เอกสารกำกับยาภาษาอังกฤษสำหรับแพทย์

VOKANAMET®

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 Special warnings and precautions for use (4.4.1)]*.**
- **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 Posology and method of administration (4.2.2), Contraindication (4.3), Special warnings and precautions for use (4.4.1), Interaction with other medicinal products and other forms of interactions (4.5), and Clinical Particulars (4.2.2, 4.2.5)]*.**
- **If metformin-associated lactic acidosis is suspected, immediately discontinue VOKANAMET and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended *[see Special warnings and precautions for use (4.4.1)]*.**

Risk of Lower Limb Amputation

- **An approximately 2-fold increased risk of lower limb amputations associated with canagliflozin, a component of VOKANAMET, 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 VOKANAMET for infection, new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue if these complications occur *[see Special warnings and precautions for use (4.4.2)]*.**

1. Name of the Medicinal Product

1.1 Product Name

VOKANAMET® (canagliflozin and metformin hydrochloride)

1.2 Strength

VOKANAMET film-coated tablets for oral administration are available in the following strengths:

- Canagliflozin 50 mg and metformin hydrochloride 500 mg
- Canagliflozin 150 mg and metformin hydrochloride 500 mg

1.3 Pharmaceutical Dosage Form

Film-coated tablets

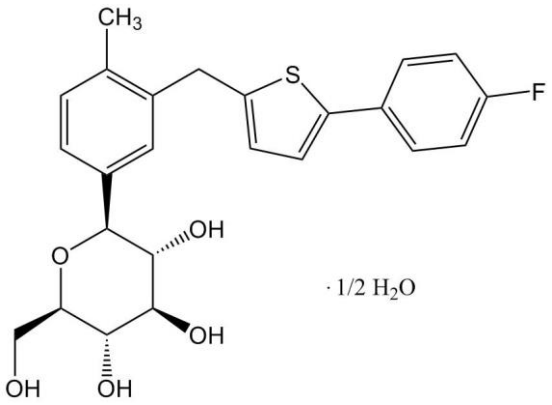
2. Quality and Quantitative Composition

2.1 Qualitative Declaration

VOKANAMET (canagliflozin and metformin hydrochloride) tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: canagliflozin and metformin hydrochloride.

Canagliflozin

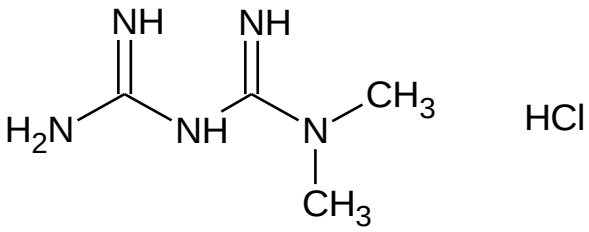
Canagliflozin is an inhibitor of sodium-glucose co-transporter 2 (SGLT2), the transporter responsible for reabsorbing the majority of glucose filtered by the kidney. Canagliflozin is chemically known as (1S)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol hemihydrate and its molecular formula and weight are C24H25FO5S•1/2 H2O and 453.53, respectively. The structural formula for canagliflozin is:



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

Metformin Hydrochloride

Metformin hydrochloride is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Metformin hydrochloride is chemically known as 1,1-Dimethylbiguanide hydrochloride and its molecular formula and weight are C4H11N5 ● HCl and 165.62, respectively. The structural formula for metformin hydrochloride is:



2.2 Quantitative Declaration

VOKANAMET is supplied as film-coated tablets for oral administration. Each 50 mg/500 mg tablet contains 51 mg of canagliflozin equivalent to 50 mg canagliflozin (anhydrous) and 500 mg metformin hydrochloride. Each 150 mg/500 mg tablet contains 153 mg of canagliflozin equivalent to 150 mg canagliflozin (anhydrous) and 500 mg metformin hydrochloride.

3. Pharmaceutical Form

• 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 150 mg and metformin hydrochloride 500 mg tablets are immediate release, capsule shaped, yellow, film-coated tablets with "CM" on one side and "215" on the other side.

4. Clinical Particulars

4.1 Therapeutic indication

VOKANAMET (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

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

4.2 Posology and method of administration

4.2.1 Recommended Dosage

- Individualize the starting dose of VOKANAMET (canagliflozin and metformin hydrochloride) based on the patient's current regimen:
  - In patients currently not treated with either canagliflozin or metformin, initiate therapy with VOKANAMET containing canagliflozin 50 mg and metformin 500 mg *[see Pharmacological Properties (5.1.2.1)]*;
  - In patients on metformin, switch to VOKANAMET containing canagliflozin 50 mg and the same, or nearest appropriate, daily dose of metformin;

- In patients on canagliflozin, switch to VOKANAMET containing metformin 500 mg with the same daily dose of canagliflozin;
- In patients already treated with canagliflozin and metformin, switch to VOKANAMET containing the same daily dose of canagliflozin and the same, or nearest appropriate, daily dose of metformin.

- Take one VOKANAMET 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, VOKANAMET 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 Strength (1.2) and Pharmacological Properties (5.1.2.1)]*.

- In patients with volume depletion not previously treated with canagliflozin, correct this condition before initiating VOKANAMET *[see Special warnings and precautions for use (4.4.3), Clinical Particulars (4.2.7, 4.2.2), and Patient Counseling Information]*.

- 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 Posology and method of administration (4.2.2)]*.

4.2.2 Recommended Dosage for Patients with Renal Impairment

- Assess renal function before initiating VOKANAMET and periodically thereafter.

- VOKANAMET is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 45 mL/min/1.73 m^2 *[see Contraindication (4.3) and Special warnings and precautions for use (4.4.1, 4.4.5)]***.**

- 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.

Canagliflozin

The efficacy and safety of canagliflozin were evaluated in a study that included 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 had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR greater than or equal to 60 mL/min/1.73 m^2). Dose-related, transient mean increases in serum potassium were observed early after initiation of canagliflozin (i.e., within 3 weeks) in this trial. Increases in serum potassium of greater than 5.4 mEq/L and 15% above baseline occurred in 16.1%, 12.4%, and 27.0% of patients treated with placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. Severe elevations (greater than or equal to 6.5 mEq/L) occurred in 1.1%, 2.2%, and 2.2% of patients treated with placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively *[see Posology and method of administration (4.2.2), Contraindication (4.3), Special warnings and precautions for use (4.4.1, 4.4.4, 4.4.5), and Undesirable effects (4.8.1)]*.

The efficacy and safety of canagliflozin have not been established in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), with ESRD, or receiving dialysis. Canagliflozin

is not expected to be effective in these patient populations *[see Contraindication (4.3) and Pharmacological Properties (5.2)]*.

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

If an inducer of UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) is co administered with VOKANAMET, consider increasing the dose to canagliflozin 150 mg twice daily in patients currently tolerating canagliflozin 50 mg twice daily who have an eGFR of 60 mL/min/1.73 m2 or greater and require additional glycemic control [see Interaction with other medicinal products and other forms of interactions (4.5.2)].

Consider another antihyperglycemic agent in patients with an eGFR of 45 to less than 60 mL/min/1.73 m2 receiving concurrent therapy with a UGT inducer.

4.2.4 Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue VOKANAMET at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 45 and 60 mL/min/1.73 m2; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart VOKANAMET if renal function is stable [see Special warnings and precautions for use (4.4.1)].

4.2.5 Hepatic Impairment

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. VOKANAMET is not recommended in patients with hepatic impairment. *[see Special warnings and precautions for use (4.4.1)]*

4.2.6 Pediatric Use

Safety and effectiveness of VOKANAMET in pediatric patients under 18 years of age have not been established.

4.2.7 Geriatric Use

VOKANAMET

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 VOKANAMET in the elderly and then adjust dose based on renal function *[see Posology and method of administration (4.2.2) and Special warnings and precautions for use (4.4.1, 4.4.5)]*.

