persists for 3 days after discontinuing INVOKAMET or INVOKAMET XR *[see Clinical Pharmacology (12.2)]*; however, there have been postmarketing reports of ketoacidosis and/or glucosuria lasting greater than 6 days and some up to 2 weeks after discontinuation of SGLT2 inhibitors.

Consider ketone monitoring in patients at risk for ketoacidosis if indicated by the clinical situation. Assess for ketoacidosis regardless of presenting blood glucose levels in patients who present with signs and symptoms consistent with severe metabolic acidosis. If ketoacidosis is suspected, discontinue INVOKAMET or INVOKAMET XR, promptly evaluate, and treat ketoacidosis, if confirmed. Monitor patients for resolution of ketoacidosis before restarting INVOKAMET or INVOKAMET XR.

Withhold INVOKAMET or INVOKAMET XR, if possible, in temporary clinical situations that could predispose patients to ketoacidosis. Resume INVOKAMET or INVOKAMET XR when the patient is clinically stable and has resumed oral intake *[see Dosage and Administration (2.6)]*.

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

5.3 Lower Limb Amputation

An increased risk of lower limb amputations associated with canagliflozin, a component of INVOKAMET or INVOKAMET XR, versus placebo was observed in CANVAS (5.9 vs 2.8 events per 1,000 patient-years) and CANVAS-R (7.5 vs 4.2 events per 1,000 patient-years), two randomized, placebo-controlled trials evaluating adult patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease *[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.

Counsel patients about the importance of routine preventative foot care. Monitor patients receiving INVOKAMET or INVOKAMET XR for signs and symptoms of infection (including osteomyelitis), new pain or tenderness, sores or ulcers involving the lower limbs, and institute appropriate treatment.

5.4 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 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating INVOKAMET or 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.

5.5 Genitourinary Infections, including Urosepsis, Pyelonephritis, Necrotizing Fasciitis of the Perineum (Fournier's Gangrene), and Genital Mycotic Infections

INVOKAMET or INVOKAMET XR increases urinary glucose excretion *[see Clinical Pharmacology (12.2)]* and increases the risk of genitourinary infections including urinary tract infections and genital mycotic infections in both male and female patients *[see Adverse Reactions (6.1)]*.

Serious genitourinary infections, including urosepsis, pyelonephritis, and necrotizing fasciitis of the perineum (Fournier's gangrene, a rare life-threatening infection requiring urgent surgical intervention), have occurred in patients receiving SGLT2 inhibitors, including INVOKAMET or INVOKAMET XR *[see Adverse Reactions (6.2)]*. Cases have required hospitalization. In patients with Fournier's gangrene, serious outcomes have included multiple surgeries and death.

Patients with a history of genitourinary infections are more likely to develop genitourinary infections when using INVOKAMET or INVOKAMET XR. Monitor patients for signs and symptoms of genitourinary infections and treat promptly, if indicated.

Immediately evaluate patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, for necrotizing fasciitis. If suspected, discontinue INVOKAMET or INVOKAMET XR and promptly institute appropriate medical and/or surgical intervention.

5.6 Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues

Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKAMET or INVOKAMET XR may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue *[see Adverse Reactions (6.1)]*. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin. Inform patients using these concomitant medications of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.

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

5.8 Bone Fracture

An increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed in adult patients using canagliflozin in the CANVAS trial *[see Clinical Studies (14.3)]*.

Consider factors that contribute to fracture risk prior to initiating INVOKAMET or INVOKAMET XR *[see Adverse Reactions (6.1)]*.

5.9 Vitamin B_{12} Deficiency

In metformin HCl clinical trials of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, may be associated with anemia but appears to be rapidly reversible with discontinuation of metformin HCl or vitamin B_{12} supplementation. Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. Measure hematologic parameters on an annual basis and vitamin B_{12} at 2- to 3-year intervals in patients on INVOKAMET or 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, 5.4)]*
- Diabetic Ketoacidosis in Patients with Type 1 Diabetes and Other Ketoacidosis *[see Warnings and Precautions (5.2)]*
- Lower Limb Amputation *[see Warnings and Precautions (5.3)]*
- Volume Depletion *[see Warnings and Precautions (5.4)]*
- Genitourinary Infections, including Urosepsis, Pyelonephritis, Necrotizing Fasciitis of the Perineum (Fournier's Gangrene), and Genital Mycotic Infections *[see Warnings and Precautions (5.5)]*
- Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues *[see Warnings and Precautions (5.6)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.7)]*
- Bone Fracture *[see Warnings and Precautions (5.8)]*
- Vitamin B_{12} Deficiency *[see Warnings and Precautions (5.9)]*

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.

Canagliflozin has been evaluated in clinical trials in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus. Additionally, canagliflozin has been studied in clinical trials in adult patients with type 2 diabetes mellitus who also have heart failure or chronic kidney disease. The overall safety profile of canagliflozin was consistent across the studied indications.

Clinical Trials in Adults with Type 2 Diabetes Mellitus

Pool of Placebo-Controlled Trials for Glycemic Control

Canagliflozin

The data in Table 3 are 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 1,667 adult 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 (50%) of the population was male and 72% were White, 12% were Asian, and 5% were Black or African American. At baseline the population had diabetes for an average of 7.3 years, had a mean HbA_{1C} of 8.0% and 20% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 88 mL/min/1.73 m^2).

Table 3 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 3: Adverse Reactions from Pool of Four 26-Week Placebo-Controlled Trials Reported in ≥ 2% of Canagliflozin-Treated Adult Patients*

Adverse Reaction	Placebo N=646	Canagliflozin 100 mg N=833	Canagliflozin 300 mg N=834
Urinary tract infections‡	3.8%	5.9%	4.4%
Increased urination§	0.7%	5.1%	4.6%
Thirst#	0.1%	2.8%	2.4%
Constipation	0.9%	1.8%	2.4%
Nausea	1.6%	2.1%	2.3%
	N=312	**N=425**	**N=430**
Female genital mycotic infections†	2.8%	10.6%	11.6%
Vulvovaginal pruritus	0.0%	1.6%	3.2%
	N=334	**N=408**	**N=404**
Male genital mycotic infections¶	0.7%	4.2%	3.8%

* 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 mycotic infections include the following adverse reactions: Vulvovaginal candidiasis, Vulvovaginal mycotic 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, Pollakiuria, Urine output increased, Micturition urgency, and Nocturia.

¶ Male genital mycotic infections include the following adverse reactions: Balanitis or Balanoposthitis, Balanitis candida, and Genital infection fungal.

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

Note: Percentages were weighted by trials. Trial weights were proportional to the harmonic mean of the three treatment sample sizes.

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

Canagliflozin and Metformin HCl

The incidence and type of adverse reactions in the three 26-week placebo-controlled metformin HCl tablets add-on trials in adults, representing a majority of data from the four 26-week placebo-controlled trials, was similar to the adverse reactions described in Table 3. There were no additional adverse reactions identified in the pooling of these three placebo-controlled trials that included metformin HCl tablets relative to the four placebo-controlled trials.

In a trial in adults with canagliflozin as initial combination therapy with metformin HCl *[see Clinical Studies (14.1)]*, an increased incidence of diarrhea was observed in the canagliflozin and metformin HCl combination groups (4.2%) compared to canagliflozin or metformin HCl monotherapy groups (1.7%).

Placebo-Controlled Trial in Diabetic Nephropathy

The occurrence of adverse reactions for canagliflozin was evaluated in patients participating in CREDENCE, a trial in adult patients with type 2 diabetes mellitus and diabetic nephropathy with albuminuria > 300 mg/day *[see Clinical Studies (14.4)]*. These data reflect exposure of 2,201 adult patients to canagliflozin and a mean duration of exposure to canagliflozin of 137 weeks.

The rate of lower limb amputations associated with the use of canagliflozin 100 mg relative to placebo was 12.3 vs 11.2 events per 1,000 patient-years, respectively, with 2.6 years mean duration of follow-up.

The incidence of hypotension was 2.8% and 1.5% on canagliflozin 100 mg and placebo, respectively.

Pool of Placebo- and Active-Controlled Trials for Glycemic Control and Cardiovascular Outcomes

The occurrence of adverse reactions for canagliflozin was evaluated in adult patients participating in placebo- and active-controlled trials and in an integrated analysis of two cardiovascular trials, CANVAS and CANVAS-R.

The types and frequency of common adverse reactions observed in the pool of eight clinical trials (which reflect an exposure of 6,177 adult patients to canagliflozin) were consistent with those listed in Table 3. Percentages were weighted by trials. Trial weights were proportional to the harmonic mean of the three treatment sample sizes. In this pool, canagliflozin was also associated with the adverse reactions of fatigue (1.8%, 2.2%, and 2.0% with comparator, canagliflozin 100 mg, and canagliflozin 300 mg, respectively) and loss of strength or energy (i.e., asthenia)

(0.6%, 0.7%, and 1.1% with comparator, canagliflozin 100 mg, and canagliflozin 300 mg, respectively).

In the pool of eight clinical trials, the incidence rate of pancreatitis (acute or chronic) was 0.1%, 0.2%, and 0.1% receiving comparator, canagliflozin 100 mg, and canagliflozin 300 mg, respectively.

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

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

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

Lower Limb Amputation

An increased risk of lower limb amputations associated with canagliflozin was observed in CANVAS (5.9 vs 2.8 events per 1,000 patient-years) and CANVAS-R (7.5 vs 4.2 events per 1,000 patient-years), two randomized, placebo-controlled trials evaluating adult patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease. Patients in CANVAS and CANVAS-R were followed for an average of 5.7 and 2.1 years, respectively *[see Clinical Studies (14.3)]*. The amputation data for CANVAS and CANVAS-R are shown in Tables 4 and 5, respectively.

Table 4: Amputations in the CANVAS Trial in Adults with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease

	Placebo N=1,441	**Canagliflozin 100 mg N=1,445**	**Canagliflozin 300 mg N=1,441**	**Canagliflozin (Pooled) N=2,886**
Patients with an amputation, n (%)	22 (1.5)	50 (3.5)	45 (3.1)	95 (3.3)
Total amputations	33	83	79	162
Amputation incidence rate (per 1,000 patient-years)	2.8	6.2	5.5	5.9
Hazard Ratio (95% CI)	--	2.24 (1.36, 3.69)	2.01 (1.20, 3.34)	2.12 (1.34, 3.38)

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 5: Amputations in the CANVAS-R Trial in Adults with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease

	Placebo N=2,903	Canagliflozin 100 mg (with up-titration to 300 mg) N=2,904
Patients with an amputation, n (%)	25 (0.9)	45 (1.5)
Total amputations	36	59
Amputation incidence rate (per 1,000 patient-years)	4.2	7.5
Hazard Ratio (95% CI)	--	1.80 (1.10, 2.93)

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 in adults (mean duration of follow-up of 5.7 years) *[see Clinical Studies (14.3)]*, the incidence of renal cell carcinoma was 0.15% (2/1,331) and 0.29% (8/2,716) 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 adult 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 m^2), and age 75 years and older (Table 6) *[see Use in Specific Populations (8.5 and 8.6)]*.

