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

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

WARNING: LACTIC ACIDOSIS and LOWER LIMB AMPUTATION
See full prescribing information for complete boxed warning.

Lactic Acidosis

- **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 and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.1)**

Risk of Lower Limb Amputation

- **In patients with type 2 diabetes who have established cardiovascular disease (CVD) or at risk for CVD, canagliflozin, a component of INVOKAMET, has been associated with lower limb amputations, most frequently of the toe and midfoot; some also involved the leg. (5.2)**
- **Before initiating, consider factors that may increase the risk of amputation. Monitor patients receiving INVOKAMET for infections or ulcers of the lower limbs, and discontinue if these occur. (5.2)**

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

Boxed Warning	07/2017
Boxed Warning	08/2017
Warnings and Precautions (5.1)	08/2017
Warnings and Precautions (5.2)	07/2017

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

INVOKAMET is a sodium-glucose co-transporter 2 (SGLT2) inhibitor and biguanide combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both canagliflozin and metformin is appropriate (1)

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

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

- Individualize based on the patient's current regimen (2)
- Take one INVOKAMET tablet twice daily with meals, recommended starting dose of canagliflozin is 50 mg twice daily and metformin 500 mg twice daily (2.1)
- Canagliflozin dose can be increased to 150 mg twice daily in patients tolerating canagliflozin 50 mg twice daily who have 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 (2.1)
- Gradually escalate metformin dose to reduce the gastrointestinal side effects while not exceeding total daily dose of 2000 mg (2.1)
- Assess renal function before initiating and periodically thereafter (2.2)
- INVOKAMET is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 45 mL/min/1.73 m^2 (2.2)
- Limit the dose of canagliflozin component to 50 mg twice daily in patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 (2.2)
- INVOKAMET may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures (2.4)

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

Film-coated tablets:

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

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

- Moderate to severe renal impairment (eGFR below 45 mL/min/1.73 m^2), end stage renal disease or dialysis (4, 5.1, 5.5)
- Metabolic acidosis, including diabetic ketoacidosis (1, 4, 5.1)
- History of serious hypersensitivity reaction to canagliflozin or metformin (4, 5.10)

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

- Lactic acidosis: See boxed warning (5.1)
- Lower limb amputation: See boxed warning (5.2)
- Hypotension: Before initiating INVOKAMET, assess volume status and correct hypovolemia in patients with renal impairment, the elderly, in patients with low systolic blood pressure, or on diuretics, ACEi, or ARB. Monitor for signs and symptoms during therapy (5.3)
- Ketoacidosis: Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue INVOKAMET, evaluate and treat promptly. Before initiating INVOKAMET, consider risk factors for ketoacidosis. Patients on INVOKAMET may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis (5.4)
- Acute kidney injury and impairment in renal function: Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and promptly treat. Monitor renal function during therapy (5.5)
- Hyperkalemia: Monitor potassium levels in patients with impaired renal function and in patients predisposed to hyperkalemia (2.2, 5.6, 6.1, 8.6)
- Urosepsis and pyelonephritis: Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated (5.7)
- Hypoglycemia: Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination with INVOKAMET (5.8)
- Genital mycotic infections: Monitor and treat if indicated (5.9)
- Hypersensitivity reactions: Discontinue INVOKAMET and monitor until signs and symptoms resolve (5.10)
- Bone fracture: Consider factors that contribute to fracture risk before initiating INVOKAMET (5.11)
- Vitamin B_{12} deficiency: Metformin may lower vitamin B_{12} levels. Monitor hematologic parameters annually (5.12)
- Increased LDL-C: Monitor LDL-C and treat if appropriate (5.13)

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

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

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

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

- Carbonic anhydrase inhibitors may increase risk of lactic acidosis. Consider more frequent monitoring (7.1)
- Drugs that reduce metformin clearance (such as ranolazine, vandetanib, dolutegravir, and cimetidine) may increase the accumulation of metformin. Consider the benefits and risks of concomitant use (7.1)
- Alcohol can potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake (7.1)
- UGT inducers (e.g., rifampin): Canagliflozin exposure is reduced. Consider increasing canagliflozin dose from 50 mg to 150 mg twice daily (2.3, 7.2)
- Digoxin: Monitor digoxin levels (7.2)