Canagliflozin

Two thousand thirty-four (2034) patients 65 years and older, and 345 patients 75 years and older were exposed to canagliflozin in nine clinical studies of canagliflozin. Of these patients, 1334 patients 65 years and older and 181 patients 75 years and older were exposed to the combination of canagliflozin and metformin *[see Pharmacological Properties (5.1.2)]*. 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 Posology*

and method of administration (4.2.1) and Undesirable effects (4.8.1)]. 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

Controlled clinical studies of metformin 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 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 Contraindication (4.3), Special warnings and precautions for use (4.4.5), and Pharmacological Properties (5.2)]*.

4.2.8 Females and Males of Reproductive Potential

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

4.3 Contraindication

VOKANAMET is contraindicated in patients with:

- Moderate to severe renal impairment (eGFR below 45 mL/min/1.73 m^2), end stage renal disease (ESRD) or patients on dialysis *[see Special warnings and precautions for use (4.4.1) and Clinical Particulars (4.2.2)]*.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis *[see Special warnings and precautions for use (4.4.4)]*.
- History of a serious hypersensitivity reaction to canagliflozin or metformin, such as anaphylaxis or angioedema *[see Special warnings and precautions for use (4.4.10) and Undesirable effects (4.8.1, 4.8.2)]*.

4.4 Special warnings and precautions for use

4.4.1 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 VOKANAMET. In VOKANAMET-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin hydrochloride is dialyzable, with a clearance of up to 170 mL/minute under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue VOKANAMET 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 Posology and method of administration (4.2.2), Pharmacological Properties (5.2)]*.

- Before initiating VOKANAMET, obtain an estimated glomerular filtration rate (eGFR).
- VOKANAMET is contraindicated in patients with an eGFR less than 45 mL/minute/1.73 m^2 *[see Contraindication (4.3)]*.
- Obtain an eGFR at least annually in all patients taking VOKANAMET. 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 VOKANAMET 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 Interaction with other medicinal products and other forms of interactions (4.5)]*. 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 Clinical Particulars (4.2.7)]*.

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 VOKANAMET 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 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 VOKANAMET 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.

VOKANAMET 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 VOKANAMET.

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 VOKANAMET.

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 VOKANAMET in patients with clinical or laboratory evidence of hepatic disease.

4.4.2 Lower Limb Amputation

An approximately 2-fold increased risk of lower limb amputations associated with canagliflozin, a component of VOKANAMET, was observed in CANVAS and CANVAS-R, two large, randomized, placebo-controlled trials evaluating patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease. In CANVAS, canagliflozin-treated patients and placebo-treated patients had 5.9 and 2.8 amputations per 1000 patients per year, respectively. In CANVAS-R, canagliflozin-treated patients and placebo-treated patients had 7.5 and 4.2 amputations per 1000 patients per year, respectively. The risk of lower limb amputations was observed at both the 100 mg and 300 mg once daily dosage regimens. The amputation data for CANVAS and CANVAS-R are shown in Tables 2 and 3, respectively *[see Undesirable effects (4.8.1)]*.

Amputations of the toe and midfoot (99 out of 140 patients with amputations receiving canagliflozin in the two trials) were the most frequent; however, amputations involving the leg, below and above the knee, were also observed (41 out of 140 patients with amputations receiving canagliflozin in the two trials). Some patients had multiple amputations, some involving both lower limbs.

Lower limb infections, gangrene, and diabetic foot ulcers were the most common precipitating medical events leading to the need for an amputation. The risk of amputation was highest in patients with a baseline history of prior amputation, peripheral vascular disease, and neuropathy.

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

4.4.3 Hypotension

Canagliflozin causes intravascular volume contraction. Symptomatic hypotension can occur after initiating VOKANAMET *[see Undesirable effects (4.8.1)]* particularly in patients with eGFR less than 60 mL/min/1.73 m^2, elderly patients, patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (e.g., angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating VOKANAMET in patients with one or more of these characteristics who were not already on canagliflozin, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.

4.4.4 Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including canagliflozin. Fatal cases of ketoacidosis have been reported in patients taking canagliflozin. VOKANAMET is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Therapeutic indication (4.1)]*.

Patients treated with VOKANAMET who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with VOKANAMET may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, VOKANAMET should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

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

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

4.4.5 Acute Kidney Injury and Impairment in Renal Function

Canagliflozin causes intravascular volume contraction *[see Special warnings and precautions for use (4.4.3)]* and can cause renal impairment *[see Undesirable effects (4.8.1)]*. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving canagliflozin; some reports involved patients younger than 65 years of age.

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

Canagliflozin increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating VOKANAMET *[see Undesirable effects (4.8.1)]*. Renal function should be evaluated prior to initiation of VOKANAMET and monitored periodically thereafter. Dosage adjustment and more frequent renal function monitoring are recommended in patients with an eGFR below 60 mL/min/1.73 m^2. VOKANAMET is contraindicated in patients with an eGFR below 45 mL/min/1.73 m^2 *[see Posology and method of administration (4.2.2), Contraindication (4.3), Special warnings and precautions for use (4.4.1) and Clinical Particulars (4.2.2)]*.

4.4.6 Hyperkalemia

Canagliflozin can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are at an increased risk of developing hyperkalemia *[see Posology and method of administration (4.2.2) and Undesirable effects (4.8.1)]*.

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

4.4.7 Urosepsis and Pyelonephritis

There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including canagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated *[see Undesirable effects (4.8)]*.

4.4.8 Hypoglycemia with Concomitant Use of Sulfonylurea or Insulin

Canagliflozin

Insulin and insulin secretagogues are known to cause hypoglycemia. Canagliflozin can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue *[see Undesirable effects (4.8.1)]*. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with VOKANAMET.

Metformin

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with

adrenal or pituitary insufficiency or alcohol intoxication, are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs. Monitor for a need to lower the dose of VOKANAMET to minimize the risk of hypoglycemia in these patients.

4.4.9 Genital Mycotic Infections

Canagliflozin increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections *[see Undesirable effects (4.8.1)]*. Monitor and treat appropriately.

4.4.10 Hypersensitivity Reactions

Hypersensitivity reactions, including angioedema and anaphylaxis, have been reported with canagliflozin. These reactions generally occurred within hours to days after initiating canagliflozin. If hypersensitivity reactions occur, discontinue use of VOKANAMET; treat and monitor until signs and symptoms resolve *[see Contraindication (4.3) and Undesirable effects (4.8.1, 4.8.2)]*.

4.4.11 Bone Fracture

An increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed in patients using canagliflozin. Consider factors that contribute to fracture risk prior to initiating VOKANAMET *[see Undesirable effects (4.8.1)]*.

4.4.12 Vitamin B12 Levels

In controlled, 29-week clinical trials of metformin, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of metformin-treated patients. Such decreases, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia or neurologic manifestations due to the short duration (less than 1 year) of the clinical trials. This risk may be more relevant to patients receiving long-term treatment with metformin and adverse hematologic and neurologic reactions have been reported postmarketing. The decrease in vitamin B_{12} levels appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Measure hematologic parameters on an annual basis in patients on VOKANAMET and investigate and treat if abnormalities occur. Patients with inadequate vitamin B_{12} or calcium intake or absorption may be predisposed to developing subnormal vitamin B_{12} levels, and routine serum vitamin B_{12} measurement at 2- to 3-year intervals is recommended in these patients.

4.4.13 Increases in Low-Density Lipoprotein (LDL-C)

Dose-related increases in LDL-C occur with canagliflozin *[see Undesirable effects (4.8.1)]*. Monitor LDL-C and treat if appropriate after initiating VOKANAMET.

4.4.14 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with VOKANAMET *[see Undesirable effects (4.8.1)]*.

4.5 Interaction with other medicinal products and other forms of interactions
4.5.1 Drug Interactions with Metformin

Carbonic Anhydrase Inhibitors

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

Drugs That Reduce Metformin Clearance

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 such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis *[see Pharmacological Properties (5.2)]*. Consider the benefits and risks of concomitant use.

Alcohol

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

Drugs Affecting Glycemic Control

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid. When such drugs are administered to a patient receiving VOKANAMET, monitor for loss of blood glucose control. When such drugs are withdrawn from a patient receiving VOKANAMET, monitor for hypoglycemia.