Table 6: Adult Patients with at Least One Volume Depletion-Related Adverse Reaction (Pooled Results from 8 Clinical Trials for Glycemic Control)

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

* Includes placebo and active-comparator groups

† Patients could have more than 1 of the listed risk factors

Falls

In a pool of nine clinical trials in adults 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 in adults for glycemic control, female genital mycotic infections (e.g., vulvovaginal mycotic infection, vulvovaginal candidiasis, and vulvovaginitis) occurred in 2.8%, 10.6%, and 11.6% of females treated with placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections on canagliflozin. Female patients who developed genital mycotic infections on canagliflozin were more likely to experience recurrence and require treatment with oral or topical antifungal agents and anti-microbial agents. In females, discontinuation due to genital mycotic infections occurred in 0% and 0.7% of patients treated with placebo and canagliflozin, respectively.

In the pool of four placebo-controlled clinical trials in adults, male genital mycotic infections (e.g., candidal balanitis, balanoposthitis) occurred in 0.7%, 4.2%, and 3.8% of males treated with placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. Male genital mycotic infections occurred more commonly in uncircumcised males and in males with a prior history of balanitis or balanoposthitis. Male patients who developed genital mycotic infections on canagliflozin were more likely to experience recurrent infections (22% on canagliflozin versus none on placebo) and require treatment with oral or topical antifungal agents and anti-microbial agents than patients on comparators. In males, discontinuations due to genital mycotic infections occurred in 0% and 0.5% of patients treated with placebo and canagliflozin, respectively.

In the pooled analysis of 8 randomized trials in adults 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 in adults *[see Clinical Studies (14.1)]*, episodes of hypoglycemia occurred at a higher rate when canagliflozin was co-administered with insulin or sulfonylureas (Table 7).

Table 7: Incidence of Hypoglycemia* in Randomized Clinical Trials of Glycemic Control in Adults

Monotherapy (26 weeks)	**Placebo (N=192)**	**Canagliflozin 100 mg (N=195)**	**Canagliflozin 300 mg (N=197)**
Overall [N (%)]	5 (2.6)	7 (3.6)	6 (3.0)

In Combination with Metformin HCl (26 weeks)	**Placebo + Metformin HCl (N=183)**	**Canagliflozin 100 mg + Metformin HCl (N=368)**	**Canagliflozin 300 mg + Metformin HCl (N=367)**
Overall [N (%)]	3 (1.6)	16 (4.3)	17 (4.6)
Severe [N (%)][†]	0 (0)	1 (0.3)	1 (0.3)
In Combination with Metformin HCl (18 weeks)[‡]	**Placebo (N=93)**	**Canagliflozin 100 mg (N=93)**	**Canagliflozin 300 mg (N=93)**
Overall [N (%)]	3 (3.2)	4 (4.3)	3 (3.2)
In Combination with Metformin HCl + Sulfonylurea (26 weeks)	**Placebo + Metformin HCl + Sulfonylurea (N=156)**	**Canagliflozin 100 mg + Metformin HCl + Sulfonylurea (N=157)**	**Canagliflozin 300 mg + Metformin HCl + Sulfonylurea (N=156)**
Overall [N (%)]	24 (15.4)	43 (27.4)	47 (30.1)
Severe [N (%)][†]	1 (0.6)	1 (0.6)	0
In Combination with Metformin HCl + Pioglitazone (26 weeks)	**Placebo + Metformin HCl + Pioglitazone (N=115)**	**Canagliflozin 100 mg + Metformin HCl + Pioglitazone (N=113)**	**Canagliflozin 300 mg + Metformin HCl + Pioglitazone (N=114)**
Overall [N (%)]	3 (2.6)	3 (2.7)	6 (5.3)
In Combination with Insulin (18 weeks)	**Placebo (N=565)**	**Canagliflozin 100 mg (N=566)**	**Canagliflozin 300 mg (N=587)**
Overall [N (%)]	208 (36.8)	279 (49.3)	285 (48.6)
Severe [N (%)][†]	14 (2.5)	10 (1.8)	16 (2.7)
In Combination with Insulin and Metformin HCl (18 weeks)[§]	**Placebo (N=145)**	**Canagliflozin 100 mg (N=139)**	**Canagliflozin 300 mg (N=148)**
Overall [N (%)]	66 (45.5)	58 (41.7)	70 (47.3)
Severe [N (%)][†]	4 (2.8)	1 (0.7)	3 (2.0)

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

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

[‡] Phase 2 clinical trial with twice daily dosing (50 mg or 150 mg twice daily in combination with metformin HCl)

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

Bone Fracture

In the CANVAS trial in adults *[see Clinical Studies (14.3)]*, 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.

Metformin HCl

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

In metformin clinical trials of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels was observed in approximately 7% of adult patients.

Laboratory and Imaging Tests

Increases in Serum Creatinine and Decreases in eGFR

Initiation of canagliflozin causes an increase in serum creatinine and decrease in estimated GFR. In patients with moderate renal impairment, the increase in serum creatinine generally does not exceed 0.2 mg/dL, occurs within the first 6 weeks of starting therapy, and then stabilizes. Increases that do not fit this pattern should prompt further evaluation to exclude the possibility of acute kidney injury *[see Clinical Pharmacology (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.

Increases in Serum Potassium

In a pooled population of adult patients (N=723) in glycemic control trials with moderate renal impairment (eGFR 45 to less than 60 mL/min/1.73 m^2), increases in serum potassium to greater than 5.4 mEq/L and 15% above occurred in 5.3%, 5.0%, and 8.8% of patients treated with placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. Severe elevations (greater than or equal to 6.5 mEq/L) occurred in 0.4% of patients treated with placebo, no patients treated with canagliflozin 100 mg, and 1.3% of patients treated with canagliflozin 300 mg.

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

In CREDENCE, no difference in serum potassium, no increase in adverse events of hyperkalemia, and no increase in absolute (> 6.5 mEq/L) or relative (> upper limit of normal and > 15% increase from baseline) increases in serum potassium were observed in adult patients treated with canagliflozin 100 mg relative to placebo.

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

In the pool of four glycemic control placebo-controlled trials in adults, dose-related increases in LDL-C with canagliflozin were observed. Mean changes (percent changes) from baseline in LDL-C relative to placebo were 4.4 mg/dL (4.5%) and 8.2 mg/dL (8.0%) with canagliflozin

100 mg and canagliflozin 300 mg, respectively. The mean baseline LDL-C levels were 104 to 110 mg/dL across treatment groups.

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

Increases in Hemoglobin

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

Decreases in Bone Mineral Density

Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry in a clinical trial of 714 older adults (mean age 64 years) *[see Clinical Studies (14.1)]*. At 2 years, adult patients randomized to canagliflozin 100 mg and canagliflozin 300 mg had placebo-corrected declines in BMD at the total hip of 0.9% and 1.2%, respectively, and at the lumbar spine of 0.3% and 0.7%, respectively. Additionally, placebo-adjusted BMD declines were 0.1% at the femoral neck for both canagliflozin doses and 0.4% at the distal forearm for patients randomized to canagliflozin 300 mg. The placebo-adjusted change at the distal forearm for patients randomized to canagliflozin 100 mg was 0%.

Clinical Trials in Pediatric Patients Aged 10 Years and Older with Type 2 Diabetes Mellitus

Canagliflozin

Canagliflozin was administered to 84 pediatric patients in a double-blind, placebo-controlled trial of 171 pediatric patients aged 10 to 17 years with a mean exposure to canagliflozin of 48.3 weeks *[see Clinical Studies (14.2)]*. At baseline, background therapies included metformin monotherapy (46%), metformin and insulin (29%), diet and exercise only (14%), and insulin monotherapy (11%). Approximately 42% were Asian, 42% were White, 11% were Black or African American, 5% were American Indian/Alaska Native, and 36% identified as Hispanic or Latino ethnicity. The mean baseline eGFR was 157.3 mL/min/1.73 m^2, and approximately 16% (24/151) of the trial population with measurements had microalbuminuria or macroalbuminuria. The safety profile of pediatric patients treated with canagliflozin was similar to that observed in adults with type 2 diabetes mellitus.

Metformin HCl

In clinical trials with metformin HCl immediate-release tablets in pediatric patients with type 2 diabetes mellitus, the profile of adverse reactions was similar to that observed in adults.

6.2 Postmarketing Experience

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

Canagliflozin

Metabolism and Nutrition

Ketoacidosis

Renal and Urinary

Acute Kidney Injury

Immune System

Anaphylaxis

Skin and Subcutaneous Tissue

Angioedema

Infections

Urosepsis and Pyelonephritis, Necrotizing Fasciitis of the Perineum (Fournier's gangrene)

Metformin HCl

Hepatobiliary

Cholestatic, hepatocellular, and mixed hepatocellular liver injury

7 DRUG INTERACTIONS

Table 8: Clinically Significant Drug Interactions with INVOKAMET or INVOKAMET XR

Carbonic Anhydrase Inhibitors	
Clinical Impact:	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 or INVOKAMET XR may increase the risk for lactic acidosis.
Intervention:	Consider more frequent monitoring of these patients.
Examples:	Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide)
Drugs That Reduce Metformin Clearance	
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, dolutegravir, and cimetidine
Alcohol	
Clinical Impact:	Alcohol is known to potentiate the effect of metformin HCl on lactate metabolism.