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

- Pregnancy: Advise females of the potential risk to a fetus especially during the second and third trimesters (8.1)
- Lactation: INVOKAMET is not recommended when breastfeeding (8.2)
- Females and Males of Reproductive Potential: Advise premenopausal females of the potential for an unintended pregnancy (8.3).
- Geriatrics: Higher incidence of adverse reactions related to reduced intravascular volume. Assess renal function more frequently (5.3, 6.1, 8.5)
- Renal impairment: Higher incidence of adverse reactions related to reduced intravascular volume and renal function (2.2, 5.5, 8.6)

Reference ID: 4138265

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS and LOWER LIMB AMPUTATION

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.**
- **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), 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 and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended *[see Warnings and Precautions (5.1)]*.**

Risk of Lower Limb Amputation

- **An approximately 2-fold increased risk of lower limb amputations associated with canagliflozin, a component of INVOKAMET, was observed in CANVAS and CANVAS-R, two large, randomized, placebo-controlled trials in patients with type 2 diabetes who had established cardiovascular disease (CVD) or were at risk for CVD.**
- **Amputations of the toe and midfoot were most frequent; however, amputations involving the leg were also observed. Some patients had multiple amputations, some involving both limbs.**
- **Before initiating, consider factors that may increase the risk of amputation, such as a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers.**
- **Monitor patients receiving INVOKAMET for infection, new pain or tenderness,**

sores or ulcers involving the lower limbs, and discontinue if these complications occur *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

INVOKAMET (canagliflozin and metformin hydrochloride) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both canagliflozin and metformin is appropriate.

Limitations of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

- Individualize the starting dose of INVOKAMET (canagliflozin and metformin hydrochloride) based on the patient's current regimen:
  - In patients currently not treated with either canagliflozin or metformin, initiate therapy with INVOKAMET containing canagliflozin 50 mg and metformin 500 mg *[see Clinical Studies (14.1)]*;
  - In patients on metformin, switch to INVOKAMET containing canagliflozin 50 mg and the same, or nearest appropriate, daily dose of metformin;
  - In patients on canagliflozin, switch to INVOKAMET containing metformin 500 mg with the same daily dose of canagliflozin;
  - In patients already treated with canagliflozin and metformin, switch to INVOKAMET containing the same daily dose of canagliflozin and the same, or nearest appropriate, daily dose of metformin.
- Take one INVOKAMET tablet twice daily with meals; in patients tolerating canagliflozin 50 mg twice daily who have an eGFR of 60 mL/min/1.73 m^2 or greater and require additional glycemic control, INVOKAMET dose can be increased for the canagliflozin component to 150 mg twice daily, with gradual metformin dose escalation to reduce the gastrointestinal side effects due to metformin *[see Dosage Forms and Strengths (3) and Clinical Studies (14.1)]*.
- In patients with volume depletion not previously treated with canagliflozin, correct this condition before initiating INVOKAMET *[see Warnings and Precautions (5.3), Use in Specific Populations (8.5, 8.6), and Patient Counseling Information (17)]*.

- Adjust dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of metformin 2000 mg and canagliflozin 300 mg in patients with an eGFR of 60 mL/min/1.73 m^2 or greater *[see Dosage and Administration (2.2)]*.

2.2 Recommended Dosage for Patients with Renal Impairment

- Assess renal function before initiating INVOKAMET and periodically thereafter.
- INVOKAMET is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 45 mL/min/1.73 m^2 *[see Contraindications (4) and Warnings and Precautions (5.1, 5.5)]*.
- Limit the dose of the canagliflozin component to 50 mg twice daily in patients with moderate renal impairment with an eGFR of 45 to less than 60 mL/min/1.73 m^2.

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

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

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

2.4 Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue INVOKAMET at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 45 and 60 mL/min/1.73 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 if renal function is stable *[see Warnings and Precautions (5.1)]*.

3 DOSAGE FORMS AND STRENGTHS

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

- Canagliflozin 50 mg and metformin hydrochloride 500 mg tablets are immediate-release, capsule-shaped, white film-coated tablets with “CM” on one side and “155” on the other side.
- Canagliflozin 50 mg and metformin hydrochloride 1,000 mg tablets are immediate-release, capsule-shaped, beige, film-coated tablets with “CM” on one side and “551” on the other side.

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