4.5.2 Drug Interactions with Canagliflozin

UGT Enzyme Inducers

Rifampin: Rifampin lowered canagliflozin exposure which may reduce the efficacy of VOKANAMET. If an inducer of UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) must be co-administered with VOKANAMET, consider increasing the dose to canagliflozin 150 mg twice daily if patients are currently tolerating VOKANAMET with 50 mg canagliflozin twice daily, have an eGFR greater than 60 mL/min/1.73 m^2, and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer and require additional glycemic control *[see Posology and method of administration (4.2.3) and Pharmacological Properties (5.2)]*.

Digoxin

Canagliflozin increased digoxin exposure. Digoxin, as a cationic drug, also has the potential to compete with metformin for common renal tubular transport systems *[see Interaction with other medicinal products and other forms of interactions (4.5.1)]*. Monitor patients taking VOKANAMET with concomitant digoxin for a need to adjust dose of either drug.

Drug/Laboratory Test Interference

Positive Urine Glucose Test
Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay
Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

4.6 Pregnancy and lactation

4.6.1. Pregnancy

Risk Summary

Based on animal data showing adverse renal effects, VOKANAMET is not recommended during the second and third trimesters of pregnancy.

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

In animal studies, adverse renal pelvic and tubule dilatations that were not reversible were observed in rats when canagliflozin was administered at an exposure 0.5-times the 300 mg clinical dose, based on AUC during a period of renal development corresponding to the late second and third trimesters of human pregnancy. No adverse developmental effects were observed when metformin was administered to pregnant Sprague Dawley rats and rabbits during the period of organogenesis at doses up to 2- and 6-times, respectively, a 2000 mg clinical dose, based on body surface area *[see Data]*.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with an 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, stillbirth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Human Data

Published data from post-marketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was used during pregnancy. However, these studies cannot 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 Hydrochloride

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

Canagliflozin and Metformin

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

4.6.2 Lactation

Risk Summary

There is no information regarding the presence of VOKANAMET or canagliflozin in human milk, the effects on the breastfed infant, or the effects on milk production. Limited published studies report that metformin is present in human milk *[see Data]*. However, there is insufficient information on the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. Canagliflozin is present in the milk of lactating rats *[see Data]*. Since human kidney maturation occurs *in utero* and during the first 2 years of life when 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 VOKANAMET is not recommended while breastfeeding.

Data

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

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

4.7 Effects on ability to drive and use machine
Not applicable.

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

- Lactic Acidosis *[see Boxed Warning and Special warnings and precautions for use (4.4.1, 4.4.5)]*
- Lower Limb Amputation *[see Boxed Warning and Special warnings and precautions for use (4.4.2)]*
- Hypotension *[see Special warnings and precautions for use (4.4.3)]*
- Ketoacidosis *[see Special warnings and precautions for use (4.4.4)]*
- Acute Kidney Injury and Impairment in Renal Function *[see Special warnings and precautions for use (4.4.5)]*
- Hyperkalemia *[see Special warnings and precautions for use (4.4.6)]*
- Urosepsis and Pyelonephritis *[see Special warnings and precautions for use (4.4.7)]*
- Hypoglycemia with Concomitant Use of Sulfonylurea or Insulin *[see Special warnings and precautions for use (4.4.8)]*
- Genital Mycotic Infections *[see Special warnings and precautions for use (4.4.9)]*
- Hypersensitivity Reactions *[see Special warnings and precautions for use (4.4.10)]*
- Bone Fracture *[see Special warnings and precautions for use (4.4.11)]*
- Vitamin B_{12} Deficiency *[see Special warnings and precautions for use (4.4.12)]*

- Increases in Low-Density Lipoprotein (LDL-C) *[see Special warnings and precautions for use (4.4.13)]*

4.8.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Pool of Placebo-Controlled Trials

Canagliflozin

The data in Table 1 is derived from four 26-week placebo-controlled trials. In one trial canagliflozin was used as monotherapy and in three trials canagliflozin was used as add-on therapy with metformin (with or without other agents) *[see Pharmacological Properties (5.1.2)]*. These data reflect exposure of 1667 patients to canagliflozin and a mean duration of exposure to canagliflozin of 24 weeks with 1275 patients exposed to a combination of canagliflozin and metformin. Patients received canagliflozin 100 mg (N=833), canagliflozin 300 mg (N=834) or placebo (N=646) once daily. The mean daily dose of metformin was 2138 mg (SD 337.3) for the 1275 patients in the three placebo-controlled metformin add-on studies. The mean age of the population was 56 years and 2% were older than 75 years of age. Fifty percent (50%) of the population was male and 72% were Caucasian, 12% were Asian, and 5% were Black or African American. At baseline the population had diabetes for an average of 7.3 years, had a mean 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 1 shows common adverse reactions associated with the use of canagliflozin. These adverse reactions were not present at baseline, occurred more commonly on canagliflozin than on placebo, and occurred in at least 2% of patients treated with either canagliflozin 100 mg or canagliflozin 300 mg.

Table 1: Adverse Reactions From Pool of Four 26−Week Placebo-Controlled Studies Reported in ≥ 2% of Canagliflozin-Treated Patients*

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, metformin and sulfonylurea, or metformin 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 studies. Study 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

The incidence and type of adverse reactions in the three 26-week placebo-controlled metformin add-on studies, representing a majority of data from the four 26-week placebo-controlled trials, was similar to the adverse reactions described in Table 1. There were no additional adverse reactions identified in the pooling of these three placebo-controlled studies that included metformin relative to the four placebo-controlled studies.

In a trial with canagliflozin as initial combination therapy with metformin *[see Pharmacological Properties (5.1.2.1)]*, an increased incidence of diarrhea was observed in the canagliflozin and metformin combination groups (4.2%) compared to canagliflozin or metformin monotherapy groups (1.7%).

Pool of Placebo- and Active-Controlled Trials - Canagliflozin

The occurrence of adverse reactions for canagliflozin was evaluated in a larger pool of patients participating in placebo- and active-controlled trials.

The data combined eight clinical trials and reflect exposure of 6177 patients to canagliflozin. The mean duration of exposure to canagliflozin was 38 weeks with 1832 individuals exposed to canagliflozin for greater than 50 weeks. Patients received canagliflozin 100 mg (N=3092), canagliflozin 300 mg (N=3085) or comparator (N=3262) once daily. The mean age of the population was 60 years and 5% were older than 75 years of age. Fifty-eight percent (58%) of the population was male and 73% were Caucasian, 16% were Asian, and 4% were Black or African American. At baseline, the population had diabetes for an average of 11 years, had a mean HbA_{1C} of 8.0% and 33% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 81 mL/min/1.73 m^2).

The types and frequency of common adverse reactions observed in the pool of eight clinical trials were consistent with those listed in Table 1. Percentages were weighted by studies. Study weights were proportional to the harmonic mean of the three treatment sample sizes. In this pool, canagliflozin was also associated with the adverse reactions of fatigue (1.8% with comparator, 2.2% with canagliflozin 100 mg, and 2.0% with canagliflozin 300 mg) and loss of strength or energy (i.e., asthenia) (0.6% with comparator, 0.7% with canagliflozin 100 mg, and 1.1% with canagliflozin 300 mg).

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

In the pool of eight clinical trials, hypersensitivity-related adverse reactions (including erythema, rash, pruritus, urticaria, and angioedema) occurred in 3.0%, 3.8%, and 4.2% of patients receiving comparator, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. Five patients experienced

serious adverse reactions of hypersensitivity with canagliflozin, which included 4 patients with urticaria and 1 patient with a diffuse rash and urticaria occurring within hours of exposure to canagliflozin. Among these patients, 2 patients discontinued canagliflozin. One patient with urticaria had recurrence when canagliflozin was re-initiated.

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

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

Lower Limb Amputation

An approximately 2-fold increased risk of lower limb amputations associated with canagliflozin, a component of VOKANAMET, was observed in CANVAS and CANVAS-R, two large, randomized, placebo-controlled trials evaluating patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease. Patients in CANVAS and CANVAS-R were followed for an average of 5.7 and 2.1 years, respectively. The amputation data for CANVAS and CANVAS-R are shown in Tables 2 and 3, respectively *[see Special warnings and precautions for use (4.4.2)]*.