Intervention:	Warn patients against excessive alcohol intake while receiving INVOKAMET or INVOKAMET XR.
UGT Enzyme Inducers	
Clinical Impact:	UGT enzyme inducers decrease canagliflozin exposure which may reduce the effectiveness of INVOKAMET or INVOKAMET XR.
Intervention:	For patients with eGFR 60 mL/min/1.73 m^2 or greater, if an inducer of UGTs is co-administered with INVOKAMET or INVOKAMET XR, increase the total daily dose of canagliflozin to 200 mg in patients currently tolerating INVOKAMET or 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. For patients with eGFR less than 60 mL/min/1.73 m^2, if an inducer of UGTs is co-administered with INVOKAMET or INVOKAMET XR, increase the total daily dose of canagliflozin to 200 mg in patients currently tolerating canagliflozin 100 mg *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.
Examples:	Rifampin, phenytoin, phenobarbital, ritonavir
Insulin or Insulin Secretagogues	
Clinical Impact:	The risk of hypoglycemia is increased when INVOKAMET or INVOKAMET XR is used concomitantly with insulin secretagogues (e.g., sulfonylurea) or insulin.
Intervention:	Concomitant use may require a lower dosage of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.
Drugs Affecting Glycemic Control	
Clinical Impact:	Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control.
Intervention:	When such drugs are administered to a patient receiving INVOKAMET or INVOKAMET XR, monitor for loss of blood glucose control. When such drugs are withdrawn from a patient receiving INVOKAMET or INVOKAMET XR, monitor for hypoglycemia.
Examples:	Thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid.
Digoxin	
Clinical Impact:	Canagliflozin increases digoxin exposure *[see Clinical Pharmacology (12.3)]*.
Intervention:	Monitor patients taking INVOKAMET or INVOKAMET XR with concomitant digoxin for a need to adjust the dosage of digoxin.
Lithium	
Clinical Impact:	Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations.
Intervention:	Monitor serum lithium concentration more frequently during INVOKAMET or INVOKAMET XR initiation and dosage changes.
Drug/Laboratory Test Interference	
Positive Urine Glucose Test	
Clinical Impact:	SGLT2 inhibitors increase urinary glucose excretion which will lead to positive urine glucose tests.
Intervention:	Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
Interference with 1,5-anhydroglucitol (1,5-AG) Assay	
Clinical Impact:	Measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors.
Intervention:	Monitoring glycemic control with 1,5-AG assay is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

Limited data with INVOKAMET, 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 juvenile animal studies, adverse renal pelvic and tubule dilatations that were not reversible were observed in rats when canagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy, at an exposure 0.5-times the 300 mg clinical dose, based on AUC. 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 2,000 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 a HbA_{1C} >7 and has been reported to be as high as 20-25% in women with a HbA_{1C} >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 definitely 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 rats and 160 mg/kg in pregnant rabbits during embryonic organogenesis or during a study in which maternal rats were dosed from gestation day (GD) 6 through PND 21, yielding exposures up to approximately 19-times the 300 mg clinical dose, based on AUC.

Metformin 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 2,000 mg clinical dose based on body surface area (mg/m^2) 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 2,000 mg clinical doses of canagliflozin and metformin HCl based on AUC.

8.2 Lactation

Risk Summary

There is no information regarding the presence of INVOKAMET, 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 INVOKAMET or 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

The safety and effectiveness of INVOKAMET and INVOKAMET XR as an adjunct to diet and exercise to improve glycemic control in type 2 diabetes mellitus have been established in pediatric patients aged 10 years and older.

Use of INVOKAMET and INVOKAMET XR for this indication is supported by evidence from a 52-week double-blind, placebo-controlled trial of canagliflozin in 171 pediatric patients aged 10 to 17 years with type 2 diabetes mellitus and in a pediatric pharmacokinetic study *[see Clinical Pharmacology (12.3) and Clinical Studies (14.2)]*. The safety profile of pediatric patients treated with canagliflozin was similar to that observed in adults with type 2 diabetes mellitus.

The use of INVOKAMET and INVOKAMET XR for this indication is also supported by evidence from adequate and well-controlled trials of metformin HCl immediate-release tablets in adults with additional data from a controlled clinical trial using metformin HCl immediate-release tablets in pediatric patients 10 to 16 years old with type 2 diabetes mellitus *[see Clinical Studies (14.1, 14.2)]*. In the clinical trial with pediatric patients receiving metformin HCl immediate-release tablets, adverse reactions with metformin HCl immediate-release tablets were similar to those described in adults *[see Adverse Reactions (6.1)]*.

The safety and effectiveness of INVOKAMET or INVOKAMET XR for glycemic control in patients with type 2 diabetes mellitus have not been established in pediatric patients under 10 years of age.

The safety and effectiveness of INVOKAMET or INVOKAMET XR have not been established in pediatric patients to reduce the risk of:

- major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in patients with type 2 diabetes mellitus and established cardiovascular disease (CVD).

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

8.5 Geriatric Use

INVOKAMET and INVOKAMET 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 INVOKAMET or INVOKAMET XR in the elderly and then adjust dose based on renal function *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1, 5.4)]*.

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 (14.1)]*. 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 HbA_{1C} with canagliflozin relative to placebo were seen in older (65 years and older; -0.61% with canagliflozin 100 mg and -0.74% with canagliflozin 300 mg relative to placebo) compared to younger patients (-0.72% with canagliflozin 100 mg and -0.87% with canagliflozin 300 mg relative to placebo).

Metformin 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 (5.4), and Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

Canagliflozin

The efficacy and safety of canagliflozin for glycemic control were evaluated in a trial that included adult patients with moderate renal impairment (eGFR 30 to less than 50 mL/min/1.73 m^2). These patients had less overall glycemic efficacy, and patients treated with canagliflozin 300 mg per day had increases in serum potassium, which were transient and similar by the end of the trial. 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 (5.4)]*.

Efficacy and safety trials with canagliflozin did not enroll adult patients with ESKD on dialysis or patients with an eGFR less than 30 mL/min/1.73 m^2 *[see Clinical Pharmacology (12.3)]*.

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 or INVOKAMET XR is contraindicated in severe renal impairment (eGFR less than 30 mL/min/1.73 m^2) or in patients on dialysis *[see Dosage and Administration (2.3), 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 or 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)]*.

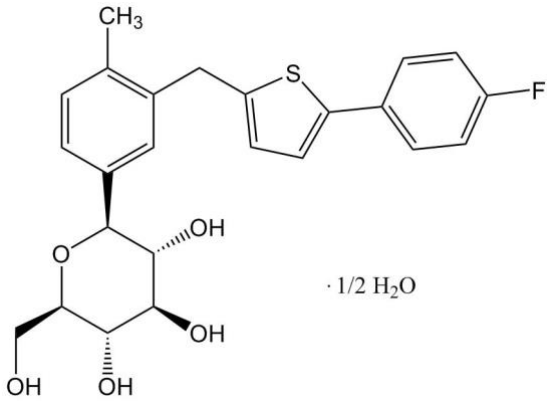
In the event of an overdose with INVOKAMET or INVOKAMET XR, contact the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations. Employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical 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 or INVOKAMET XR overdosage is suspected.

11 DESCRIPTION

INVOKAMET® (canagliflozin and metformin HCl immediate-release tablets) and INVOKAMET® XR (canagliflozin and metformin HCl extended-release tablets) contain canagliflozin and metformin HCl.

Canagliflozin

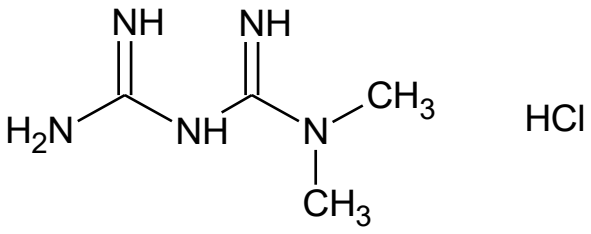
Canagliflozin is an inhibitor of SGLT2, the transporter responsible for reabsorbing the majority of glucose filtered by the kidney. Canagliflozin is chemically known as (1*S*)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol hemihydrate and its molecular formula and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



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

Metformin HCl

Metformin HCl is a biguanide chemically known as 1,1-Dimethylbiguanide HCl and its molecular formula and weight are $C_4H_{11}N_5 \bullet HCl$ and 165.62, respectively. The structural formula for metformin HCl is:



INVOKAMET and INVOKAMET XR

INVOKAMET or INVOKAMET XR are supplied as film-coated tablets for oral administration. Each 50 mg/500 mg tablet and 50 mg/1,000 mg tablet contains 51 mg of canagliflozin equivalent

to 50 mg canagliflozin (anhydrous) and 500 mg or 1,000 mg metformin HCl (equivalent to metformin 389.93 mg and 779.86 mg, respectively).

Each 150 mg/500 mg tablet and 150 mg/1,000 mg tablet contains 153 mg of canagliflozin equivalent to 150 mg canagliflozin (anhydrous) and 500 mg or 1,000 mg metformin HCl (equivalent to metformin 389.93 mg and 779.86 mg, respectively).

INVOKAMET contains the following inactive ingredients: croscarmellose sodium (E468), hypromellose, magnesium stearate (E572), and microcrystalline cellulose (E460[i]). The magnesium stearate is vegetable-sourced. The tablets are finished with a commercially available film-coating consisting of the following inactive ingredients: macrogol/PEG3350 (E1521), polyvinyl alcohol (E1203) (partially hydrolyzed), talc (E553b), titanium dioxide (E171), iron oxide yellow (E172) (50 mg/1,000 mg and 150 mg/500 mg tablets only), iron oxide red (E172) (50 mg/1,000 mg, 150 mg/500 mg and 150 mg/1,000 mg tablets only), and iron oxide black (E172) (150 mg/1,000 mg tablets only).

INVOKAMET XR contains the following inactive ingredients: croscarmellose sodium (E468), hydroxypropyl cellulose (E463), hypromellose, lactose anhydrous, magnesium stearate (E572) (vegetable-sourced), microcrystalline cellulose (E460[i]), polyethylene oxide, and silicified microcrystalline cellulose (50 mg/500 mg and 50 mg/1,000 mg tablets only). The tablets are finished with a commercially available film-coating consisting of the following inactive ingredients: macrogol/PEG3350 (E1521), polyvinyl alcohol (E1203) (partially hydrolyzed), talc (E553b), titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172), and iron oxide black (E172) (50 mg/1,000 mg and 150 mg/1,000 mg tablets only).

INVOKAMET XR tablets provide canagliflozin for immediate-release and metformin HCl for extended-release. Each bilayer tablet is compressed from two separate granulates, one for each active ingredient of the tablet, and finished with a film-coating. The metformin HCl extended-release layer is based on a polymer matrix which controls the drug release by passive diffusion through the swollen matrix in combination with tablet erosion.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Canagliflozin

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

Canagliflozin increases the delivery of sodium to the distal tubule by blocking SGLT2-dependent glucose and sodium reabsorption. This is believed to increase tubuloglomerular feedback and reduce intraglomerular pressure.

Metformin HCl

Metformin HCl is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin HCl decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may decrease.

12.2 Pharmacodynamics

Canagliflozin

Following single and multiple oral doses of canagliflozin in adult patients with type 2 diabetes, dose-dependent decreases in RT_G and increases in urinary glucose excretion were observed. From a starting RT_G value of approximately 240 mg/dL, canagliflozin at 100 mg and 300 mg once daily suppressed RT_G throughout the 24-hour period. Data from single oral doses of canagliflozin in healthy volunteers indicate that, on average, the elevation in urinary glucose excretion approaches baseline by about 3 days for doses up to 300 mg once daily. Maximal suppression of mean RT_G over the 24-hour period was seen with the 300 mg daily dose to approximately 70 to 90 mg/dL in patients with type 2 diabetes in Phase 1 trials. The reductions in RT_G led to increases in mean UGE of approximately 100 g/day in patients with type 2 diabetes treated with either 100 mg or 300 mg of canagliflozin. The 24-h mean RT_G at steady state was similar following once daily and twice daily dosing regimens at the same total daily dose of 100 mg or 300 mg. In patients with type 2 diabetes given 100 to 300 mg once daily over a 16-day dosing period, reductions in RT_G and increases in urinary glucose excretion were observed over the dosing period. In this trial, plasma glucose declined in a dose-dependent fashion within the first day of dosing.

