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 (HCl) tablets), for oral use
INVOKAMET® XR (canagliflozin and metformin HCl 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, and hepatic impairment. Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the Full Prescribing Information. (5.1)**
- **If lactic acidosis is suspected, discontinue INVOKAMET or INVOKAMET XR and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.1)**

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

Indications and Usage (1)	07/2023
Dosage and Administration (2.2, 2.3, 2.4, 2.5, 2.7)	07/2023
Contraindications (4)	07/2023
Warnings and Precautions (5.2)	07/2023

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

INVOKAMET and INVOKAMET XR are a combination of canagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, and metformin HCl, a biguanide, indicated:

- As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1)
- Canagliflozin is indicated to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease (1)
- Canagliflozin is indicated to reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria (1).

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

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

- Individualize starting dose based on the patient's current regimen and renal function (2.2, 2.3, 2.4)
- 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 component (2.4)
- INVOKAMET: one tablet, twice daily with meals, recommended starting dose of canagliflozin is 50 mg twice daily and metformin HCl 500 mg twice daily (2.2)
- INVOKAMET XR: two tablets, once daily with the morning meal. Swallow whole. Never crush, cut, or chew (2.2)
- Canagliflozin dose can be increased to a total daily dose of 300 mg in patients tolerating 100 mg who have an eGFR of 60 mL/min/1.73 m^2 or greater and require additional glycemic control. Do not exceed a total daily canagliflozin dose of 300 mg (2.2)
- Gradually escalate metformin HCl dose to reduce the gastrointestinal side effects while not exceeding a total daily dose of 2,000 mg (2.3)
- Assess renal function before initiating and as clinically indicated (2.1, 2.3)
- Dose adjustment for patients with renal impairment may be required (2.4)
- See full prescribing information for INVOKAMET and INVOKAMET XR dosage modifications due to drug interactions. (2.5)
- May need to be discontinued at time of, or prior to, iodinated contrast imaging procedures (2.6)
- Withhold INVOKAMET or INVOKAMET XR at least 3 days, if possible, prior to major surgery or procedures associated with prolonged fasting (2.7).

----------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, 5.1)
- Serious hypersensitivity reaction to canagliflozin or metformin HCl (4, 5.9)

----------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: Consider factors that may increase the risk of amputation before initiating INVOKAMET or INVOKAMET XR. Monitor patients for infection or ulcers of lower limb and discontinue if these occur (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)
- Urosepsis and pyelonephritis: Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated (5.5)
- Hypoglycemia: Consider a lower dose of insulin or insulin secretagogue to reduce the risk of hypoglycemia when used in combination (5.6)
- Necrotizing fasciitis of the perineum (Fournier's gangrene): Serious, life-threatening cases have occurred in both females and males. Assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment (5.7)
- Genital mycotic infections: Monitor and treat if indicated (5.8)
- Hypersensitivity reactions: Discontinue and monitor until signs and symptoms resolve (5.9)
- Bone fracture: Consider factors that contribute to fracture risk before initiating INVOKAMET or INVOKAMET XR (5.10)
- 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 (5.11)

----------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 (6.1, 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: 07/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*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, and hepatic impairment *[see Warnings and Precautions (5.1)]*.**
- **Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the full prescribing information *[see Dosage and Administration (2.2, 2.3), Contraindications (4), Warnings and Precautions (5.1), Drug Interactions (7), and Use in Specific Populations (8.6, 8.7)]*.**
- **If metformin-associated lactic acidosis is suspected, immediately discontinue INVOKAMET 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 and INVOKAMET XR are a combination of canagliflozin and metformin HCl indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

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

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

Limitations of Use

INVOKAMET or INVOKAMET XR is 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 (2.4) and Warnings and Precautions (5.1, 5.4), Contraindications (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 Dosage Overview

INVOKAMET

Take one tablet of INVOKAMET orally twice daily with meals *[see Dosage and Administration (2.3)]*.

INVOKAMET XR

Take two tablets of INVOKAMET XR orally once daily with the morning meal *[see Dosage and Administration (2.3)]*. Swallow each tablet whole and never crush, cut, or chew.

2.3 Recommended Dosage and Administration

Individualize the starting dose of INVOKAMET or INVOKAMET XR based on the patient's current regimen and renal function *[see Dosage and Administration (2.4)]*. Table 1 presents the recommended starting dosage of INVOKAMET and INVOKAMET XR based on the patient's current regimen. For the available strengths of the canagliflozin and metformin components in INVOKAMET and INVOKAMET XR, see *Dosage Forms and Strengths (3)*.

Table 1. Recommended Starting Dosage Based on the Patient's Current Regimen

Current Regimen	**INVOKAMET Recommended Dosage** Administered as one tablet, orally, twice daily with meals	**INVOKAMET XR Recommended Dosage** Administered as two tablets, orally, once daily with the morning meal
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

INVOKAMET
Canagliflozin may be increased to the maximum recommended dosage of 150 mg twice daily in patients tolerating 50 mg twice daily and metformin may be increased to the maximum recommended dosage of 1,000 mg twice daily, with gradual escalation to reduce gastrointestinal adverse reactions with metformin *[see Adverse Reactions (6.1)]*.

INVOKAMET XR
Canagliflozin may be increased to the maximum recommended dosage of 300 mg once daily in patients tolerating 100 mg once daily and metformin may be increased to the maximum recommended dosage of 2,000 mg once daily, with gradual escalation to reduce gastrointestinal adverse reactions with metformin *[see Adverse Reactions (6.1)]*.

2.4 Recommended Dosage for Patients with Renal Impairment

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

- Table 2 provides dosage recommendations for patients with renal impairment, based on eGFR *[see Use in Specific Populations (8.6) and Clinical Studies (14.3)]*.

Table 2 Recommended Dosage in Patients with Renal Impairment

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

2.5 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 recommended dosage of canagliflozin is 300 mg daily.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.