Table 2: CANVAS Amputations

	Placebo N=1441	**Canagliflozin 100 mg N=1445**	**Canagliflozin 300 mg N=1441**	**Canagliflozin (Pooled) N=2886**
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 1000 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 3: CANVAS-R Amputations

	Placebo N=2903	**Canagliflozin 100 mg (with up-titration to 300 mg) N=2904**
Patients with an amputation, n (%)	25 (0.9)	45 (1.5)
Total amputations	36	59
Amputation incidence rate (per 1000 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.

Volume Depletion-Related Adverse Reactions

Canagliflozin results in an osmotic diuresis, which may lead to reductions in intravascular volume. In clinical studies, treatment with canagliflozin was associated with a dose-dependent increase in the incidence of volume depletion-related adverse reactions (e.g., hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration). An increased incidence was observed in patients on the 300 mg dose. The three factors associated with the largest increase in volume depletion-related

adverse reactions were the use of loop diuretics, moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2), and age 75 years and older (Table 4) *[see Posology and method of administration (4.2.2), Special warnings and precautions for use (4.4.3), and Clinical Particulars (4.2.7, 4.2.2)]*.

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

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

Impairment in Renal Function

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

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

			Placebo N=646	**Canagliflozin 100 mg N=833**	**Canagliflozin 300 mg N=834**
Pool of Four Placebo-Controlled Trials	Baseline	Creatinine (mg/dL)	0.84	0.82	0.82
		eGFR (mL/min/1.73 m^2)	87.0	88.3	88.8
	Week 6 Change	Creatinine (mg/dL)	0.01	0.03	0.05
		eGFR (mL/min/1.73 m^2)	-1.6	-3.8	-5.0
	End of Treatment Change*	Creatinine (mg/dL)	0.01	0.02	0.03
		eGFR (mL/min/1.73 m^2)	-1.6	-2.3	-3.4
			Placebo N=90	**Canagliflozin 100 mg N=90**	**Canagliflozin 300 mg N=89**
Moderate Renal Impairment Trial	Baseline	Creatinine (mg/dL)	1.61	1.62	1.63
		eGFR (mL/min/1.73 m^2)	40.1	39.7	38.5
	Week 3 Change	Creatinine (mg/dL)	0.03	0.18	0.28
		eGFR (mL/min/1.73 m^2)	-0.7	-4.6	-6.2
	End of Treatment Change*	Creatinine (mg/dL)	0.07	0.16	0.18
		eGFR (mL/min/1.73 m^2)	-1.5	-3.6	-4.0

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

* Week 26 in mITT LOCF population

In the pool of four placebo-controlled trials where patients had normal or mildly impaired baseline renal function, the proportion of patients who experienced at least one event of significant renal function decline, defined as an eGFR below 80 mL/min/1.73 m^2 and 30% lower than baseline, was 2.1% with placebo, 2.0% with canagliflozin 100 mg, and 4.1% with canagliflozin 300 mg. At the end of treatment, 0.5% with placebo, 0.7% with canagliflozin 100 mg, and 1.4% with canagliflozin 300 mg had a significant renal function decline.

In a trial carried out in patients with moderate renal impairment with a baseline eGFR of 30 to less than 50 mL/min/1.73 m^2 (mean baseline eGFR 39 mL/min/1.73 m^2), the proportion of patients who experienced at least one event of significant renal function decline, defined as an eGFR 30% lower than baseline, was 6.9% with placebo, 18% with canagliflozin 100 mg, and 22.5% with canagliflozin 300 mg. At the end of treatment, 4.6% with placebo, 3.4% with canagliflozin 100 mg, and 2.2% with canagliflozin 300 mg had a significant renal function decline.

In a pooled population of patients with moderate renal impairment (N=1085) with baseline eGFR of 30 to less than 60 mL/min/1.73 m^2 (mean baseline eGFR 48 mL/min/1.73 m^2), the overall incidence of these events was lower than in the dedicated trial but a dose-dependent increase in incident episodes of significant renal function decline compared to placebo was still observed. Use of canagliflozin has been associated with an increased incidence of renal-related adverse reactions (e.g., increased blood creatinine, decreased glomerular filtration rate, renal impairment, and acute renal failure), particularly in patients with moderate renal impairment.

In the pooled analysis of patients with moderate renal impairment, the incidence of renal-related adverse reactions was 3.7% with placebo, 8.9% with canagliflozin 100 mg, and 9.3% with canagliflozin 300 mg. Discontinuations due to renal-related adverse events occurred in 1.0% with placebo, 1.2% with canagliflozin 100 mg, and 1.6% with canagliflozin 300 mg *[see Special warnings and precautions for use (4.4.5)]*.

Genital Mycotic Infections

In the pool of four placebo-controlled clinical trials, female genital mycotic infections (e.g., vulvovaginal mycotic infection, vulvovaginal candidiasis, and vulvovaginitis) occurred in 2.8%, 10.6%, and 11.6% of females treated with placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections on canagliflozin. Female patients who developed genital mycotic infections on canagliflozin were more likely to experience recurrence and require treatment with oral or topical antifungal agents and anti-microbial agents. In females, discontinuation due to genital mycotic infections occurred in 0% and 0.7% of patients treated with placebo and canagliflozin, respectively *[see Special warnings and precautions for use (4.4.9)]*.

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

treatment with oral or topical antifungal agents and anti-microbial agents than patients on comparators. In males, discontinuations due to genital mycotic infections occurred in 0% and 0.5% of patients treated with placebo and canagliflozin, respectively. In the pooled analysis of 8 controlled trials, phimosis was reported in 0.3% of uncircumcised male patients treated with canagliflozin and 0.2% required circumcision to treat the phimosis *[see Special warnings and precautions for use (4.4.9)]*.

Hypoglycemia

In canagliflozin clinical trials, hypoglycemia was defined as any event regardless of symptoms, where biochemical hypoglycemia was documented (any glucose value below or equal to 70 mg/dL). Severe hypoglycemia was defined as an event consistent with hypoglycemia where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained). In individual clinical trials *[see Pharmacological Properties (5.1.2.8)]*, episodes of hypoglycemia occurred at a higher rate when canagliflozin was co-administered with insulin or sulfonylureas (Table 6) *[see Special warnings and precautions for use (4.4.8)]*.

Table 6: Incidence of Hypoglycemia* in Controlled Clinical Studies

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 (26 weeks)	**Placebo + Metformin (N=183)**	**Canagliflozin 100 mg + Metformin (N=368)**	**Canagliflozin 300 mg + Metformin (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 (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 + Sulfonylurea (26 weeks)	**Placebo + Metformin + Sulfonylurea (N=156)**	**Canagliflozin 100 mg + Metformin + Sulfonylurea (N=157)**	**Canagliflozin 300 mg + Metformin + 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 + Pioglitazone (26 weeks)	**Placebo + Metformin + Pioglitazone (N=115)**	**Canagliflozin 100 mg + Metformin + Pioglitazone (N=113)**	**Canagliflozin 300 mg + Metformin + 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 (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)

Table 6: Incidence of Hypoglycemia* in Controlled Clinical Studies

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

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

‡ Phase 2 clinical study with twice daily dosing (50 mg or 150 mg twice daily in combination with metformin)

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

Bone Fracture

The occurrence of bone fractures was evaluated in a pool of nine clinical trials with a mean duration of exposure to canagliflozin of 85 weeks. The incidence rates of adjudicated bone fractures were 1.1, 1.4, and 1.5 per 100 patient-years of exposure in the comparator, canagliflozin 100 mg, and canagliflozin 300 mg groups, respectively. Fractures were observed as early as 12 weeks after treatment initiation and were more likely to be low trauma (e.g., fall from no more than standing height), and affect the upper extremities *[see Special warnings and precautions for use (4.4.11)]*.

Metformin

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

Long-term treatment with metformin has been associated with a decrease in vitamin B_{12}, which may very rarely result in clinically significant vitamin B_{12} deficiency (e.g., megaloblastic anemia) *[see Special warnings and precautions for use (4.4.12)]*.

Laboratory and Imaging Tests

Increases in Serum Potassium

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

In these patients, increases in potassium were more commonly seen in those with elevated potassium at baseline. Among patients with moderate renal impairment, approximately 84% were taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor blockers *[see Special warnings and precautions for use (4.4.3, 4.4.6) and Clinical Particulars (4.2.2)]*.