Cardiac Electrophysiology

In a randomized, double-blind, placebo-controlled, active-comparator, 4-way crossover trial, 60 healthy adult 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 10.6 hours and 13.1 hours for the 100 mg and 300 mg doses, respectively. Steady-state was reached after 4 to 5 days of once-daily dosing with canagliflozin 100 mg to 300 mg. Canagliflozin does not exhibit time-dependent pharmacokinetics and accumulated in plasma up to 36% following multiple doses of 100 mg and 300 mg. The mean systemic exposure (AUC) at steady state was similar following once daily and twice daily dosing regimens at the same total daily dose of 100 mg or 300 mg.

Absorption

Canagliflozin

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

Metformin HCl

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 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 HCl

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 sulfonylureas, 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 HCl

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

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

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

Metformin HCl

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 or INVOKAMET XR were not conducted in patients with renal and hepatic

impairment. Descriptions of the individual components in this patient population are described below.

Pediatric Patients

Canagliflozin

The pharmacokinetics and pharmacodynamics of canagliflozin were investigated in pediatric patients aged 10 years and older with type 2 diabetes mellitus. Oral administration of canagliflozin at 100 mg and 300 mg resulted in exposures and responses consistent with those found in adult patients.

Metformin HCl

After administration of a single oral metformin 500 mg immediate-release tablet with food, geometric mean metformin C_{max} and AUC differed less than 5% between pediatric type 2 diabetic patients (12-16 years of age) and gender-and weight-matched healthy adults (20-45 years of age), all with normal renal function.

Patients with Renal Impairment

Canagliflozin

A single-dose, open-label trial evaluated the pharmacokinetics of canagliflozin 200 mg in adult 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 adult 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 (5.4)]*.

Canagliflozin was negligibly removed by hemodialysis.

Metformin HCl

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 (5.4)]*. 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)]*.

Patients with Hepatic Impairment

Canagliflozin

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

These differences are not considered to be clinically meaningful. There is no clinical experience in adult patients with Child-Pugh class C (severe) hepatic impairment *[see Warnings and Precautions (5.1)]*.

Metformin HCl

No pharmacokinetic trials of metformin HCl tablets have been conducted in patients with hepatic insufficiency *[see Warnings and Precautions (5.1)]*.

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

Canagliflozin

Based on the population PK analysis with data collected from 1,526 adult subjects, age, body mass index (BMI)/weight, gender, and race do not have a clinically meaningful effect on the pharmacokinetics of canagliflozin *[see Use in Specific Populations (8.5)]*.

Metformin HCl

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 HCl

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 C_{max} is increased, compared with healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function *[see Warnings and Precautions (5.1, 5.4) and Use in Specific Populations (8.5)]*.

Drug Interaction Studies

INVOKAMET and INVOKAMET XR

Pharmacokinetic drug interaction trials with INVOKAMET or 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

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

* Single dose unless otherwise noted

† AUC_{inf} for drugs given as a single dose and AUC_{24h} for drugs given as multiple doses

QD = once daily; BID = twice daily

Table 10: Effect of Canagliflozin on Systemic Exposure of Co-Administered Drugs

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

* Single dose unless otherwise noted

† AUC_{inf} for drugs given as a single dose and AUC_{24h} for drugs given as multiple doses

‡ AUC_{0-12h}

QD = once daily; BID = twice daily; INR = International Normalized Ratio

Metformin HCl

Table 11: Effect of Co−Administered Drugs on Plasma Metformin Systemic Exposures

Co-Administered Drug	Dose of Co-Administered Drug*	Dose of Metformin HCl*	Geometric Mean Ratio (Ratio With/Without Co-Administered Drug) No Effect = 1.00	
			AUC†	C_{max}

No dose adjustments required for the following:				
Glyburide	5 mg	500 mg‡	0.98§	0.99§
Furosemide	40 mg	850 mg	1.09§	1.22§
Nifedipine	10 mg	850 mg	1.16	1.21
Propranolol	40 mg	850 mg	0.90	0.94
Ibuprofen	400 mg	850 mg	1.05§	1.07§
Drugs that are eliminated by renal tubular secretion increase the accumulation of metformin *[see Warnings and Precautions (5) and Drug Interactions (7)]*				
Cimetidine	400 mg	850 mg	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis *[see Warnings and Precautions (5) and Drug Interactions (7)]*				
Topiramate¶	100 mg	500 mg	1.25#	1.18

* Single dose unless otherwise noted

† AUC = $AUC_{0-\infty}$

‡ Metformin HCl extended-release tablets 500 mg

§ Ratio of arithmetic means

¶ Healthy volunteer study at steady state with topiramate 100 mg every 12 hours and metformin 500 mg every 12 hours for 7 days. Study conducted to assess pharmacokinetics only

Steady state AUC_{0-12h}.

Table 12: Effect of Metformin HCl on Co-Administered Drug Systemic Exposures

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

* Single dose unless otherwise noted

† AUC = $AUC_{0-\infty}$

‡ $AUC_{0-24\ hr}$ reported

§ Ratio of arithmetic means, p-value of difference <0.05

¶ Ratio of arithmetic means.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

INVOKAMET and INVOKAMET XR

No animal studies have been conducted with the combined products in INVOKAMET or INVOKAMET 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 1,500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2,000 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 stromal 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 (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Impairment of Fertility

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

Fertility of male or female rats was unaffected by metformin 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

The effectiveness of INVOKAMET and INVOKAMET XR have been established in clinical trials with canagliflozin 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 (glimepiride), both as add-on combination therapy with metformin HCl.

Canagliflozin as Initial Combination Therapy with Metformin HCl Extended-Release

A total of 1,186 adult 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 extended-release. The median age was 56 years, 48% of patients were male, and the mean baseline eGFR was 87.6 mL/min/1.73 m^2. The median duration of diabetes was 1.6 years, and 72% of patients were treatment naïve. 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 extended-release dose was initiated at 500 mg/day for the first week of treatment and then increased to 1,000 mg/day. Metformin HCl extended-release 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 extended-release resulted in a statistically significant greater improvement in HbA_{1C} compared to their respective canagliflozin doses (100 mg and 300 mg) alone or metformin HCl extended-release alone.

Table 13: Results from 26-Week Active-Controlled Clinical Trial of Canagliflozin Alone or Canagliflozin as Initial Combination Therapy with Metformin HCl Extended-Release in Adults with Type 2 Diabetes Mellitus*

Efficacy Parameter	Metformin HCl extended-release (N=237)	Canagliflozin 100 mg (N=237)	Canagliflozin 300 mg (N=238)	Canagliflozin 100 mg + Metformin HCl extended-release (N=237)	Canagliflozin 300 mg + Metformin HCl extended-release (N=237)
HbA_{1C} (%)					
Baseline (mean)	8.81	8.78	8.77	8.83	8.90
Change from baseline (adjusted mean)¶	-1.30	-1.37	-1.42	-1.77	-1.78
Difference from canagliflozin 100 mg (adjusted mean) (95% CI)†				-0.40‡ (-0.59, -0.21)	
Difference from canagliflozin 300 mg (adjusted mean) (95% CI)†					-0.36‡ (-0.56, -0.17)
Difference from metformin HCl extended-release (adjusted mean) (95% CI)†				-0.46‡ (-0.66, -0.27)	-0.48‡ (-0.67, -0.28)
Percent of patients achieving HbA_{1C} < 7%	38	34	39	47§§	51§§

* Intent-to-treat population

† Least squares mean adjusted for covariates including baseline value and stratification factor

‡ Adjusted p=0.001

§§ Adjusted p<0.05

¶ There were 121 patients without week 26 efficacy data. Analyses addressing missing data gave consistent results with the results provided in this table.

Canagliflozin as Add-on Combination Therapy with Metformin HCl

A total of 1,284 adult patients with type 2 diabetes inadequately controlled on metformin HCl monotherapy (greater than or equal to 2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated) participated in a 26-week, double-blind, placebo- and active-controlled trial to evaluate the efficacy and safety of canagliflozin in combination with metformin HCl. The mean age was 55 years, 47% of patients were male, and the mean baseline eGFR was 89 mL/min/1.73 m^2. Patients already on the required metformin HCl dose (N=1,009) were randomized after completing a 2-week, single-blind, placebo run-in period. Patients taking less than the required metformin HCl dose or patients on metformin HCl in combination with another antihyperglycemic agent (N=275) were switched to metformin HCl monotherapy (at doses described above) for at least 8 weeks before entering the 2-week, single-blind, placebo run-in. After the placebo run-in period, patients

were randomized to canagliflozin 100 mg, canagliflozin 300 mg, sitagliptin 100 mg, or placebo, administered once daily as add-on therapy to metformin HCl.

At the end of treatment, canagliflozin 100 mg and 300 mg once daily resulted in a statistically significant improvement in HbA_{1C} ($p<0.001$ for both doses) compared to placebo when added to metformin HCl. Canagliflozin 100 mg and 300 mg once daily also resulted in a greater proportion of patients achieving an HbA_{1C} less than 7%, in significant reduction in fasting plasma glucose (FPG), in improved postprandial glucose (PPG), and in percent body weight reduction compared to placebo when added to metformin HCl (see Table 14). Statistically significant ($p<0.001$ for both doses) mean changes from baseline in systolic blood pressure relative to placebo were -5.4 mmHg and -6.6 mmHg with canagliflozin 100 mg and 300 mg, respectively.

Table 14: Results from 26-Week Placebo-Controlled Clinical Trial of Canagliflozin in Combination with Metformin HCl in Adults with Type 2 Diabetes Mellitus*

Efficacy Parameter	Placebo + Metformin HCl (N=183)	Canagliflozin 100 mg + Metformin HCl (N=368)	Canagliflozin 300 mg + Metformin HCl (N=367)
HbA_{1C} (%)			
Baseline (mean)	7.96	7.94	7.95
Change from baseline (adjusted mean)	-0.17	-0.79	-0.94
Difference from placebo (adjusted mean) (95% CI)†		-0.62‡ (-0.76, -0.48)	-0.77‡ (-0.91, -0.64)
Percent of patients achieving HbA_{1C} < 7%	30	46‡	58‡
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	164	169	173
Change from baseline (adjusted mean)	2	-27	-38
Difference from placebo (adjusted mean) (95% CI)†		-30‡ (-36, -24)	-40‡ (-46, -34)
2-hour Postprandial Glucose (mg/dL)			
Baseline (mean)	249	258	262
Change from baseline (adjusted mean)	-10	-48	-57
Difference from placebo (adjusted mean) (95% CI)†		-38‡ (-49, -27)	-47‡ (-58, -36)
Body Weight			
Baseline (mean) in kg	86.7	88.7	85.4
% change from baseline (adjusted mean)	-1.2	-3.7	-4.2
Difference from placebo (adjusted mean) (95% CI)†		-2.5‡ (-3.1, -1.9)	-2.9‡ (-3.5, -2.3)

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

† Least squares mean adjusted for baseline value and stratification factors

‡ $p<0.001$

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

A total of 1,450 adult patients with type 2 diabetes inadequately controlled on metformin HCl monotherapy (greater than or equal to 2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated) participated in a 52-week, double-blind, active-controlled trial to evaluate the efficacy and safety of canagliflozin in combination with metformin HCl.