Increases in Serum Magnesium

Dose-related increases in serum magnesium were observed early after initiation of canagliflozin (within 6 weeks) and remained elevated throughout treatment. In the pool of four placebo-controlled trials, the mean percent change in serum magnesium levels was 8.1% and 9.3% with canagliflozin 100 mg and canagliflozin 300 mg, respectively, compared to -0.6% with placebo. In a trial of patients with moderate renal impairment, serum magnesium levels increased by 0.2%, 9.2%, and 14.8% with placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively.

Increases in Serum Phosphate

Dose-related increases in serum phosphate levels were observed with canagliflozin. In the pool of four placebo-controlled trials, the mean percent change in serum phosphate levels were 3.6% and 5.1% with canagliflozin 100 mg and canagliflozin 300 mg, respectively, compared to 1.5% with placebo. In a trial of patients with moderate renal impairment, the mean serum phosphate levels increased by 1.2%, 5.0%, and 9.3% with placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively.

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

In the pool of four placebo-controlled trials, dose-related increases in LDL-C with canagliflozin were observed. Mean changes (percent changes) from baseline in LDL-C relative to placebo were 4.4 mg/dL (4.5%) and 8.2 mg/dL (8.0%) with canagliflozin 100 mg and canagliflozin 300 mg, respectively. The mean baseline LDL-C levels were 104 to 110 mg/dL across treatment groups *[see Special warnings and precautions for use (4.4.13)]*.

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

Increases in Hemoglobin

In the pool of four placebo-controlled trials, 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 levels 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). At 2 years, 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%.

4.8.2 Postmarketing Experience

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

Canagliflozin

Ketoacidosis *[see Special warnings and precautions for use (4.4.4)]*

Acute Kidney Injury and Impairment in Renal Function *[see Special warnings and precautions for use (4.4.5)]*

Anaphylaxis, Angioedema *[see Special warnings and precautions for use (4.4.10)]*

Urosepsis and Pyelonephritis *[see Special warnings and precautions for use (4.4.7)]*

Metformin hydrochloride

Cholestatic, hepatocellular, and mixed hepatocellular liver injury

4.9 Overdose

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

Canagliflozin

There were no reports of overdose during the clinical development program of canagliflozin.

Metformin

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases *[see Special warnings and precautions for use (4.4.1)]*.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

5.1.1 Mechanism of Action

VOKANAMET

VOKANAMET (canagliflozin and metformin hydrochloride) combines two oral antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: canagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, and metformin hydrochloride, a member of the biguanide class.

Canagliflozin

Sodium-glucose co-transporter 2 (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).

Metformin

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose

production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal patients except in special circumstances *[see Special warnings and precautions for use (4.4.8)]* and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

5.1.2 Clinical Studies

Canagliflozin

Following single and multiple oral doses of canagliflozin in 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. 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 studies. 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 study, 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 study, 60 healthy subjects were administered a single oral dose of canagliflozin 300 mg, canagliflozin 1,200 mg (4 times the maximum recommended dose), moxifloxacin, and placebo. No meaningful changes in QTc interval were observed with either the recommended dose of 300 mg or the 1,200 mg dose.

Canagliflozin has been studied in combination with metformin alone, metformin and sulfonylurea, metformin and sitagliptin, metformin and a thiazolidinedione (i.e. pioglitazone), and metformin and insulin (with or without other anti-hyperglycemic agents). The efficacy of canagliflozin was compared to a dipeptidyl peptidase-4 (DPP-4) inhibitor (sitagliptin), both as add-on combination therapy with metformin and sulfonylurea, and a sulfonylurea (glimepiride), both as add-on combination therapy with metformin.

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

In patients with type 2 diabetes, treatment with canagliflozin and metformin produced clinically and statistically significant improvements in HbA_{1C} compared to placebo. Reductions in HbA_{1C} were observed across subgroups including age, gender, race, and baseline body mass index (BMI).

5.1.2.1 Canagliflozin as Initial Combination Therapy with Metformin

A total of 1186 patients with type 2 diabetes inadequately controlled with diet and exercise participated in a 26-week double-blind, active-controlled, parallel-group, 5-arm, multicenter study to evaluate the efficacy and safety of initial therapy with canagliflozin in combination with

metformin XR. The median age was 56 years, 48% of patients were men, 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 7). The metformin XR dose was initiated at 500 mg/day for the first week of treatment and then increased to 1000 mg/day. Metformin XR or matching placebo was up-titrated every 2-3 weeks during the next 8 weeks of treatment to a maximum daily dose of 1500 to 2000 mg/day, as tolerated; about 90% of patients reached 2000 mg/day.

At the end of treatment, canagliflozin 100 mg and canagliflozin 300 mg in combination with metformin XR resulted in a statistically significant greater improvement in HbA_{1C} compared to their respective canagliflozin doses (100 mg and 300 mg) alone or metformin XR alone.

Table 7: Results from 26-Week Active-Controlled Clinical Study of Canagliflozin Alone or Canagliflozin as Initial Combination Therapy with Metformin*

Efficacy Parameter	Metformin XR (N=237)	Canagliflozin 100 mg (N=237)	Canagliflozin 300 mg (N=238)	Canagliflozin 100 mg + Metformin XR (N=237)	Canagliflozin 300 mg + Metformin XR (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 XR (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.

5.1.2.2 Canagliflozin as Add-on Combination Therapy with Metformin

A total of 1284 patients with type 2 diabetes inadequately controlled on metformin monotherapy (greater than or equal to 2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated) participated in a 26-week, double-blind, placebo- and active-controlled study to evaluate the efficacy and safety of canagliflozin in combination with metformin. The mean age was 55 years, 47% of patients were men, and the mean baseline eGFR was 89 mL/min/1.73 m^2. Patients already on the required metformin dose (N=1009) were randomized after completing a 2-week, single-blind, placebo run-in period. Patients taking less than the required metformin dose or patients on metformin in combination with another antihyperglycemic agent (N=275) were switched to metformin monotherapy (at doses described above) for at least 8 weeks before entering the 2-week, single-blind,

placebo run-in. After the placebo run-in period, patients were randomized to canagliflozin 100 mg, canagliflozin 300 mg, sitagliptin 100 mg, or placebo, administered once daily as add-on therapy to metformin.

At the end of treatment, canagliflozin 100 mg and 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. 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 (see Table 8). 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 8: Results from 26-Week Placebo-Controlled Clinical Study of Canagliflozin in Combination with Metformin*

Efficacy Parameter	Placebo + Metformin (N=183)	Canagliflozin 100 mg + Metformin (N=368)	Canagliflozin 300 mg + Metformin (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 study prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value and stratification factors
‡ $p<0.001$

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

A total of 1450 patients with type 2 diabetes inadequately controlled on metformin monotherapy (greater than or equal to 2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated) participated in a 52-week, double-blind, active-controlled study to evaluate the efficacy and safety of canagliflozin in combination with metformin.

The mean age was 56 years, 52% of patients were men, and the mean baseline eGFR was 90 mL/min/1.73 m^2. Patients tolerating maximally required metformin dose (N=928) were randomized after completing a 2-week, single-blind, placebo run-in period. Other patients (N=522)

were switched to metformin 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 study to 6 or 8 mg), administered once daily as add-on therapy to metformin.

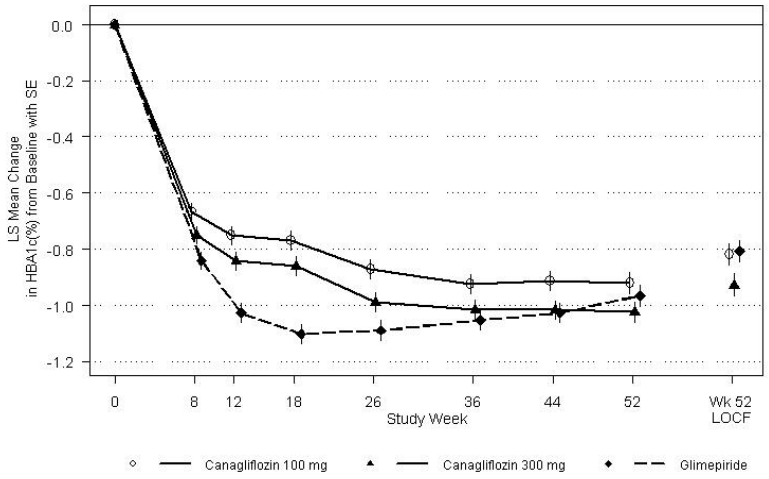
As shown in Table 9 and Figure 1, at the end of treatment, canagliflozin 100 mg provided similar reductions in HbA_{1C} from baseline compared to glimepiride when added to metformin therapy. Canagliflozin 300 mg provided a greater reduction from baseline in HbA_{1C} compared to glimepiride, and the relative treatment difference was -0.12% (95% CI: −0.22; −0.02). As shown in Table 13, treatment with canagliflozin 100 mg and 300 mg daily provided greater improvements in percent body weight change, relative to glimepiride.

Table 9: Results from 52−Week Clinical Study Comparing Canagliflozin to Glimepiride in Combination with Metformin*

Efficacy Parameter	**Canagliflozin 100 mg + Metformin (N=483)**	**Canagliflozin 300 mg + Metformin (N=485)**	**Glimepiride (titrated) + Metformin (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 study prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value and stratification factors
‡ Canagliflozin + metformin is considered non-inferior to glimepiride + metformin 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 at Each Time Point (Completers) and at Week 52 Using Last Observation Carried Forward (mITT Population)



5.1.2.4 Canagliflozin as Add-on Combination Therapy with Metformin and Sitagliptin

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

Table 10: Results from 26−Week Placebo-Controlled Clinical Study of Canagliflozin in Combination with Metformin and Sitagliptin

Efficacy Parameter	**Placebo + Metformin and Sitagliptin (N=108*)**	**Canagliflozin + Metformin 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

Table 10: Results from 26−Week Placebo-Controlled Clinical Study of Canagliflozin in Combination with Metformin and Sitagliptin

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

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

A total of 469 patients with type 2 diabetes inadequately controlled on the combination of metformin (greater than or equal to 2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated) and sulfonylurea (maximal or near-maximal effective dose) participated in a 26-week, double-blind, placebo-controlled study to evaluate the efficacy and safety of canagliflozin in combination with metformin and sulfonylurea. The mean age was 57 years, 51% of patients were men, and the mean baseline eGFR was 89 mL/min/1.73 m^2. Patients already on the protocol-specified doses of metformin and sulfonylurea (N=372) entered a 2-week, single-blind, placebo run-in period. Other patients (N=97) were required to be on a stable protocol-specified dose of metformin and sulfonylurea for at least 8 weeks before entering the 2-week run-in period. Following the run-in period, patients were randomized to canagliflozin 100 mg, canagliflozin 300 mg, or placebo administered once daily as add-on to metformin and sulfonylurea.

At the end of treatment, canagliflozin 100 mg and 300 mg once daily resulted in a statistically significant improvement in HbA_{1C} (p<0.001 for both doses) compared to placebo when added to metformin and sulfonylurea. Canagliflozin 100 mg and 300 mg once daily also resulted in a greater proportion of patients achieving an 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 and sulfonylurea (see Table 11).

Table 11: Results from 26−Week Placebo-Controlled Clinical Study of Canagliflozin in Combination with Metformin and Sulfonylurea*

Efficacy Parameter	**Placebo + Metformin and Sulfonylurea (N=156)**	**Canagliflozin 100 mg + Metformin and Sulfonylurea (N=157)**	**Canagliflozin 300 mg + Metformin 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

Table 11: Results from 26−Week Placebo-Controlled Clinical Study of Canagliflozin in Combination with Metformin and Sulfonylurea*

Efficacy Parameter	Placebo + Metformin and Sulfonylurea (N=156)	Canagliflozin 100 mg + Metformin and Sulfonylurea (N=157)	Canagliflozin 300 mg + Metformin and Sulfonylurea (N=156)
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 study prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value and stratification factors
‡ $p<0.001$

5.1.2.6 Canagliflozin Compared to Sitagliptin, Both as Add-on Combination Therapy with Metformin and Sulfonylurea

A total of 755 patients with type 2 diabetes inadequately controlled on the combination of metformin (greater than or equal to 2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated) and sulfonylurea (near-maximal or maximal effective dose) participated in a 52 week, double-blind, active-controlled study to compare the efficacy and safety of canagliflozin 300 mg versus sitagliptin 100 mg in combination with metformin and sulfonylurea. The mean age was 57 years, 56% of patients were men, and the mean baseline eGFR was 88 mL/min/1.73 m^2. Patients already on protocol-specified doses of metformin 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 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 and sulfonylurea.

As shown in Table 12 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 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 12: Results from 52−Week Clinical Study Comparing Canagliflozin to Sitagliptin in Combination with Metformin and Sulfonylurea*

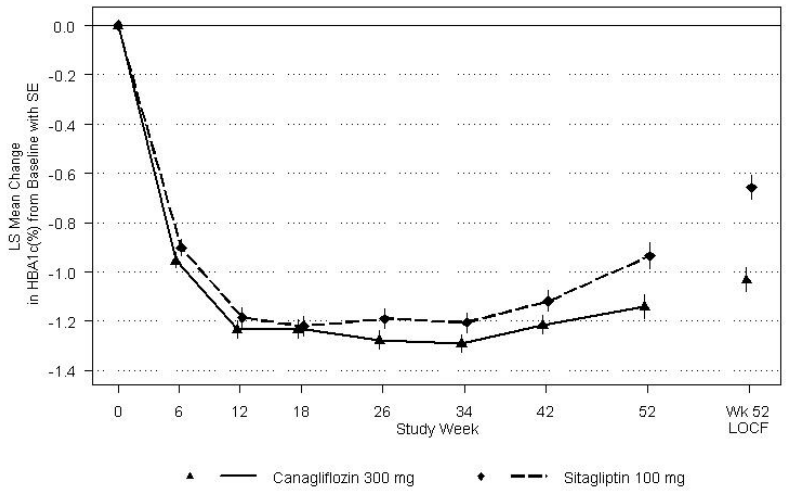
Efficacy Parameter	Canagliflozin 300 mg + Metformin and Sulfonylurea (N=377)	Sitagliptin 100 mg + Metformin and Sulfonylurea (N=378)
HbA_{1C} (%)		
Baseline (mean)	8.12	8.13
Change from baseline (adjusted mean)	-1.03	-0.66
Difference from sitagliptin (adjusted mean) (95% CI)†	-0.37‡ (-0.50, -0.25)	
Percent of patients achieving HbA_{1C} < 7%	48	35

Table 12: Results from 52−Week Clinical Study Comparing Canagliflozin to Sitagliptin in Combination with Metformin and Sulfonylurea*

Efficacy Parameter	Canagliflozin 300 mg + Metformin and Sulfonylurea (N=377)	Sitagliptin 100 mg + Metformin and Sulfonylurea (N=378)
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 study prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value and stratification factors
‡ Canagliflozin + metformin+ sulfonylurea is considered non-inferior to sitagliptin + metformin+ sulfonylurea because the upper limit of this confidence interval is less than the pre-specified non-inferiority margin of < 0.3%.
§ p<0.001

Figure 2: Mean HbA_{1C} Change at Each Time Point (Completers) and at Week 52 Using Last Observation Carried Forward (mITT Population)



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

A total of 342 patients with type 2 diabetes inadequately controlled on the combination of metformin (greater than or equal to 2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated) and pioglitazone (30 or 45 mg/day) participated in a 26-week, double-blind, placebo-controlled study to evaluate the efficacy and safety of canagliflozin in combination with metformin and pioglitazone. The mean age was 57 years, 63% of patients were men, and the mean baseline eGFR was 86 mL/min/1.73 m^2. Patients already on protocol-specified doses of metformin 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 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 and pioglitazone.