The mean age was 56 years, 52% of patients were male, and the mean baseline eGFR was 90 mL/min/1.73 m^2. Patients tolerating maximally required metformin HCl dose (N=928) were randomized after completing a 2-week, single-blind, placebo run-in period. Other patients (N=522) were switched to metformin HCl monotherapy (at doses described above) for at least 10 weeks, then completed a 2-week single-blind run-in period. After the 2-week run-in period, patients were randomized to canagliflozin 100 mg, canagliflozin 300 mg, or glimepiride (titration allowed throughout the 52-week 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 HbA_{1C} from baseline compared to glimepiride when added to metformin HCl therapy. Canagliflozin 300 mg provided a greater reduction from baseline in HbA_{1C} 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 Trial Comparing Canagliflozin to Glimepiride in Combination with Metformin HCl in Adults with Type 2 Diabetes Mellitus*

Efficacy Parameter	Canagliflozin 100 mg + Metformin HCl (N=483)	Canagliflozin 300 mg + Metformin HCl (N=485)	Glimepiride (titrated) + Metformin HCl (N=482)
HbA_{1C} (%)			
Baseline (mean)	7.78	7.79	7.83
Change from baseline (adjusted mean)	-0.82	-0.93	-0.81
Difference from glimepiride (adjusted mean) (95% CI)†	-0.01‡ (-0.11, 0.09)	-0.12‡ (-0.22, -0.02)	
Percent of patients achieving HbA_{1C} < 7%	54	60	56
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	165	164	166
Change from baseline (adjusted mean)	-24	-28	-18
Difference from glimepiride (adjusted mean) (95% CI)†	-6 (-10, -2)	-9 (-13, -5)	
Body Weight			
Baseline (mean) in kg	86.8	86.6	86.6
% change from baseline (adjusted mean)	-4.2	-4.7	1.0
Difference from glimepiride (adjusted mean) (95% CI)†	-5.2§ (-5.7, -4.7)	-5.7§ (-6.2, -5.1)	

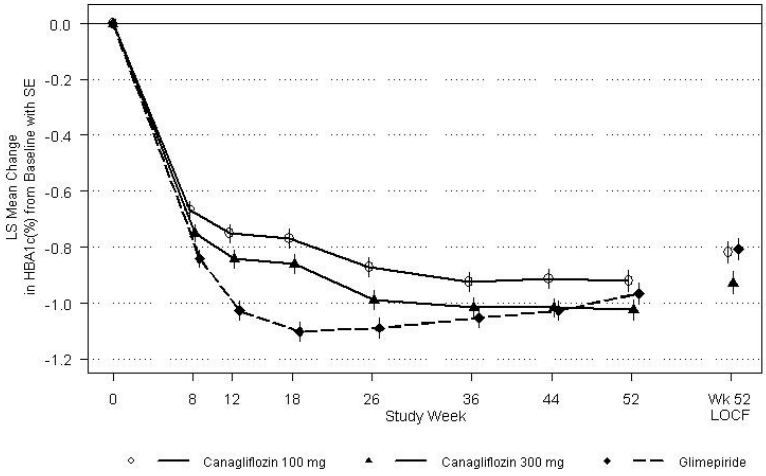
* Intent-to-treat population using last observation in the trial prior to glycemic rescue therapy

† 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%.

§ p<0.001

Figure 1: Mean HbA_{1C} Change in Adults with Type 2 Diabetes Mellitus Treated with Canagliflozin or Glimepiride in Combination with Metformin HCl 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 adult 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 male, 73% of patients were White, 15% were Asian, and 12% were Black or African American. The mean baseline eGFR was 90 mL/min/1.73 m^2 and the mean baseline BMI was 32 kg/m^2. 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 m^2 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-titration occurred as early as Week 4, most (90%) patients randomized to canagliflozin were up-titrated to canagliflozin 300 mg by 6 to 8 weeks.

At the end of 26 weeks, canagliflozin once daily resulted in a statistically significant improvement in HbA_{1C} ($p<0.001$) compared to placebo when added to metformin HCl and sitagliptin (see Table 16).

Table 16: Results from 26-Week Placebo-Controlled Clinical Trial of Canagliflozin in Combination with Metformin HCl and Sitagliptin in Adults with Type 2 Diabetes Mellitus

Efficacy Parameter	Placebo + Metformin HCl and Sitagliptin (N=108*)	Canagliflozin + Metformin HCl and Sitagliptin (N=109*)
HbA_{1C} (%)		

Baseline (mean)	8.40	8.50
Change from baseline (adjusted mean)	-0.03	-0.83
Difference from placebo (adjusted mean) (95% CI)[†§]		-0.81[#] (-1.11; -0.51)
Percent of patients achieving HbA_{1C} < 7%[‡]	9	28
Fasting Plasma Glucose (mg/dL)[¶]		
Baseline (mean)	180	185
Change from baseline (adjusted mean)	-3	-28
Difference from placebo (adjusted mean) (95% CI)		-25[#] (-39; -11)

[*] 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 HbA_{1C} < 7%.

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

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

[#] p<0.001

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

A total of 469 adult 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 sulfonylurea (maximal or near-maximal effective dose) participated in a 26-week, double-blind, placebo-controlled trial to evaluate the efficacy and safety of canagliflozin in combination with metformin HCl and sulfonylurea. The mean age was 57 years, 51% of patients were male, and the mean baseline eGFR was 89 mL/min/1.73 m^2. Patients already on the protocol-specified doses of metformin HCl and sulfonylurea (N=372) entered a 2-week, single-blind, placebo run-in period. Other patients (N=97) were required to be on a stable protocol-specified dose of metformin HCl and sulfonylurea for at least 8 weeks before entering the 2-week run-in period. Following the run-in period, patients were randomized to canagliflozin 100 mg, canagliflozin 300 mg, or placebo administered once daily as add-on to metformin HCl and sulfonylurea.

At the end of treatment, canagliflozin 100 mg and 300 mg once daily resulted in a statistically significant improvement in HbA_{1C} (p<0.001 for both doses) compared to placebo when added to metformin HCl and sulfonylurea. Canagliflozin 100 mg and 300 mg once daily also resulted in a greater proportion of patients achieving an HbA_{1C} 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 sulfonylurea (see Table 17).

Table 17: Results from 26−Week Placebo-Controlled Clinical Trial of Canagliflozin in Combination with Metformin HCl and Sulfonylurea in Adults with Type 2 Diabetes Mellitus*

Efficacy Parameter	**Placebo + Metformin HCl and Sulfonylurea (N=156)**	**Canagliflozin 100 mg + Metformin HCl and Sulfonylurea (N=157)**	**Canagliflozin 300 mg + Metformin HCl and Sulfonylurea (N=156)**
HbA_{1C} (%)			

Baseline (mean)	8.12	8.13	8.13
Change from baseline (adjusted mean)	-0.13	-0.85	-1.06
Difference from placebo (adjusted mean) (95% CI)†		-0.71‡ (-0.90, -0.52)	-0.92‡ (-1.11, -0.73)
Percent of patients achieving HbA_{1C} < 7%	18	43‡	57‡
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	170	173	168
Change from baseline (adjusted mean)	4	-18	-31
Difference from placebo (adjusted mean) (95% CI)†		-22‡ (-31, -13)	-35‡ (-44, -25)
Body Weight			
Baseline (mean) in kg	90.8	93.5	93.5
% change from baseline (adjusted mean)	-0.7	-2.1	-2.6
Difference from placebo (adjusted mean) (95% CI)†		-1.4‡ (-2.1, -0.7)	-2.0‡ (-2.7, -1.3)

* Intent-to-treat population using last observation in the trial 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 Sulfonylurea

A total of 755 adult 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 sulfonylurea (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 sulfonylurea. The mean age was 57 years, 56% of patients were male, and the mean baseline eGFR was 88 mL/min/1.73 m^2. Patients already on protocol-specified doses of metformin HCl and sulfonylurea (N=716) entered a 2-week single-blind, placebo run-in period. Other patients (N=39) were required to be on a stable protocol-specified dose of metformin HCl and sulfonylurea for at least 8 weeks before entering the 2-week run-in period. Following the run-in period, patients were randomized to canagliflozin 300 mg or sitagliptin 100 mg as add-on to metformin HCl and sulfonylurea.

As shown in Table 18 and Figure 2, at the end of treatment, canagliflozin 300 mg provided greater HbA_{1C} reduction compared to sitagliptin 100 mg when added to metformin HCl and sulfonylurea ($p<0.05$). Canagliflozin 300 mg resulted in a mean percent change in body weight from baseline of -2.5% compared to +0.3% with sitagliptin 100 mg. A mean change in systolic 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 Trial Comparing Canagliflozin to Sitagliptin in Combination with Metformin HCl and Sulfonylurea in Adults with Type 2 Diabetes Mellitus*

Efficacy Parameter	**Canagliflozin 300 mg + Metformin HCl and Sulfonylurea (N=377)**	**Sitagliptin 100 mg + Metformin HCl and Sulfonylurea (N=378)**
HbA_{1C} (%)		

Baseline (mean)	8.12	8.13
Change from baseline (adjusted mean)	-1.03	-0.66
Difference from sitagliptin (adjusted mean) (95% CI)†	-0.37‡ (-0.50, -0.25)	
Percent of patients achieving HbA_{1C} < 7%	48	35
Fasting Plasma Glucose (mg/dL)		
Baseline (mean)	170	164
Change from baseline (adjusted mean)	-30	-6
Difference from sitagliptin (adjusted mean) (95% CI)†	-24 (-30, -18)	
Body Weight		
Baseline (mean) in kg	87.6	89.6
% change from baseline (adjusted mean)	-2.5	0.3
Difference from sitagliptin (adjusted mean) (95% CI)†	-2.8§ (-3.3, -2.2)	

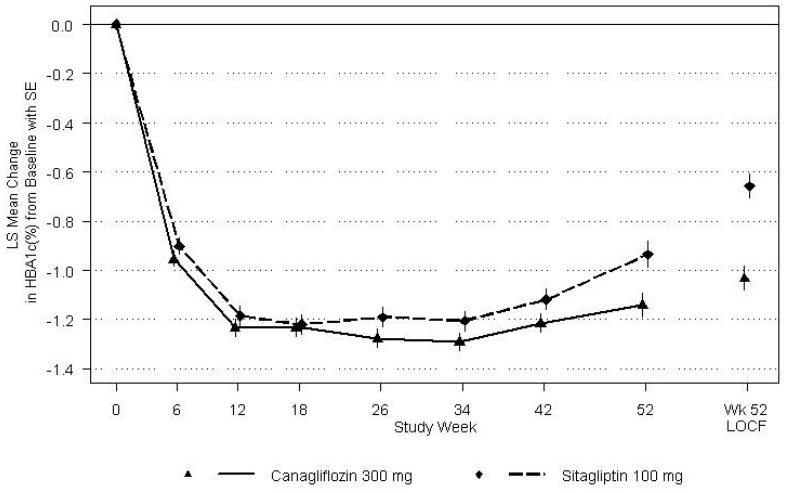
* Intent-to-treat population using last observation in the trial prior to glycemic rescue therapy

† 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 HbA_{1C} Change in Adults with Type 2 Diabetes Mellitus Treated with Canagliflozin or Sitagliptin in Combination with Metformin HCl and Sulfonylurea 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 adult 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 male, and the mean baseline eGFR was 86 mL/min/1.73 m^2. 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.

At the end of treatment, canagliflozin 100 mg and 300 mg once daily resulted in a statistically significant improvement in HbA_{1C} ($p<0.001$ 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 HbA_{1C} 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.

Table 19: Results from 26−Week Placebo-Controlled Clinical Trial of Canagliflozin in Combination with Metformin HCl and Pioglitazone in Adults with Type 2 Diabetes Mellitus*

Efficacy Parameter	Placebo + Metformin HCl and Pioglitazone (N=115)	Canagliflozin 100 mg + Metformin HCl and Pioglitazone (N=113)	Canagliflozin 300 mg + Metformin HCl and Pioglitazone (N=114)
HbA_{1C} (%)			
Baseline (mean)	8.00	7.99	7.84
Change from baseline (adjusted mean)	-0.26	-0.89	-1.03
Difference from placebo (adjusted mean) (95% CI)†		-0.62‡ (-0.81, -0.44)	-0.76‡ (-0.95, -0.58)
Percent of patients achieving HbA_{1C} < 7%	33	47‡	64‡
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	164	169	164
Change from baseline (adjusted mean)	3	-27	-33
Difference from placebo (adjusted mean) (95% CI)†		-29‡ (-37, -22)	-36‡ (-43, -28)
Body Weight			
Baseline (mean) in kg	94.0	94.2	94.4
% change from baseline (adjusted mean)	-0.1	-2.8	-3.8
Difference from placebo (adjusted mean) (95% CI)†		-2.7‡ (-3.6, -1.8)	-3.7‡ (-4.6, -2.8)

* Intent-to-treat population using last observation in the trial 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)

A total of 1,718 adult 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 subtrial 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 male, and the mean baseline eGFR was 81 mL/min/1.73 m^2. 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 HbA_{1C} ($p<0.001$ 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 HbA_{1C} 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 (5.6) and Adverse Reactions (6.1)]*.

Table 20: Results from 18−Week Placebo-Controlled Clinical Trial of Canagliflozin in Combination with Metformin HCl and Insulin ≥ 30 Units/Day in Adults with Type 2 Diabetes Mellitus*

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

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

† Least squares mean adjusted for baseline value and stratification factors

‡ p≤0.001

§ p≤0.01

14.2 Glycemic Control Trial in Pediatric Patients Aged 10 Years and Older with Type 2 Diabetes Mellitus

Glycemic Control Trial of Canagliflozin in Pediatric Patients Aged 10 years and Older with Type 2 Diabetes Mellitus

In a double-blind, placebo-controlled, parallel-group pediatric trial (NCT03170518), 171 pediatric patients aged 10 to 17 years with inadequately controlled type 2 diabetes mellitus (HbA_{1C} ≥6.5% and ≤11.0%) were randomized to canagliflozin (84 patients) or placebo (87 patients) as add-on to diet and exercise, metformin HCl (≥1,000 mg per day or maximally tolerated dosage), insulin, or a combination of metformin HCl and insulin, for a total of 52-weeks. At Week 13, patients in the canagliflozin arm whose HbA_{1C} was ≥7.0% and eGFR ≥60 mL/min/1.73m^2 were re-randomized to either continue on canagliflozin 100 mg orally once daily (n=16) or to up-titrate to 300 mg orally once daily (n=17).

At baseline, background therapies included diet and exercise only (14%), insulin monotherapy (11%), metformin HCl and insulin (29%), and metformin HCl monotherapy (46%). The mean HbA_{1C} at baseline was 8.0% and the mean duration of type 2 diabetes mellitus was 2 years. The mean eGFR at baseline was 157.3 mL/min/1.73 m^2, and approximately 16% (24/151) of the trial population with measurements had microalbuminuria or macroalbuminuria. Patients with an eGFR less than 60 mL/min/1.73 m^2 were not enrolled in the trial; no patients in the trial reached an eGFR < 60 mL/min/1.72 m^2. The mean age was 14.3 years, 47% were under 15 years of age, and 68% were female. Approximately 42% were Asian, 42% were White, 11% were Black or African American, 5% were American Indian/Alaska Native, and 36% were of Hispanic or Latino ethnicity. The mean BMI was 30.8 kg/m^2 (range 18-57 kg/m^2) and the mean BMI Z-score was 1.84.

At Week 26, treatment with canagliflozin provided statistically significant improvement in HbA_{1C} from baseline, compared with placebo (see Table 21).

The treatment effect with canagliflozin was consistent in the subgroup of patients with metformin with or without insulin as background therapy [adjusted mean change in HbA_{1C} relative to placebo from baseline to Week 26 was –0.74% (95% CI -1.37, -0.11; p = 0.02)].

Table 21: Results at Week 26 in a Placebo-Controlled Trial of Canagliflozin in Combination with Metformin HCl and/or Insulin or as Monotherapy in Pediatric Patients Aged 10 Years and Older with Type 2 Diabetes Mellitus*

Efficacy Parameter	Placebo (N=87)	Canagliflozin (N=84)
HbA_{1C} (%)		
Baseline (mean)	8.3	7.8
Change from baseline†‡	0.34	-0.38
Difference from placebo 95% CI†‡		-0.73 (-1.26, -0.19)§
FPG (mg/dL)		
Baseline (mean)	156.5	154.8

Change from baseline†‡	17.29	-8.22
Difference from placebo 95% CI†‡		-25.51 (-49.55, -1.47) ¶

* Modified intent-to-treat set (All randomized and treated patients with baseline HbA_{1C} measurement).

† Multiple imputation using retrieved dropout approach with 1,000 iterations for missing data (canagliflozin N=7 (8.3%), placebo N=7 (8.1%) for HbA_{1C} and canagliflozin N=9 (10.7%), placebo N=7 (8.1%) for FPG).

‡ Least-Square Mean from Analysis of Covariance (ANCOVA) adjusted for baseline value, baseline age stratum (< 15 years vs 15 to < 18 years) and baseline antihyperglycemic agent (AHA) background (i.e., diet and exercise only, metformin monotherapy, insulin monotherapy, or combination of insulin and metformin).

§ P-value=0.008 (two-sided)

¶ Not evaluated for statistical significance, not part of sequential testing procedure.

Glycemic Control Trial of Metformin HCl Immediate-Release in Pediatric Patients Aged 10 to 16 Years with Type 2 Diabetes Mellitus

A double-blind, placebo-controlled trial was conducted in pediatric patients aged 10 to 16 years with type 2 diabetes mellitus (mean FPG 182.2 mg/dL), where patients were treated with metformin HCl immediate-release tablets (up to 2,000 mg/day) for up to 16 weeks (mean duration of treatment 11 weeks). The results are displayed in Table 22.

Table 22: Mean Change in Fasting Plasma Glucose at Week 16 Comparing Metformin HCl versus Placebo in Pediatric Patients[a] with Type 2 Diabetes Mellitus

	Metformin HCl	**Placebo**	**p-value**
FPG	**(n=37)**	**(n=36)**	
Baseline	162.4	192.3	
Change at Final Visit	-42.9	21.4	<0.001

[a] Pediatric patients mean age 13.8 years (range 10-16 years)

Mean baseline body weight was 205 lbs and 189 lbs in the metformin HCl immediate-release and placebo arms, respectively. Mean change in body weight from baseline to week 16 was -3.3 lbs and -2.0 lbs in the metformin HCl and placebo arms, respectively.

14.3 Canagliflozin Cardiovascular Outcomes in Adults 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 (66% 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 adult 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 White, 13% was Asian, and 3% was Black or African American. The mean age was 63 years and approximately 64% were male.

The mean HbA_{1C} 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 m^2. At baseline, patients were treated with one (19%) or more (80%) antidiabetic medications including metformin HCl (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, 36% 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-thrombotics (5.2% vs 4.2%) and statins (5.8% vs 4.8%) 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 23. 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 23: Treatment Effect for the Primary Composite Endpoint, MACE, and its Components in the Integrated Analysis of CANVAS and CANVAS-R Trials in Adults with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease*

	Placebo N=4,347 (%)	Canagliflozin N=5,795 (%)	Hazard ratio (95% CI)¶
Composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke (time to first occurrence)†, ‡, §,	426 (10.4)	585 (9.2)	0.86 (0.75, 0.97)
Non-fatal myocardial infarction‡, §	159 (3.9)	215 (3.4)	0.85 (0.69, 1.05)
Non-fatal Stroke‡, §	116 (2.8)	158 (2.5)	0.90 (0.71, 1.15)
Cardiovascular Death‡, §	185 (4.6)	268 (4.1)	0.87 (0.72, 1.06)

* Intent-To-Treat Analysis Set

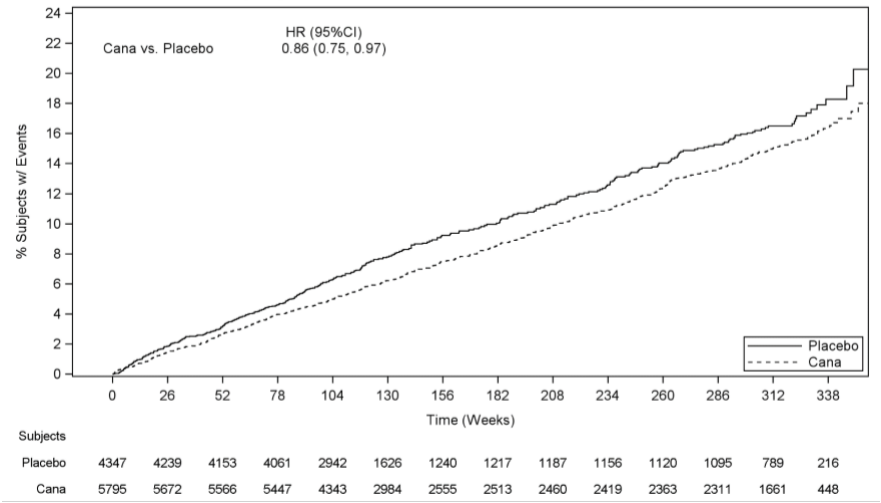
† P-value for superiority (2-sided) = 0.0158

‡ Number and percentage of first events

§ Due to pooling of unequal randomization ratios, Cochran-Mantel-Haenszel weights were applied to calculate percentages

¶ Stratified Cox-proportional hazards model with treatment as a factor and stratified by the trial and by prior CV disease

Figure 3: Time to First Occurrence of MACE



14.4 Canagliflozin Renal and Cardiovascular Outcomes in Adults 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 Clinical Evaluation Trial (CREDENCE) was a multinational, randomized, double-blind, placebo-controlled trial comparing canagliflozin with placebo in adult patients with type 2 diabetes mellitus, an eGFR ≥ 30 to < 90 mL/min/1.73 m^2 and albuminuria (urine albumin/creatinine > 300 to ≤ 5,000 mg/g) who were receiving standard of care including a maximum-tolerated, labeled daily dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB).