At the of 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 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 and pioglitazone (see Table 13). 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 13: Results from 26−Week Placebo-Controlled Clinical Study of Canagliflozin in Combination with Metformin and Pioglitazone*

Efficacy Parameter	Placebo + Metformin and Pioglitazone (N=115)	Canagliflozin 100 mg + Metformin and Pioglitazone (N=113)	Canagliflozin 300 mg + Metformin 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 study prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value and stratification factors
‡ $p<0.001$

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

A total of 1718 patients with type 2 diabetes inadequately controlled on insulin greater than or equal to 30 units/day or insulin in combination with other antihyperglycemic agents participated in an 18-week, double-blind, placebo-controlled substudy of a cardiovascular study to evaluate the efficacy and safety of canagliflozin in combination with insulin. Of these patients, a subgroup of 432 patients with inadequate glycemic control received canagliflozin or placebo plus metformin and ≥ 30 units/day of insulin over 18 weeks.

In this subgroup, the mean age was 61 years, 67% of patients were men, and the mean baseline eGFR was 81 mL/min/1.73 m^2. Patients on metformin in combination with basal, bolus, or basal/bolus insulin for at least 10 weeks entered a 2-week, single-blind, placebo run-in period. Approximately 74% of these patients were on a background of metformin and basal/bolus insulin regimen. After the run-in period, patients were randomized to canagliflozin 100 mg, canagliflozin 300 mg, or placebo, administered once daily as add-on to metformin and insulin. The mean daily insulin dose at baseline was 93 units, which was similar across treatment groups.

At the of 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 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 14). 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 and insulin required glycemic rescue therapy: 3.6% of patients receiving canagliflozin 100 mg, 2.7% of patients receiving canagliflozin 300 mg, and 6.2% of patients receiving placebo. An increased incidence of hypoglycemia was observed in this study, which is consistent with the expected increase of hypoglycemia when an agent not associated with hypoglycemia is added to insulin *[see Special warnings and precautions for use (4.4.8) and Undesirable effects (4.8.1)]*.

Table 14: Results from 18−Week Placebo-Controlled Clinical Study of Canagliflozin in Combination with Metformin and Insulin ≥ 30 Units/Day*

Efficacy Parameter	Placebo + Metformin + Insulin (N=145)	Canagliflozin 100 mg + Metformin + Insulin (N=139)	Canagliflozin 300 mg + Metformin + 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 study prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value and stratification factors
‡ $p\leq0.001$
§ $p\leq0.01$

5.2 Pharmacokinetic properties

VOKANAMET

The results of a bioequivalence study in healthy subjects demonstrated that VOKANAMET 50 mg/500 mg and 150 mg/500 mg combination tablets are bioequivalent to co-administration of corresponding doses of canagliflozin and metformin hydrochloride as individual tablets under fed conditions.

Administration of VOKANAMET 150 mg/1,000 mg fixed-dose combination with food resulted in no change in overall exposure of canagliflozin. There was no change in metformin AUC; however,

the mean peak plasma concentration of metformin was decreased by 16% when administered with food. A delayed time to peak plasma concentration was observed for both components (a delay of 2 hours for canagliflozin and 1 hour for metformin) under fed conditions. These changes are not likely to be clinically meaningful.

Canagliflozin
The pharmacokinetics of canagliflozin is essentially similar in healthy subjects and patients with type 2 diabetes. Following single-dose oral administration of 100 mg and 300 mg of canagliflozin, peak plasma concentrations (median T_{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
The absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of metformin hydrochloride 500 to 1,500 mg, and 850 to 2,550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination.

Distribution

Canagliflozin
The mean steady-state volume of distribution of canagliflozin following a single intravenous infusion in healthy subjects was 83.5 L, suggesting extensive tissue distribution. Canagliflozin is extensively bound to proteins in plasma (99%), mainly to albumin. Protein binding is independent of canagliflozin plasma concentrations. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment.

Metformin
The apparent volume of distribution (V/F) of metformin following single oral doses of metformin hydrochloride 850 mg tablets averaged 654 ± 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. At usual clinical doses and dosing schedules of metformin tablets, steady-state plasma concentrations of metformin are reached within 24 to 48 hours and are generally less than 1 mcg/mL. During controlled clinical trials of metformin, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

Metabolism

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

Metformin
Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion.

Excretion

Canagliflozin
Following administration of a single oral [^{14}C] canagliflozin dose to healthy subjects, 41.5%, 7.0%, and 3.2% of the administered radioactive dose was recovered in feces as canagliflozin, a hydroxylated metabolite, and an *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
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
Studies characterizing the pharmacokinetics of canagliflozin and metformin after administration of VOKANAMET were not conducted in patients with renal and hepatic impairment. Descriptions of the individual components in this patient population are described below.

Renal Impairment
Canagliflozin
A single-dose, open-label study evaluated the pharmacokinetics of canagliflozin 200 mg in subjects with varying degrees of renal impairment (classified using the MDRD-eGFR formula) compared to healthy subjects.

Renal impairment did not affect the C_{max} of canagliflozin. Compared to healthy subjects (N=3; eGFR greater than or equal to 90 mL/min/1.73 m^2), plasma AUC of canagliflozin was increased by

approximately 15%, 29%, and 53% in subjects with mild (N=10), moderate (N=9), and severe (N=10) renal impairment, respectively, (eGFR 60 to less than 90, 30 to less than 60, and 15 to less than 30 mL/min/1.73 m^2, respectively) but was similar for ESRD (N=8) subjects and healthy subjects. Increases in canagliflozin AUC of this magnitude are not considered clinically relevant. The pharmacodynamic response to canagliflozin declines with increasing severity of renal impairment *[see Contraindication (4.3) and Special warnings and precautions for use (4.4.5)]*.

Canagliflozin was negligibly removed by hemodialysis.

Metformin

In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased *[see Contraindication (4.3) and Special warnings and precautions for use (4.4.1)]*.

Hepatic Impairment

Canagliflozin

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

These differences are not considered to be clinically meaningful. There is no clinical experience in patients with Child-Pugh class C (severe) hepatic impairment *[see Special warnings and precautions for use (4.4.1)]*.

Metformin

No pharmacokinetic studies of metformin have been conducted in patients with hepatic insufficiency *[see Special warnings and precautions for use (4.4.1)]*.

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

Canagliflozin

Based on the population PK analysis with data collected from 1526 subjects, age, body mass index (BMI)/weight, gender, and race do not have a clinically meaningful effect on the pharmacokinetics of canagliflozin *[see Clinical Particulars (4.2.7)]*.

Metformin

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analyzed according to gender.

No studies of metformin pharmacokinetic parameters according to race have been performed.

Geriatric

VOKANAMET

Studies characterizing the pharmacokinetics of canagliflozin and metformin after administration of VOKANAMET in geriatric patients have not been performed *[see Special warnings and precautions for use (4.4.1, 4.4.5) and Clinical Particulars (4.2.7)]*.

Canagliflozin

Age had no clinically meaningful effect on the pharmacokinetics of canagliflozin based on a population pharmacokinetic analysis *[see Undesirable effects (4.8.1) and Clinical Particulars (4.2.7)]*.

Metformin

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared with healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Pediatric

Studies characterizing the pharmacokinetics of canagliflozin and metformin after administration of VOKANAMET in pediatric patients have not been performed.

Drug-Drug Interactions

VOKANAMET

Pharmacokinetic drug interaction studies with VOKANAMET have not been performed; however, such studies have been conducted with the individual components canagliflozin and metformin hydrochloride.

Co-administration of multiple doses of canagliflozin (300 mg) and metformin (2,000 mg) given once daily did not meaningfully alter the pharmacokinetics of either canagliflozin or metformin in healthy subjects.