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 or African American; 32% were of Hispanic or Latino ethnicity. The mean age was 63 years and 66% were male.

At randomization, the mean HbA_{1C} was 8.3%, the median urine albumin/creatinine was 927 mg/g, the mean eGFR was 56.2 mL/min/1.73 m^2, 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 trial was the time to first occurrence of ESKD (defined as an eGFR < 15 mL/min/1.73 m^2, 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<0.0001] (see Figure 4). The treatment effect reflected a reduction in progression to ESKD, doubling of serum creatinine and cardiovascular death as shown in Table 24 and Figure 4. There were few renal deaths during the trial. Canagliflozin 100 mg also significantly reduced the risk of hospitalization for heart failure [HR: 0.61; 95% CI: 0.47 to 0.80; p<0.001].

Table 24: Analysis of Primary Endpoint (including the Individual Components) and Secondary Endpoints from the CREDENCE Trial in Adults with Diabetic Nephropathy and Albuminuria

	Placebo		canagliflozin		
Endpoint	**N=2,199 (%)**	**Event Rate***	**N=2,202 (%)**	**Event Rate***	**HR† (95% CI)**
Primary Composite Endpoint (ESKD, doubling of serum creatinine, renal death, or CV death)	340 (15.5)	6.1	245 (11.1)	4.3	0.70 (0.59, 0.82)‡
ESKD	165 (7.5)	2.9	116 (5.3)	2.0	0.68 (0.54, 0.86)
Doubling of serum creatinine	188 (8.5)	3.4	118 (5.4)	2.1	0.60 (0.48, 0.76)
Renal death	5 (0.2)	0.1	2 (0.1)	0.0	
CV death	140 (6.4)	2.4	110 (5.0)	1.9	0.78 (0.61, 1.00)
CV death or hospitalization for heart failure	253 (11.5)	4.5	179 (8.1)	3.1	0.69 (0.57, 0.83)§
CV death, non-fatal myocardial infarction or non-fatal stroke	269 (12.2)	4.9	217 (9.9)	3.9	0.80 (0.67, 0.95)¶
Non-fatal myocardial infarction	87 (4.0)	1.6	71 (3.2)	1.3	0.81 (0.59, 1.10)

Non-fatal stroke	66 (3.0)	1.2	53 (2.4)	0.9	0.80 (0.56, 1.15)
Hospitalization for heart failure	141 (6.4)	2.5	89 (4.0)	1.6	0.61 (0.47, 0.80)§
ESKD, doubling of serum creatinine or renal death	224 (10.2)	4.0	153 (6.9)	2.7	0.66 (0.53, 0.81)‡

Intent-To-Treat Analysis Set (time to first occurrence)
The individual components do not represent a breakdown of the composite outcomes, but rather the total number of subjects experiencing an event during the course of the trial.

* Event rate per 100 patient-years.

† Hazard ratio (canagliflozin compared to placebo), 95% CI and p-value are estimated using a stratified Cox proportional hazards model including treatment as the explanatory variable and stratified by screening eGFR (≥ 30 to < 45, ≥ 45 to < 60, ≥ 60 to < 90 mL/min/1.73 m^2). HR is not presented for renal death due to the small number of events in each group.

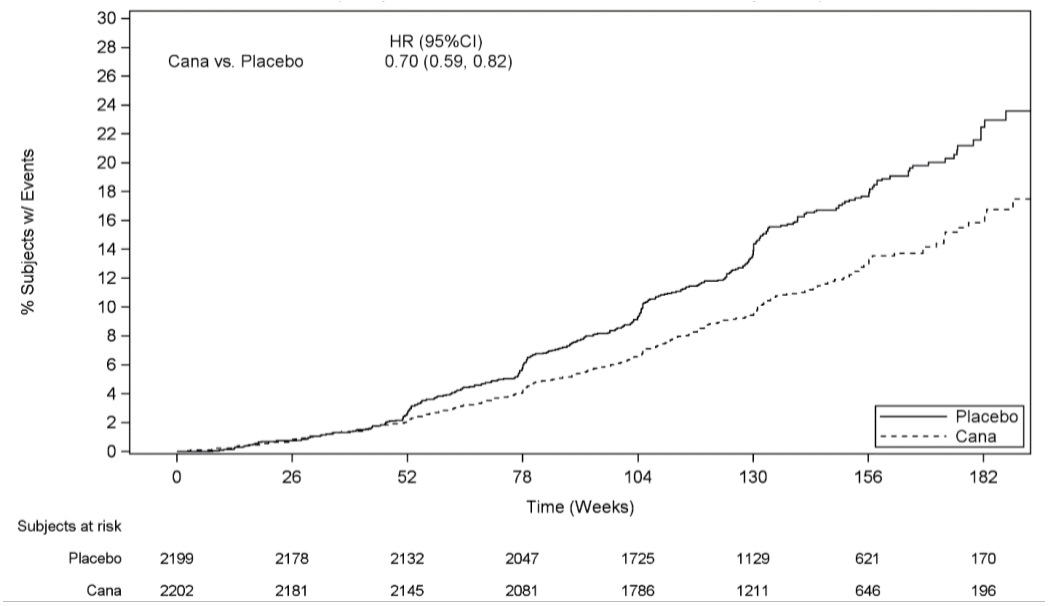
‡ P-value <0.0001

§ P-value <0.001

¶ P-value <0.02

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



16 HOW SUPPLIED/STORAGE AND HANDLING

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

INVOKAMET	TABLET STRENGTH			
canagliflozin/metformin HCl tablets	50 mg/500 mg	50 mg/1,000 mg	150 mg/500 mg	150 mg/1,000 mg
Color	White	Beige	Yellow	Purple
Tablet Identification	CM	CM	CM	CM
	155	551	215	611

	Capsule-shaped, film-coated tablets			
NDC	50458-540-60	50458-541-60	50458-542-60	50458-543-60

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

INVOKAMET XR	**TABLET STRENGTH**			
canagliflozin/metformin HCl extended-release tablets	50 mg/500 mg	50 mg/1,000 mg	150 mg/500 mg	150 mg/1,000 mg
Color	Almost White to Light Orange	Pink	Orange	Reddish Brown
Tablet Identification	CM1	CM3	CM2	CM4
	Oblong, biconvex, film-coated tablets, a thin line on the tablet side may be visible.			
NDC	50458-940-01	50458-941-01	50458-942-01	50458-943-01

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

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Lactic Acidosis

Explain the risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in *Warnings and Precautions (5.1)*. Advise patients to discontinue INVOKAMET or INVOKAMET XR immediately and to promptly notify their health care provider if unexplained hyperventilation, myalgias, malaise, unusual somnolence or other nonspecific symptoms occur. Once a patient is stabilized on INVOKAMET or INVOKAMET XR, gastrointestinal symptoms, which are common during initiation of metformin HCl, 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 or INVOKAMET XR.

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

Instruct patients to inform their doctor that they are taking INVOKAMET or INVOKAMET XR prior to any surgical or radiological procedure, as temporary discontinuation of INVOKAMET or INVOKAMET XR may be required until renal function has been confirmed to be normal *[see Warnings and Precautions (5.1)]*.

Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis

Inform patients that INVOKAMET or INVOKAMET XR can cause potentially fatal ketoacidosis and that type 2 diabetes mellitus and pancreatic disorders (e.g., history of pancreatitis or pancreatic surgery) are risk factors.

Educate all patients on precipitating factors (such as insulin dose reduction or missed doses, infection, reduced caloric intake, ketogenic diet, surgery, dehydration, and alcohol abuse) and symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing). Inform patients that blood glucose may be normal even in the presence of ketoacidosis.

Advise patients that they may be asked to monitor ketones. If symptoms of ketoacidosis occur, instruct patients to discontinue INVOKAMET or INVOKAMET XR and seek medical attention immediately *[see Warnings and Precautions (5.2)]*.

Lower Limb Amputation

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 (5.3)]*.

Volume Depletion

Inform patients that symptomatic hypotension may occur with INVOKAMET or INVOKAMET XR and advise them to contact their doctor if they experience such symptoms *[see Warnings and Precautions (5.4)]*. Inform patients that dehydration may increase the risk for hypotension and to have adequate fluid intake.

Genitourinary Infections, including Urosepsis, Pyelonephritis, Necrotizing Fasciitis of the Perineum (Fournier's Gangrene), and Genital Mycotic Infections

Counsel patients that genitourinary infections may occur when taking INVOKAMET or INVOKAMET XR and may become serious. Educate patients on the symptoms and advise them to seek medical advice if symptoms occur. Specifically, advise 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 (5.5)]*.

Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues

Inform patients that hypoglycemia has been reported when INVOKAMET or INVOKAMET XR is used with insulin or insulin secretagogues. Educate patients or caregivers on the signs and symptoms of hypoglycemia *[see Warnings and Precautions (5.6)]*.

Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions, such as urticaria, rash, anaphylaxis, and angioedema, have been reported with canagliflozin. Advise patients to report immediately any

signs or symptoms suggesting allergic reaction and to discontinue drug until they have consulted prescribing physicians *[see Warnings and Precautions (5.7)]*.

Bone Fracture

Inform patients that bone fractures have been reported in adult patients taking canagliflozin. Provide them with information on factors that may contribute to fracture risk *[see Warnings and Precautions (5.8)]*.

Vitamin B_{12} Deficiency

Inform patients about importance of regular hematological parameters while receiving INVOKAMET or INVOKAMET XR *[see Warnings and Precautions (5.9)]*.