Canagliflozin

In Vitro Assessment of Drug Interactions

Canagliflozin did not induce CYP450 enzyme expression (3A4, 2C9, 2C19, 2B6, and 1A2) in cultured human hepatocytes. Canagliflozin did not inhibit the CYP450 isoenzymes (1A2, 2A6, 2C19, 2D6, or 2E1) and weakly inhibited CYP2B6, CYP2C8, 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 15: 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 Interaction with other medicinal products and other forms of interactions (4.5.2)* 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	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 16: 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 Interaction with other medicinal products and other forms of interactions (4.5.2)* 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	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	1.05

Table 16: Effect of Canagliflozin on Systemic Exposure of Co-Administered Drugs

				(0.98; 1.03)	(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

Table 17: Effect of Co−Administered Drugs on Plasma Metformin Systemic Exposures

Co-Administered Drug	**Dose of Co-Administered Drug***	**Dose of Metformin***	**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 Special warnings and precautions for use (4.4) and Interaction with other medicinal products and other forms of interactions (4.5)]*				
Cimetidine	400 mg	850 mg	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis *[see Special warnings and precautions for use (4.4) and Interaction with other medicinal products and other forms of interactions (4.5)]*				
Topiramate¶	100 mg	500 mg	1.25#	1.18

* Single dose unless otherwise noted
† AUC = $AUC_{0-\infty}$
‡ Metformin hydrochloride 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 18: Effect of Metformin on Co−Administered Drug Systemic Exposures

Co-Administered Drug	**Dose of Co-Administered Drug***	**Dose of Metformin***	**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.

5.3 Preclinical Safety data

5.3.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

VOKANAMET

No animal studies have been conducted with the combined products in VOKANAMET to evaluate carcinogenesis, mutagenesis, or impairment of fertility. The following data are based on findings in studies with canagliflozin and metformin individually.

Canagliflozin

Carcinogenesis

Carcinogenicity was evaluated in 2-year studies conducted in CD1 mice and Sprague-Dawley rats. Canagliflozin did not increase the incidence of tumors in mice dosed at 10, 30, or 100 mg/kg (less than or equal to 14 times exposure from a 300 mg clinical dose).

Testicular Leydig cell tumors, considered secondary to increased luteinizing hormone (LH), increased significantly in male rats at all doses tested (10, 30, and 100 mg/kg). In a 12-week clinical study, LH did not increase in males treated with canagliflozin.

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 studies 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

Carcinogenesis

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

Mutagenesis

There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Impairment of Fertility

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

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 3 times the maximum recommended human daily dose based on body surface area comparisons.

6. Pharmaceutical Particulars

6.1 List of excipient

Inactive ingredients of the core tablet are croscarmellose sodium, hypromellose, magnesium stearate, and microcrystalline cellulose. The magnesium stearate is vegetable-sourced. The tablets are finished with a commercially available film-coating consisting of the following excipients: Macrogol 3350, polyvinyl alcohol (partially hydrolyzed), talc, titanium dioxide, iron oxide yellow, (150 mg/500 mg tablets only), and iron oxide red (150 mg/500 mg tablets only).

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

See expiry date on the outer pack.

6.4 Special precautions for storage

Do not store above 30°C. Store and dispense in the original container. Storage in a pill box or pill organizer is allowed for up to 30 days.
Keep out of reach of children.

6.5 Nature and contents of container

HDPE bottle child-resistant, induction seal, and desiccant. Bottle sizes of 20, 60 and 180 film-coated tablets.

7. Marketing Authorization Holder

See the end of the leaflet.

8. Marketing Authorization Number

VOKANAMET 50/500 MG: 2C 15022/61 (NC)
VOKANAMET 150/500 MG: 2C 15023/61 (NC)

9. Date of authorization

17 April 2018

10. Date of revision of the text

11/2017

Patient Counseling Information

Advise patients to read the approved patient labeling (Patient Information)

- Lactic Acidosis: Explain the risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in *Special warnings and precautions for use (4.4.1)*. Advise patients to discontinue VOKANAMET immediately and to promptly notify their healthcare provider if unexplained hyperventilation, myalgias, malaise, unusual somnolence or other nonspecific symptoms occur. Once a patient is stabilized on VOKANAMET, gastrointestinal symptoms, which are common during initiation of metformin, are unlikely to recur. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

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

- Counsel patients against excessive alcohol intake while receiving VOKANAMET.

- Inform patients about importance of regular testing of renal function and hematological parameters while receiving VOKANAMET.

- Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

- Instruct patients to inform their doctor that they are taking VOKANAMET prior to any surgical or radiological procedure, as temporary discontinuation of VOKANAMET may be required until renal function has been confirmed to be normal *[see Special warnings and precautions for use (4.4.1)]*.

- Instruct patients to take VOKANAMET only as prescribed twice daily with food. If a dose is missed, advise patients not to take two doses of VOKANAMET at the same time.

- Lower Limb Amputation: Inform patients that VOKANAMET is associated with an increased risk of amputations. Counsel patients about the importance of routine preventative foot care. Instruct patients to monitor for new pain or tenderness, sores or ulcers, or infections involving the leg or foot and to seek medical advice immediately if such signs or symptoms develop *[see Boxed Warning and Special warnings and precautions for use (4.4.2)]***.**

- Hypotension: Inform patients that symptomatic hypotension may occur with VOKANAMET and advise them to contact their doctor if they experience such symptoms *[see Special warnings and precautions for use (4.4.3)]*. Inform patients that dehydration may increase the risk for hypotension and to have adequate fluid intake.

- Ketoacidosis: Inform patients that ketoacidosis is a serious life-threatening condition. Cases of ketoacidosis have been reported during use of canagliflozin. Instruct patients to check ketones (when possible) if symptoms consistent with ketoacidosis occur even if blood glucose is not elevated. If symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing) occur, instruct patients to discontinue VOKANAMET and seek medical advice immediately *[see Special warnings and precautions for use (4.4.4)]*.

- Acute Kidney Injury: Inform patients that acute kidney injury has been reported during use of canagliflozin. Advise patients to seek medical advice immediately if they have reduced oral

intake (such as due to acute illness or fasting), or increased fluid losses (such as due to vomiting, diarrhea, or excessive heat exposure), as it may be appropriate to temporarily discontinue VOKANAMET use in those settings *[see Special warnings and precautions for use (4.4.5)]*.

- Serious Urinary Tract Infections: Inform patients of the potential for urinary tract infections, which may be serious. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur *[see Special warnings and precautions for use (4.4.7)]*.

- Genital Mycotic Infections in Females: Inform female patients that vaginal yeast infection (e.g., vulvovaginitis) may occur and provide them with information on the signs and symptoms of a vaginal yeast infection. Advise them of treatment options and when to seek medical advice *[see Special warnings and precautions for use (4.4.9)]*.

- Genital Mycotic Infections in Males: Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with prior history. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Special warnings and precautions for use (4.4.9)]*.

- 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 Special warnings and precautions for use (4.4.10)]*.

- Bone Fracture: Inform patients that bone fractures have been reported in patients taking canagliflozin. Provide them with information on factors that may contribute to fracture risk.

- Laboratory Tests: Inform patients that they will test positive for glucose in their urine while on VOKANAMET *[see Interaction with other medicinal products and other forms of interactions (4.5.2)]*.

- Pregnancy: Advise pregnant women, and females of reproductive potential of the potential risk to a fetus with treatment with VOKANAMET *[see Pregnancy and lactation (4.6.1)]*. Instruct females of reproductive potential to report pregnancies to their physicians as soon as possible.

- Lactation: Advise women that breastfeeding is not recommended during treatment with VOKANAMET *[see Pregnancy and lactation (4.6.2)]*.

- Inform females that treatment with VOKANAMET may result in ovulation in some premenopausal anovulatory women which may lead to unintended pregnancy *[see Clinical Particulars (4.2.8)]*.

- Inform patients that the most common adverse reactions associated with canagliflozin are genital mycotic infection, urinary tract infection, and increased urination. Most common adverse reactions associated with metformin are diarrhea, nausea, vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache.

Warning according to the announcement of Ministry of Public Health

1. Do not use in people with known allergy to this medicine.
2. Do not use for treatment of diabetes mellitus type 1, patients with ketoacidosis, patients with severe infection, people having severe accident.
3. Pregnant women should avoid using this medicine and nursing women should be cautious of using this medicine.
4. Should not use this medicine with alcoholic beverages.
5. If patients have nausea, vomiting, anorexia, stomachache, abnormal thirsty, weakness, difficult breath, and confusion, even though the level of blood sugar is not quite high, consult doctor or pharmacist as diabetic ketoacidosis may occur.
6. Should be cautious of bacterial and mycotic infection of genital and urinary tract system in patients using this medicine.
7. This medicine must be used as prescribed only. In case of faint, consult the physician immediately.

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