Laboratory Tests

Inform patients that they will test positive for glucose in their urine while on INVOKAMET or INVOKAMET XR *[see Drug Interactions (7)]*.

Females of Reproductive Age

Advise pregnant women, and females of reproductive potential of the potential risk to a fetus with treatment with INVOKAMET or 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 or INVOKAMET XR may result in ovulation in some premenopausal anovulatory women which may lead to unintended pregnancy *[see Use in Specific Populations (8.3)]*.

Lactation

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

Administration

Instruct patients to keep INVOKAMET or INVOKAMET XR in the original bottle to protect from moisture. Advise patients that storage in a pill box or pill organizer is allowed for up to 30 days.

Instruct patients to take INVOKAMET only as prescribed twice daily with food.

Instruct patients to take INVOKAMET XR only as prescribed once daily with the morning meal. If a dose of INVOKAMET or INVOKAMET XR is missed, it should be taken as soon as possible. Advise patients not to double their next dose *[see Dosage and Administration (2.7)]*.

Instruct patients that INVOKAMET XR must be swallowed whole and never crushed, cut, or chewed, and that the inactive ingredients may occasionally be eliminated in the feces as a soft mass that may resemble the original tablet.

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

Licensed from Tanabe Pharma Corporation

For patent information: www.janssenpatents.com

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Medication Guide
INVOKAMET® (in vok' a met)
(canagliflozin and metformin hydrochloride)
tablets, for oral use
and
INVOKAMET® (in vok' a met) XR
(canagliflozin and metformin hydrochloride)
extended-release tablets, for oral use

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 healthcare provider 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 healthcare provider 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. Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids.
- have surgery.
- have new or worsening symptoms of congestive heart failure such as shortness of breath or increased fluid or swelling of the legs.
- have a heart attack, severe infection, or stroke.
- are 65 years of age or older.
- have a genetically inherited disease affecting mitochondria (the energy-producing parts within cells) such as mitochondrial encephalomyopathy with lactic acidosis, and stroke-like episodes (MELAS) syndrome and maternally inherited diabetes and deafness (MIDD).

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

- **Diabetic ketoacidosis (increased ketones in your blood or urine) in people with type 1 and other ketoacidosis.** INVOKAMET and INVOKAMET XR can cause ketoacidosis that can be life-threatening and may lead to death. Ketoacidosis is a serious condition which needs to be treated in a hospital. People with type 1 diabetes have a high risk of getting ketoacidosis. People with type 2 diabetes or pancreas problems also have an increased risk of getting ketoacidosis. Ketoacidosis can also happen in people who: are sick, cannot eat or drink as usual, skip meals, are on a diet high in fat and low in carbohydrates (ketogenic diet), take less than the usual amount of insulin or miss insulin doses, drink too much alcohol, have a loss of too much fluid from the body (volume depletion), or who have surgery or a procedure that requires not having food for a long time (prolonged fasting). Ketoacidosis can happen even if your blood sugar is less than 250 mg/dL. Your health care provider may ask you to periodically check ketones in your urine or blood.
- **Stop taking INVOKAMET or INVOKAMET XR and call your health care provider or get medical help right away if you get any of the following. If possible, check for ketones in your urine or blood, even if your blood sugar is less than 250 mg/dL:**
  - nausea
  - vomiting
  - stomach-area (abdominal) pain
  - tiredness
  - trouble breathing
  - ketones in your urine or blood
- Amputations. INVOKAMET or INVOKAMET XR may increase your risk of lower limb amputations. You may be at a higher risk of lower limb amputation if you:
  - have a history of amputation
  - 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 healthcare provider right away if you have new pain or tenderness, any sores, ulcers, or infections in your leg or foot.

Talk to your healthcare provider 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 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 healthcare provider about what you can do to prevent dehydration including how much fluid you should drink on a daily basis. Call your health care 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.

- **Genital and urinary tract infections.** INVOKAMET or INVOKAMET XR can cause serious infections in your genital area or urinary tract that could require hospitalization. **A rare but serious bacterial infection called necrotizing fasciitis can cause damage to the tissue under the skin in the area between and around the anus and genitals (perineum).** This infection may require hospitalization, multiple surgeries, and could 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 skin (erythema)

Also tell your healthcare provider if you have any of these signs or symptoms of urinary tract infections or yeast infections:

- **Urinary tract infection:**
  - burning feeling when you urinate
  - need to urinate often or right away
  - pain in the lower part of your stomach (pelvis)
  - blood in your urine

You may also have a fever, back pain, nausea, or vomiting.

- **Vaginal yeast infection:**
  - vaginal odor
  - white or yellowish vaginal discharge (may be lumpy or look like cottage cheese)
  - vaginal itching
- **Yeast infection of the skin around the penis (balanitis or balanoposthitis):** If you are uncircumcised, swelling may make it difficult to pull back the skin around the tip of your penis. Other symptoms include:
  - redness, itching, or swelling of the penis
  - rash on the penis
  - bad smelling discharge from the penis
  - pain in the skin around the penis

Talk to your healthcare provider about what to do if you get symptoms of a yeast infection. They may suggest you use an over-the-counter antifungal medicine. Contact your healthcare provider right away if your symptoms do not improve after using an over-the-counter antifungal medicine.

What is INVOKAMET or INVOKAMET XR?

- INVOKAMET contains 2 prescription medicines called canagliflozin (INVOKANA) and metformin hydrochloride (HCl).
- INVOKAMET XR contains 2 prescription medicines called canagliflozin (INVOKANA) and metformin HCL extended-release.
- INVOKAMET or INVOKAMET XR can be used along with diet and exercise to lower blood sugar (glucose) in adults and children aged 10 years and older with type 2 diabetes.
  - One of the medicines in INVOKAMET or INVOKAMET XR, canagliflozin (INVOKANA), can also be used in adults with type 2 diabetes who have:
  - cardiovascular disease and canagliflozin is needed to reduce the risk of major cardiovascular events such as heart attack, stroke, or death.
  - diabetic kidney disease (nephropathy) with a certain amount of protein in the urine, and canagliflozin 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 used to lower blood sugar (glucose) in people with type 1 diabetes. It is not known if INVOKAMET or INVOKAMET XR is safe and effective in children under 10 years of age.

Do not take INVOKAMET or INVOKAMET XR if you:

- have severe kidney problems
- have a condition called metabolic acidosis, including diabetic ketoacidosis (increased ketones in the blood or urine).
- are allergic to canagliflozin, 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 healthcare provider about all of your medical conditions, including if you:

- have type 1 diabetes or have had diabetic ketoacidosis.
- have a decrease in your insulin dose.
- have a serious infection.
- have a history of infection of the vagina or penis.
- have a history of amputation.
- 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 healthcare provider 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 healthcare provider 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 or a procedure that requires not having food for a long time (prolonged fasting). Your healthcare provider may stop your INVOKAMET or INVOKAMET XR before you have surgery. Talk to your healthcare provider 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.
- are dehydrated.
- 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 B_{12} 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 healthcare provider as soon as possible. Talk with your healthcare provider 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 healthcare provider about birth control choices while taking INVOKAMET or INVOKAMET XR, if you are not planning to become pregnant. Tell your healthcare provider 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 healthcare provider 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.
- have a genetically inherited disease affecting mitochondria (the energy-producing parts within cells) such as MELAS syndrome and MIDD.

Tell your healthcare provider 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. Know the medicines you take. Keep a list of them and show it to your healthcare provider 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 healthcare provider 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 healthcare provider 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 healthcare provider may change your dose if needed.
- Your healthcare provider 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?**"
- Your healthcare provider may tell you to stop taking INVOKAMET or INVOKAMET XR at least 3 days before any surgery or procedure that requires not having food for a long time (prolonged fasting).
- 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 healthcare provider if you have questions about a missed dose.
- 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 healthcare provider if you have questions about a missed dose.
- If you take too much INVOKAMET or INVOKAMET XR, call your healthcare provider or Poison Help line at 1-800-222-1222 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 healthcare provider right away if you have any of these conditions and follow your healthcare provider's instructions.
- INVOKAMET and INVOKAMET XR will cause your urine to test positive for glucose.
- Your healthcare provider may do certain blood tests before you start INVOKAMET or INVOKAMET XR and during treatment as needed. Your healthcare provider may change your dose of INVOKAMET or INVOKAMET XR based on the results of your blood tests.

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:

- See **"What is the most important information I should know about INVOKAMET or INVOKAMET XR?"**
- **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 healthcare provider 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
    - confusion
    - hunger
    - shaking or feeling jittery
    - drowsiness
    - dizziness
    - fast heartbeat
    - weakness
    - irritability
    - sweating

- **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 healthcare provider right away or go to the nearest hospital emergency room. See "**Do not take INVOKAMET or INVOKAMET XR if you:**". Your healthcare provider 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 healthcare provider about factors that may increase your risk of bone fracture.
- **low vitamin B_{12} (vitamin B_{12} deficiency).** Using metformin for long periods of time may cause a decrease in the amount of vitamin B_{12} in your blood, especially if you have had low vitamin B_{12} blood levels before. Your healthcare provider may order blood tests to check your vitamin B_{12} levels.

Other common side effects of INVOKAMET or INVOKAMET XR include:

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

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 healthcare provider for information about INVOKAMET or INVOKAMET XR that is written for health professionals.

What are the ingredients in INVOKAMET?

Active ingredients: canagliflozin and metformin HCl

Inactive ingredients: The tablet core contains croscarmellose sodium (E468), hypromellose, magnesium stearate (E572), and microcrystalline cellulose (E460[i]). The magnesium stearate is vegetable-sourced. In addition, the tablet coating contains Macrogol/PEG3350 (E1521), polyvinyl alcohol (E1203) (partially hydrolyzed), talc (E553b), titanium dioxide (E171), iron oxide yellow (E172) (50 mg/1,000 mg and 150 mg/500 mg tablets only), iron oxide red (E172) (50 mg/1,000 mg, 150 mg/500 mg and 150 mg/1,000 mg tablets only), and iron oxide black (E172) (150 mg/1,000 mg tablets only).

What are the ingredients of INVOKAMET XR?

Active ingredients: canagliflozin and metformin HCl

Inactive ingredients: The tablet core contains croscarmellose sodium (E468), hydroxypropyl cellulose (E463), hypromellose, lactose anhydrous, magnesium stearate (E572) (vegetable-sourced), microcrystalline cellulose (E460[i]), 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 (E1521), polyvinyl alcohol (E1203) (partially hydrolyzed), talc (E553b), titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172), and iron oxide black (E172) (50 mg/1,000 mg and 150 mg/1,000 mg tablets only).

Manufactured for: Janssen Pharmaceuticals, Inc., Titusville, NJ 08560, USA. Licensed from Tanabe Pharma Corporation. For patent information: www.janssenpatents.com © Johnson & Johnson and its affiliates 2014 - 2024

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.